Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355-65. DOI: 10.1056/NEJMoa1214609

Supplement to the INTERACT2 study main results

This supplement contains the following items:

1. Original protocol, final protocol with a summary of changes.

2. Original statistical analysis plan without subsequent modifications.

THE SECOND INTENSIVE BLOOD PRESSURE REDUCTION IN ACUTE CEREBRAL HAEMORRHAGE TRIAL

An international randomised controlled trial to establish the effects of early intensive blood pressure lowering in patients with intracerebral haemorrhage

STUDY PROTOCOL

(Version 1.1 – 21 July 2008)

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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.

_____

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

_____

Name of Investigator (Printed)

_____

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24 April 2008
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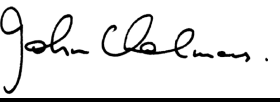
24 April 2008
Date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Trial Statistician
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Protocol Version History and Amendments

Date	Version Number
24 April 2008	1.0
21 July 2008	1.1

Amendments

Amendment 1*:* page 17 under point 3. INCLUSION AND EXCLUSION CRITERIA, under c, line 5: "provided systolic BP is **≤** 220 mmHg within 6 hours of symptom onset)" instead of **<** 220
Amendment 2: page 21 under point 6.2 Control / Conservative BP Management Group line 2: "in Background section). Appendix **1F**" *instead of* **1E**
Amendment 3: page 21 under 8. BACKGROUND CARE, line 4: "as per the schedule outlined in Appendices 1A to 1**D**" instead of 1**C**
Amendment 4: page 24: changes highlighted in yellow:

Table 5 Schedule of evaluations

		Day			
		1	7(b)	28(c)	90(c)
BP/Heart rate	**X** BP x 2	**X **** q 15 min 1 h hourly 2-6h 6 hourly 6-24h	***X deleted***		
Physical exam GCS/NIHSS	**X**	**X** ***instead of 0***	**X**		
Functional assessment with mRS			**X**	**X** ***instead of 0***	**X** ***instead of 0***

Amendment 5: Throughout the document (page 6, in title Appendix C and page 38 in title Appendix 1 C and in the table): "**Urapadil**" has been changed to "**Urapidil**"

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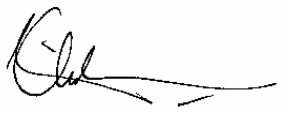


Signature

List of abbreviations and definition of terms

ACE-I	Angiotensin Converting Enzyme Inhibitor
AE/SAE	Adverse Event/ Serious AE
AHA	American Heart Association
ANZ	Australia and New Zealand
ARCOS	Auckland Regional Community Stroke Study
BP	Blood Pressure
CEC	Clinical Endpoints Committee
CHF	Congestive Heart Failure
CI	Confidence Interval
CRF/eCRF	Case record form /Electronic CRF
CT	Computerised tomography
CV	Curriculum Vitae
CVD	Cardiovascular Disease
DAP	Data Analysis Plan
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
EC	Executive Committee
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GI	The George Institute for International Health
HR	Heart Rate
HREC	Human Research Ethics Committee
HRQoL	Health Related Quality of Life
ICC	International Co-ordinating Centre
ICH	Intracerebral Haemorrhage
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intention to Treat
MI	Myocardial infarction
mRS	Modified Rankin Scale
NB	Note
NHMRC	National Health and Medical Research Council
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio
PI	Principal Investigator
SAH	Subarachnoid Haemorrhage
SAP	Statistical Analysis Plan
SD	Standard Deviation
TIA	Transient Ischaemic Attack
WHO	World Health Organisation

CONTENTS

SUMMARY PROTOCOL

THE SECOND INTENSIVE BLOOD PRESSURE REDUCTION IN ACUTE CEREBRAL HAEMORRHAGE TRIAL

The main phase of an academic lead and conducted, international, multi-centre, open label, blinded endpoint, randomised controlled trial to establish the balance of benefits and risks of a treatment strategy of early intensive lowering of blood pressure (BP) compared to a conservative BP lowering policy in patients with acute primary intracerebral haemorrhage (ICH) and co-existing elevated BP without any definite indication or contraindication to treatment.

Background and rationale

Intracerebral haemorrhage (ICH) is one of the most serious subtypes of stroke, affecting over a million people worldwide each year, most of whom live in Asia. About one third of people with ICH die early after onset and the majority of survivors are left with major long-term disability. Despite the magnitude of the disease burden and cost on healthcare resources, there remains uncertainty about the role of surgery for ICH and no acute medical therapies have been shown to definitely alter outcome in ICH. Although administration of activated recombinant human Factor VII (ie rFVIIa; NovoSeven®) has been shown to limit haematoma expansion, a recent clinical trial failed to show that this effect translated into improved survival and less major disability in ICH. Moreover, future use of this agent will be limited by its short therapeutic time window, contraindication in patients at risk of thromboembolism, and high cost. The management of ICH, therefore, contrasts sharply with that of acute ischaemic stroke, where there is now strong evidence to support the routine use of thrombolysis in carefully selected patients, and aspirin in the majority.

Blood pressure (BP) levels are strongly and positively associated with the incidence of first and recurrent stroke, and there is definitive evidence that BP lowering reduces stroke risk. Although BP levels are commonly elevated early after the onset of stroke, particularly in ICH, 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 the setting of acute ICH. While these provide an indication of perceived harm associated with 'very high' BP levels (>220mmHg), they also highlight persisting clinical uncertainty about what comprises optimal management of BP in this patient group.

The adverse effect of high BP levels on outcome in ICH is likely to involve a number of different mechanisms: elevated hydrostatic pressure at the site of bleed is likely to result in a larger initial bleed and early haematoma expansion, while elevated BP increases the likelihood of early re-bleeding, more severe oedema and early recurrent stroke. The first of these mechanisms is likely to be most relevant in the first several hours after onset, as haematoma expansion is most frequent in the first several hours after onset. Reduction of BP may also be important sub-acutely, as peri-haematomal oedema, which appears to be plasma derived, increases in volume over several days. Against this background of processes is the increased risk of early stroke recurrence from elevated BP levels.

The INTERACT2 study follows the recently completed initial pilot study (vanguard phase) which established the feasibility of the protocol, safety of early intensive BP lowering, and effects on haematoma expansion within 6 hours of onset of ICH. Having established 'proof-of-concept' that BP lowering may improve outcome by reducing haematoma expansion, INTERACT2 aims to establish the effects of the treatment on major clinical endpoints in patients with ICH recruited from an expanding clinical network around the world.

Aims

To establish the effects of a management policy of early intensive BP lowering on death and disability in patients with acute spontaneous, primary, ICH and co-existing elevated BP compared to a more conservative BP management policy that is based on a commonly used guideline for the management of high BP in this clinical setting. The study uses a similar design to the pilot study - INTERACT1 - undertaken in 44 sites in Australia, China and South Korea during 2005-2007. All patients will contribute to assessment of the mortality/dependency endpoint at 90 days follow-up post-randomisation.

Design

A multi-centre, prospective, open label, blinded outcome, randomised, controlled, trial involving 2800 patients with acute ICH recruited from approximately 140 sites in the world.

Patient recruitment

Patients with CT-confirmed acute ICH within 6 hours of onset are potentially eligible if they have a sustained elevated systolic BP level (≥150 to ≤220 mmHg) and where an intensive BP lowering management strategy and active ancillary care are available. Exclusion criteria include: (a) clear indication to BP lowering (eg very high BP >220 mmHg or hypertensive encephalopathy); (b) a contraindication to intensive BP lowering (eg known severe carotid stenosis or uncontrolled heart failure); (c) the attending clinician considers the patient to be unlikely to benefit from any therapy due to existing severe illness or medical condition (eg advanced dementia, known serious pre-stroke disability) or because they have a very high likelihood of death within 24

hours (ie GCS score 3-5) or massive ICH with major cerebral midline shift; (d) there is concomitant medical illness that would interfere with outcome assessments and follow-up; and (e) arrangements have been made for early surgical removal of the haematoma. .

Randomised interventions
Patients will be randomised via a 24-hour central internet-based randomisation system (or IVRS system, currently in development) to either (a) intensive or (b) conservative management of BP. Treatment is to start as soon as possible after randomisation (eg in the emergency department) and will be continued in a monitored facility (ie intensive care unit, high dependency unit, or stroke unit) for all randomised patients.

Intensive BP lowering - patients allocated to the intensive BP lowering group will be started on a standardised treatment regime commencing with intravenous and then changed when feasible to oral (or via a nasogastric tube) agent(s). The treatment goal is to achieve a systolic BP goal (<140 mmHg) within one hour of commencing the randomised treatment. The second goal will be to maintain the systolic BP to 140 mmHg or less or at least 7 days in hospital, and subsequently on discharge and for 90 days post-randomisation. Specific treatment protocols are developed for each participating region/centre based on the availability of BP lowering agents for routine use.

Conservative BP lowering - patients allocated to this group will receive BP management that is based on American Heart Association (AHA) guidelines. In this group, the threshold to be considered for the initiation of treatment will be a systolic BP ≥180 mmHg.

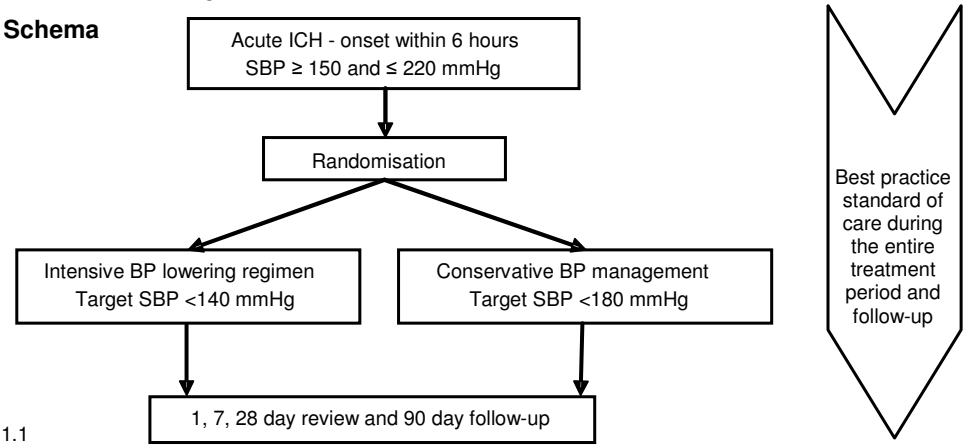
For both groups, patients must be on an oral anti-hypertensive agent by day 7 or discharge from acute care hospital, with a long-term target systolic BP of 140 mmHg, as per secondary stroke prevention guidelines.

Data collection and follow-up
Key baseline information will be collected at the time of randomisation. Follow-up data will be collected on four occasions: 24 hours and 7 days (or at the time of death or hospital discharge, if this should occur before day 7), and 28 days and 90 days, with the latter two assessments able to be carried out either in-person or over the telephone. The clinical assessments are to be undertaken by a person who was not involved in the initial treatment of the patient and kept blind to the treatment allocation. Data collection and trial management will be facilitated by an established internet-based system.

Outcomes
Primary outcome: the efficacy of the treatment regime will be evaluated on the combined endpoint of death and dependency at the end of follow-up. Key secondary outcome: to assess efficacy of the primary outcome in those patients treated within 4 hours of ICH onset. Other secondary outcomes: to determine effects of treatment on (a) physical function, health-related quality of life, recurrent stroke and other vascular events, days of hospitalisation, and requirement for permanent residential care, and (b) other serious adverse events.

Statistical power
The sample size of 2,800 provides at least 90% power (alpha=0.05) to detect a beneficial effect of early treatment on the primary outcome, which equates to one or more cases of death or dependency prevented among every 14 patients treated. This assumes primary outcome event rates of about 50% in the control group and 43% in the active group, a 14% difference in relative risk between the groups, a 10% non-adherence (drop-out) to treatment, and a 3% loss to follow-up. This sample size also provides 90% power to detect a 20% relative risk reduction on the primary endpoint among those patients treated within 4 hours of ICH onset, expected to be about half (1400) of the study population. This size of absolute benefit of the treatment has been considered clinically valuable in other areas of neurology and is comparable to the magnitude of benefit seen with calcium channel blockers in acute subarachnoid haemorrhage and the use of stroke units for the management of acute stroke.

Study Schema



INTRODUCTION

Primary ICH, defined as the spontaneous rupture of an intraparenchymal blood vessel, affects over a million people worldwide each year.[1] Of these, around one third will die within one month, while the majority of survivors will be left with significant long-term disability.[2 3] ICH is associated with very high medical and socio-economic costs.

Despite the magnitude of the disease burden, there are currently no routine acute therapies for ICH that have been proven beyond doubt to improve outcomes. This contrasts sharply with the management of acute ischaemic stroke where thrombolysis has been shown to be highly effective in certain subgroups of patients. There is increasing evidence to suggest that early intensive BP lowering therapy is a safe and effective treatment, but a large-scale clinical trial is required to reliably determine the overall balance of risks and benefits of such an intervention.

INTERACT2 has been designed to resolve an area 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. The results of the study will have significant impact on future clinical practice in ICH management.

BACKGROUND

1. EPIDEMIOLOGY

Stroke accounts for around 5 million deaths in the world every year and according to projections by the World Health Organisation (WHO), will remain the second leading cause of death in both developed and developing countries for at least the next few decades.[4] Among the major pathological stroke subtypes, ICH accounts for approximately 10-15% of all strokes in Western countries,[5] but this figure is up to 20-30% in African and Asian populations.[6, 7] The incidence of ICH varies by country; results from the International Stroke Incidence Collaboration estimate the standardised annual incidence of ICH in the 45-84 year age group to be between 26 and 60 per 100,000 population.[8] In the USA, this equates to about 70,000 cases of ICH annually,[9] and in China, the number is estimated to be 300,000.[10]

ICH is associated with very high early mortality and morbidity, with case fatality ratios of between 30% and 50%,[11 12-14 15-18 19, 20 21] and about one half of survivors being dependent on long-term care.[14, 21, 22] Thus, between 65% and 75% of all ICH patients will either die or be permanently disabled by the disease. In 2004, the estimated direct and indirect cost of stroke in the US is approximately $54 billion.[9]

Elevated BP or 'hypertension' is well established as the major risk factor for ICH, with several large-scale observational studies demonstrating that BP levels are positively and continuously associated with risks of ICH.[23, 24] The association between hypertension and ICH risk appears to be much stronger than that for ischaemic stroke.[23, 24] There is also evidence that BP levels are strongly and positively associated with the long-term risks of recurrent stroke for both haemorrhagic[25] and ischaemic events.[26, 27] In a systematic review, systolic BP elevations of 10 mmHg were associated with a 42% (95% confidence interval [95% CI] 39-44%) increase in the risk of haemorrhagic stroke.[24] The relative risk of ICH in hypertensive individuals is 2-3 times that of non-hypertensive individuals.[28] In addition, among hypertensive individuals, those who have ceased taking medication appear to be at significantly greater risk of ICH.[29]

The other major modifiable risk factor for ICH is high alcohol intake, with intake greater than 56 g/day being associated with crude odds ratio (OR) of 3.36 (95% CI 2.21-5.12).[28] The data for hypercholesterolemia as a risk factor are conflicting, with cohort studies showing a clear association for decreasing risk of ICH with increasing serum cholesterol levels.[28] Diabetes may be a weak risk factor (OR 1.27; 95% CI 0.99-1.62), whilst data for physical activity are inconclusive.[28] Certain genetic factors such as the presence of an apolipoprotein E2 or E4 allele and a first degree relative with ICH have also been shown to be significant independent risk factors for ICH.[30]

2. PATHOPHYSIOLOGY

ICH usually results from spontaneous rupture of a small penetrating artery or arteriole deep in the brain. The most common sites are the basal ganglia (lentiform nucleus, caudate and thalamus), cerebral hemispheres (lobar), cerebellum and pons. Modern neuro-imaging studies indicate that continued bleeding and expansion of the haematoma of ICH occurs in up to one third of patients within several hours of onset, and probably over 3 to 24 hours in another 10%.[31-34] Further neurological deterioration may occur over several days secondary to the adverse effects of oedema[35-37] and inflammation[38-41] in the peri-haematomal region.

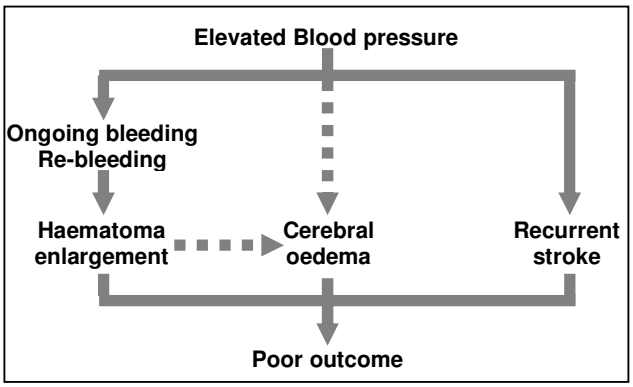


Figure 1. The mechanism by which higher blood pressure levels may lead to a poor clinical outcome in patients with intracerebral haemorrhage

High BP levels in acute ICH have been shown to be associated with poor outcome.[42] The adverse effect of high BP levels on outcome in patients with ICH are likely to involve a number of different mechanisms (**Figure 1**): an elevated hydrostatic pressure at the site of the haemorrhage is likely to result in a larger initial bleed and early haematoma expansion,[43-48] while elevated BP levels increase the likelihood of early re-bleeding, more severe oedema,[35, 36] and early stroke recurrence.[25]

The first of these mechanisms resulting from elevated BP level is considered to be the result of persistent bleeding or re-bleeding from the ruptured vessel. Several observational studies have reported the frequency of early haematoma expansion **(Table 1)**. In the only prospective study, Brott et al. performed a baseline CT scan within 3 hours of onset and found a haematoma expansion (>33% volume expansion) in 26% of patients within the subsequent hour.[31] An additional 12% of patients exhibited expansion by 20 hours post-ictus. Most haematoma expansion appears to occur within the first several hours after onset, although continued growth up to 24 hours in a limited number of patients is suggested by retrospective studies.[34] CT angiographic studies also suggest that bleeding may continue for up to 24 hours in some patients.[43] In patients taking anticoagulants, haematoma expansion appears to persist even longer.[49]

Table 1 Frequency of early haematoma expansion*

Interval from symptom onset to first CT (hours)	Prospective	Retrospective		
	Brott et al.[31] (n=103)	Fujii et al[32] (n=627)	Kazui et al[34] (n=204)	Takizawa et al[33] (n=369)
0 to 3	38%	18%	36%	14%
3 to 6	N/A	8%	16%	4%
0 to 6	N/A	17%	29%	12%
6 to 24	N/A	2%	10%	0%

*Haematoma expansion defined as >33% increase in volume by Brott et al, >50% (or 20ml) increase by Fuji et al, and >40% (or 12.5ml) increase by Kazui et al. No expansion criteria specified by Takizawa et al. N/A = data not available.

Although haematoma expansion is an important predictor of poor outcome in patients with ICH,[31, 34, 43, 47, 50-54] other mechanisms may also contribute to overall morbidity and mortality. Early re-bleeding occurs in a substantial proportion of patients in the first 12 hours. However, peri-haematomal oedema persists in the majority for at least several days.[35-37] The effect of BP reduction on oedema development is unknown. Elevated BP levels also increase the risk of early stroke recurrence through similar mechanisms responsible for the primary ICH event.[25] Thus, BP lowering has potential to reduce ICH related morbidity within a wide therapeutic time window.

3. CLINICAL PRESENTATION AND ACUTE MANAGEMENT

Time of presentation to hospital of patients with all forms of acute stroke varies widely **(Table 2)**. However, many patients arrive at hospital within 6 hours after onset of symptoms in Australia and New Zealand (ANZ), China, the United Kingdom (UK), and the USA. Thus, it appears feasible to evaluate the effects of early BP lowering treatment in ICH.

Table 2 Time from onset to hospital presentation in acute stroke

	n	Time of hospital presentation (hours)		
		0 to 3	0 to 6	0 to 12
Australia and New Zealand				
ICH in the Auckland, ARCOS study of 2002-03 (C Anderson, personal communication)	112	64%	82%	87%
China				
Cheung et al.[55]	71	N/A	56%	N/A
UK				
Salisbury et al.[56]	128	37%	52%	75%
Harraf et al.[57]	729	37%	50%	62%
USA				
Barsan et al.[58]	1159	59%	N/A	N/A
Smith et al.[59]	1334	50%	65%	80%
Kothari et al.[60]	119	30%	50%	N/A
Willmot et al[61]	553	46%	61%	70%

*N/A = data not available

Elevated BP occurs commonly after the onset of stroke, and is more frequent in patients with ICH compared to patients with ischaemic stroke.[62 63 64] Hypertension has been reported in up to 90% of patients presenting with acute ICH.[62 63 64] Although BP levels decline spontaneously in most patients, they remain elevated in a substantial proportion.[62 63] Observational studies have shown a clear association between high BP levels in ICH and subsequent death or dependency.[42] Other factors such as reduced level of consciousness,[12 13, 43] continued bleeding suggested by extravasation,[43] haematoma expansion,[31, 53] large haemorrhage size,[12 14-16, 44 54 65 66, 67] intra-ventricular extension[12 14, 16 43 54 66] and older age,[17, 43] have also been associated with poor outcome.

The goals of treatment of ICH, as with other forms of stroke and brain injury, are firstly to prevent or reverse acute brain injury; and secondly to prevent future neurological impairment and disability. A meta analysis of all randomised controlled trials has shown that treatment of patients in stroke units reduces mortality, dependency and the need for institutional care.[68] An observational study has also shown benefit of semi-intensive monitoring.[69] Although very high BP levels are generally considered to require treatment, the effects of BP lowering treatment in the acute phase of stroke are less well established. Despite there being an indication of harm associated with high BP levels, there are wide ranging recommendations for the management of BP expressed in current guidelines **(Table 3)**, which highlight the persisting clinical uncertainty surrounding what comprises 'optimal management' for acute ICH patients. In particular, there is uncertainty over the level at which BP lowering should commence, how quickly the BP should be lowered, and the ultimate target BP level to be reached.

Table 3 Guideline recommendations for BP lowering treatment in patients with acute ICH

	Start medication	Target
ICH		
American Heart Association[70]	>180 mmHg	160/95 mmHg
International Society of Hypertension[71]	>220/120 mmHg	Up to 20% reduction
Stroke Foundation of New Zealand[72]	Mean BP ≥ 130 mmHg	Mean BP <130 mmHg
Any stroke		
European Stroke Initiative[73]	>220/120 mmHg	Hypertensive - 180/100-105 mmHg Non-hypertensive - 160-180/90-100 mmHg
National Stroke Foundation (Australia)[74]	≥200/110 mmHg	Up to 20% reduction
Royal Collage of Physicians (UK)[75]	If complications are apparent	Not described

There are a small number of randomised controlled trials of other medical treatments (steroid, haemodilution and glycerol) in ICH.[76-78] None of these treatments have shown to be effective.

Most recently, evidence has emerged of potential benefit of use of activated recombinant human factor VII (rFVIIa/NovoSeven®) when administered within 4 hours after the onset of ICH.[79,80] Although rFVIIa has been shown to reduce haematoma expansion, it has not been demonstrated to clearly improve clinical outcome. The reason for this is not entirely clear but may be due to the benefit being offset by major thromboembolic events (eg ischaemic stroke and myocardial infarction), imbalances in stroke severity at baseline favouring the placebo group in the first clinical trial, and ancillary care attenuating any modest treatment effect. Even if the rFVIIa was approved for clinical use, it seems that it will have limited applicability due to the restricted therapeutic time window, the risk of thromboembolic complications, and high cost.

Despite the completion of a large-scale international study (the Surgical Trial in ICH [STICH] trial with a neutral overall result of treatment)[81] and several smaller trials,[82] the decision about whether and when to operate on patients with ICH remains controversial. However, guideline recommendations for surgical treatment are mainly based on severity, clinical course and size and location of the haematoma.[70 72 75] The proportion of patients treated surgically varies considerably, both between and within countries around the world, but is probably less than 10% in Australia, New Zealand, the US, and China.[83] BP lowering treatment has been shown to be associated with lower re-bleeding after surgical treatment,[84] and patients who undergo surgery usually receive intensive BP lowering treatment.

4. EVIDENCE FOR BP LOWERING IN ICH

a) Observational studies

A number of studies have also examined the short-term effects of BP with prognosis of acute ICH.[12-15 18-20, 44, 54, 65-67, 85-88] Most have shown that higher BP levels are associated with worse outcomes.[13-15, 18-20, 54 66, 67, 86 87, 88] In the largest of these studies,[67] the mean arterial pressure was 134 mmHg on admission in patients who died, compared with 124 mmHg in those that survived ($p<0.01$). In the second largest study,[13] the risk of early death was greatest among the quartile of patients with the highest BP levels at presentation, and risks declined progressively in each of the other three groups **(Figure 2)**.

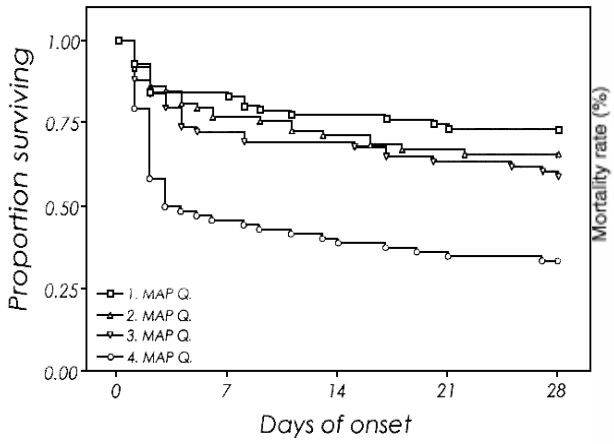


Figure 2. Twenty-eight day survival of patients with acute intracerebral haemorrhage in four groups defined by mean arterial pressure (MAP) quartiles (Q)
From Fogelholm et al.[13]

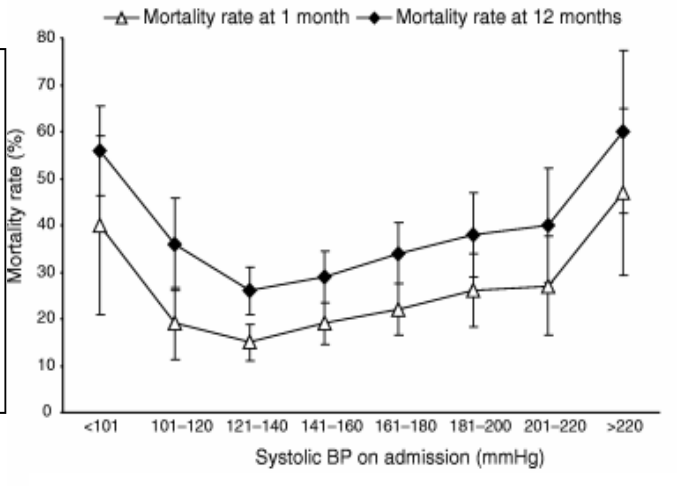


Figure 3. Proportion of patients who died at 1 (triangle) and 12 months (circle) by baseline systolic blood pressure
From Vemmos et al.[85]

A systematic review of these observational studies has also shown a clear association between high BP and subsequent death or dependency in acute ICH.[42] Only one study has suggested a J-shaped association between BP levels and outcome, with both the highest and lowest BP levels being associated with increased risks of adverse outcomes **(Figure 3)**.[85] In this study, however, it is uncertain whether the low BP level is a cause of adverse outcomes. It could be reverse causation that low BP levels and death are caused by the most severe haemorrhages.

It is clear that if there is any adverse effect of low BP on outcome, it does not seem to be apparent until systolic BP levels reach 140 mmHg or less, which is well below the level observed in most acute ICH patients and the level recommended for intervention in current guidelines.

b) Randomised trials

Randomised trials have clearly demonstrated that BP lowering reduces the risk of initial stroke, both ischaemic and haemorrhagic.[89, 90] Clear evidence from PROGRESS[91] has also shown that BP lowering reduces the risk of recurrent stroke. PROGRESS recruited approximately 6,000 patients from 172 collaborating centres in 9 countries (Australia, Belgium, China, France, Japan, New Zealand, Sweden, the United Kingdom and Ireland) during 1995-2001. This study showed that a regimen based on an angiotensin converting enzyme (ACE) inhibitor significantly reduced the risk of recurrent stroke by 28% (95% CI 17 to 38%).

In PROGRESS, subsidiary analyses suggested that the benefits of treatment were particularly large among patients with a history of ICH at baseline.[91, 92] In this subgroup, treatment reduced the risk of a recurrent stroke by 49% (95% CI 18 to 68%) compared to a reduction of 17% (95% CI 12 to 38%) among patients with an ischaemic stroke. The overall reduction in the risk of ICH (50%; 95% CI 26 to 67%) appeared to be greater than the reduction in the risk of ischaemic events (24%; 95% CI 10 to 35%) and tracking of stroke subtypes within individuals appears to explain much of the additional benefit observed in patients with a baseline history of haemorrhage. Subsidiary analyses of PROGRESS which examined the effects of BP lowering in a third of the study population defined by time between qualifying event and randomisation,[91] showed no evidence of any difference in the benefits of treatment between patients commenced within an average of 1.5, 7.2, or 30 months of the first stroke registered in the study (p homogeneity = 0.3). However, this study did not provide any information about the effects of BP lowering commenced in the acute phase of either ischaemic or haemorrhagic stroke subtypes, and there remains great uncertainty about the overall balance of risks and benefits of BP lowering in this scenario.[93, 94]

Several small clinical trials have examined the effects of BP lowering in the acute phase of stroke, but these included predominantly patients with cerebral ischaemia.[95-97 98-100] Systematic overviews summarise the findings for BP lowering treatment in general,[100] and of calcium channel antagonists specifically.[99] No individual study or overview has conclusively identified significant beneficial (or harmful) effects of BP lowering treatment in acute stroke. Overall, the studies suggest blood pressure reduction is associated with lower mortality rates **(Figure 4)** but the 95% CIs for the estimates are wide.

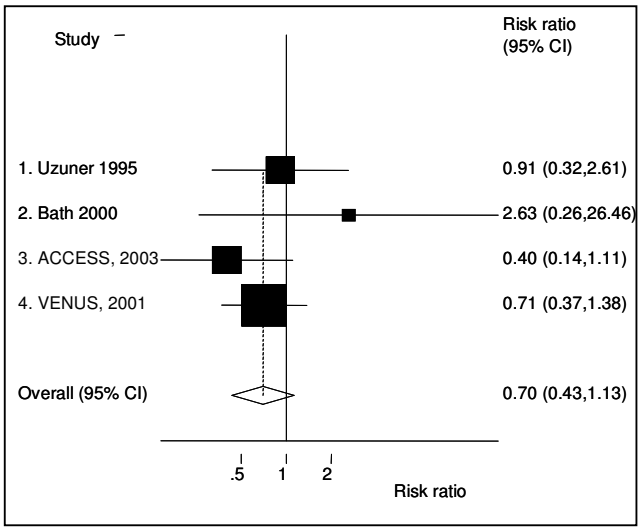


Figure 4. Summary of studies of acute blood pressure lowering on mortality after acute stroke.[98,100,101]

Adapted from the Blood Pressure in Acute Stroke Collaboration.[101]

To date, the largest randomised blood pressure treatment trial conducted in the acute phase of stroke is the Acute Candesartan Cilexitil Evaluation in Stroke Survivors (ACCESS) study,[98] which included 339 patients with acute ischaemic stroke. Patients were randomised to receive candesartan cilexitil (an angiotensin II receptor blocker) or placebo, within 48 hours of stroke onset. The study was stopped early due to a significant reduction in the frequency of a composite secondary endpoint (combining death, cerebrovascular and cardiovascular events at 12 months) in the actively treated group compared to control group (OR 0.48; 95% CI 0.25 to 0.90).

The ACCESS results are difficult to interpret, since the secondary outcome could be due to chance, and there was no significant effect on the primary outcome (the Barthel Index at 3 months). Thus, although the study certainly provides some reassurance that use of a BP lowering agent in the acute phase of ischaemic stroke is unlikely to be seriously harmful, the study does not

provide the level of evidence required to recommend the routine use of BP lowering in acute ischaemic stroke and does not appear to have resulted in widespread change in clinical practice. In addition, even when the ACCESS mortality data are combined with the results for all the other completed trials of BP lowering in acute stroke,[96, 98, 100] the effect of BP lowering on mortality remains unclear **(Figure 4).**

There has been only one study that has reported separately the effects of early BP lowering in patients with acute ICH.[96] This trial enrolled a total of 296 patients, 35 of whom had suffered an acute primary ICH. The trial evaluated the effects of the calcium antagonist nimodipine orally commenced within 6 hours of stroke onset and showed no effect (relative risk 1.0, 95% CI 0.6 to 1.7) on the primary study outcome of death or dependency after 3 months. However, no BP differences were observed between the oral nimodipine and placebo groups. Furthermore, there were few events recorded and the wide CIs around the point estimate make the trial of little clinical relevance. This trial does, however, provide further reassurance that early BP lowering is unlikely to be seriously harmful for the majority of ICH patients.

Aside from this randomised trial, there are some prospective non-randomised studies[86, 101] which have sought to determine the effects of early BP lowering in hypertensive patients with ICH. One early study of 167 individuals with hypertensive ICH, were divided into three groups that were 'untreated', 'inadequately treated' or 'adequately treated' with the antihypertensive agent reserpine.[86] A poor outcome was most frequently observed in the group that received no BP lowering treatment, and least common in those that received effective BP lowering. In another study of 27 ICH patients, aggressive BP reduction was associated with a lower rate of neurological deterioration and haematoma expansion.[102] In another observational study,[101] 76 individuals with hypertensive acute ICH were treated with different systolic BP targets.

A target systolic BP of less than 160 to 170 mmHg was associated with haematoma enlargement more frequently than those patients in whom BP was reduced to less than 140 to 150 mmHg. In another study of 369 ICH patients,[33] intensive BP lowering treatment to a target systolic BP of 140 to 160 mmHg (systolic BP levels were reduced to 140 mmHg in most patients) was associated with less frequent haematoma enlargement than other studies **(Table 1)**.[31, 32, 34, 53] These prospective studies suggest that intensive BP lowering treatment with target systolic BP to less than 140 mmHg, which is 20 to 40 mmHg lower than that of present guideline recommendations,[70 71 72, 73, 75 74] is associated with reduced haematoma expansion in acute ICH. However, just as the randomised trials were too small to reliably determine the effects of BP lowering, the non-randomised design of these studies makes it impossible to know whether the observed beneficial effects were due to the different BP lowering strategies or other factors.

Some further indirect evidence to support the safety and potential benefit of BP lowering in acute ICH is provided by the results of trials of calcium antagonists in patients with subarachnoid haemorrhage. In these trials there is clear evidence of benefit associated with the use of calcium antagonist-based regimens, with overall reductions in the rate of poor outcome at 3 to 6 months of 18% (95% CI 7% to 28%).[103] While the aetiology of subarachnoid haemorrhage is different to that of ICH,[104, 105] BP is an important determinant of risk in both,[104 105 106] and there is some evidence of associations of early high BP levels with the risk of haemorrhage extension.[107]

5. CHOICE OF BP LOWERING AGENT

There are a number of different drug classes that may be used to lower BP in acute stroke,[100] 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.[108, 109] 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 ICH 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 of action	Duration of action	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

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,[71] and profound BP lowering effects.

Guidelines only recommend use of sodium nitroprusside in patients with extremely high BP levels.[70] 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.

6. FINDINGS OF THE PILOT STUDY – INTERACT1

The results of INTERACT1 have been published in Lancet Neurology, May 2008.[110] The study enrolled 404 patients from 44 hospitals in Australia, China and Korea from November 2005 to April 2007. Eligible patients were aged ≥18 years with CT-confirmed ICH and elevated systolic BP (≥150 and ≤220 mm Hg), with the capacity to commence randomly assigned BP lowering treatment within 6 hours of ICH in a monitored environment. A central randomization system was used to assign patients, either to a treatment strategy of intensive BP lowering (target systolic BP of 140 mm Hg) based on a stepped protocol of routinely available intravenous agents, or to previous version AHA guidelines for BP lowering (target systolic BP of 180 mm Hg). Digital images of baseline and repeat CT (24±3 hours) performed using standardized techniques were analysed centrally. The primary efficacy measure was proportional change ('growth') in haematoma volume at 24 hours. Clinical outcomes were assessed over 90 days.

At baseline, the characteristics of patients were similar between groups, but mean haematoma volumes were slightly smaller in the control group (12.7, SD 11.6) compared to the intensive group (14.2, SD 14.5). From randomisation to 1 hour, mean systolic BP was 153 mmHg and 167 mmHg in the intensive and guideline groups, respectively (difference 13.3 mmHg, p<0.0001), and from 1 to 24 hours, levels were 146 and 157 mmHg, respectively (difference 10.8 mmHg, p<0.0001).. Mean proportional haematoma growth was 36.3% in the guideline group and 13.7% in the intensive group, a significant difference of 22.6% (95% CI 0.6-44.5%; p=0.04) at 24 hours. After adjustment for initial haematoma volume and time from onset to CT, the difference was borderline significant (adjusted p=0.06). Likewise, 'substantial' haematoma growth (i.e. >33% or >12.5 ml) was 36% (95% CI 0-59%, p=0.05) lower in the intensive group. Intensive BP lowering treatment did not alter the risks of adverse events nor clinical outcomes at 90 days.

The study has shown that early intensive BP lowering treatment is well tolerated and appears to attenuate the growth of haematoma in ICH. These data provide the basis for proceeding with the main phase of the study with project grant funding from the National Health and Medical Research Council (NHMRC) of Australia during 2008-2011.

7. SUMMARY OF RATIONALE FOR A TRIAL OF BP LOWERING IN ICH

There is currently insufficient evidence to recommend a specific management strategy for BP in the acute phase of stroke.[93, 94] However, on the basis of available evidence, there is a strong rationale to expect beneficial effects of early intensive BP lowering in acute ICH. While ongoing trials will provide new information about the effects of BP lowering in acute ischaemic stroke, there are no other corollary large-scale studies in ICH yet being undertaken. As the basis for anticipating a beneficial effect of BP lowering in patients with acute ICH is strong INTERACT2 has been designed as a large-scale study to determine the overall balance of risks and benefits associated with the use of BP lowering in patients with acute ICH and co-existing elevated BP with no definite indication or contraindication to the treatment.

AIMS AND OBJECTIVES

The primary null hypothesis to be tested is that there is no effect of early intensive BP lowering compared with a conservative BP treatment policy, on death and dependency in patients with acute spontaneous ICH.

1. PRIMARY AIM

To determine the effects of the randomised BP management on all-cause mortality and dependency at 90 days.

2. KEY SECONDARY AIM

To evaluate the clinical benefit in those patients treated within 4 hours of onset of ICH.

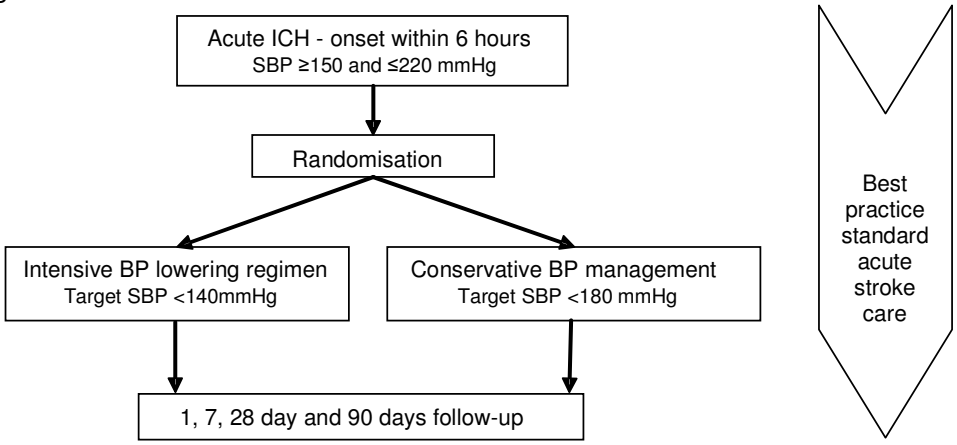
3. OTHER SECONDARY AIMS

To determine the effects of the treatment separately on death and dependency, as well as on physical function, health-related quality of life (HRQoL), recurrent stroke and other vascular events, days of hospitalisation, and requirement for permanent residential care.

METHODS

1. OVERALL DESIGN

This study is an open label, prospective, randomised, controlled, multi-centre trial that, will involve 2800 patients with acute primary ICH recruited from approximately 140 Clinical Centres from Asia, Europe and other regions of the world. Endpoint assessment will be blinded to treatment. The study design is summarised in the schema below.



2. STUDY POPULATION

All patients presenting to participating centres with suspected acute ICH 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:

(1) Completion of CT scan;

(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 ARE to satisfy all of the following criteria:

a. Aged 18 years or above.

b. Acute stroke syndrome due to spontaneous ICH, defined as the sudden occurrence of bleeding into the parenchyma of the brain that may extend into the ventricles and, in rare cases, into the subarachnoid space, confirmed by clinical history and CT scan. (NB Patients with ICH secondary to medical treatment, eg antiplatelet or antithrombotic therapy, are eligible, but ICH secondary to thrombolysis are ineligible).

c. At least two systolic BP measurements of ≥150 mmHg and ≤220 mmHg, recorded 2 or more minutes apart. (NB Patients with initial systolic BP levels outside this range, eg <150 or >220 mmHg, may be randomised should the BP levels fulfil entry criteria on re-checking up to 6 hours. Moreover, patients with systolic BP >220 mmHg may receive initial BP lowering and then randomised, provided systolic BP is ≤220 mmHg within 6 hours of symptom onset).

d. Able to commence randomly assigned BP lowering regimen within 6 hours of stroke onset. (NB If the precise timing of the first symptoms or signs of the qualifying event are unknown then the time of onset will be taken as the last time at which the patient was known to be well).

e. Able to be 'actively' treated and admitted to a monitored facility, such as an acute stroke unit, high dependency unit or intensive care unit. It is recognized that many ICH patients are designated 'Not For Resuscitation' or 'Do Not Resuscitate' after appropriated consultation with family members. This in itself is not a contraindication to enrolment in the trial, as long as management is otherwise active.

Patients will **NOT** be eligible if there is one or more of the following:

a. Known definite *contraindication* to an intensive BP lowering regimen (eg severe carotid, vertebral or cerebral arterial stenosis, known Moya Moya disease or Takayasu's arteritis, high-grade stenotic valvular heart disease, or severe renal failure).

b. Known definite *indication* for an intensive BP lowering regimen that is similar or more intensive than the active treatment arm of this study (eg very high systolic BP >220 mmHg, hypertensive encephalopathy, or aortic dissection).

c. Definite evidence that the ICH is secondary to a structural abnormality in the brain (eg an AVM, intracranial aneurysm, tumour, trauma, or previous cerebral infarction) or previous thrombolysis.

d. Previous ischaemic stroke within 30 days.

e. A very high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria (eg massive haematoma with mid-line shift of hemisphere or deep coma on presentation, defined by Glasgow Coma Scale Score of 3-5), (NB seizures occur commonly after the onset of ICH, so a reduction in the level of consciousness that is

disproportionate to the size of the haematoma may be secondary to epilepsy rather than mass effect from the ICH).

f. Known advanced dementia or significant pre-stroke disability (eg modified Rankin Score [mRS][111] of 3 or more).
g. Concomitant medical illness that would interfere with outcome assessments and follow-up (eg advanced cancer or respiratory disease).
h. Already booked for surgical evacuation of haematoma.
i. Previous participation in this trial or current participation in another investigational drug trial.
j. A high likelihood that the patient will not adhere to the study treatment and follow-up regimen.

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

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 (ie 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 ICH require emergency care. One aspect of this care is the 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 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.

Surrogate 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 next of kin or surrogate will be approached to provide informed consent on his or her behalf. 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 dieing or is still unable to record their personal consent by the time of completed follow up on the study, the consent given by their next of kin or surrogate 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 next of kin or surrogate 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.

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 surrogate is not available or cannot be contacted, clinicians may enrol eligible patients and inform the patient or their surrogate 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 surrogate 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 surrogate 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 National Health and Medical Research Council also give 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 BP management in the medical profession and the current guidelines. Moreover, the INTERACT1 study has shown that there is no major hazard associated with the treatments under investigation in INTERACT2.

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 International Coordinating Centre (ICC) at The George Institute for International 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 eligibility to the study has been confirmed, the responsible clinician will access a 24-hour password protected, internet-based randomisation system. This will be done by connecting the study centre (eg emergency department or stroke unit) to the server at the ICC where the patient will be registered and the randomised BP management will be assigned for that particular patient. This system has been used successfully in other large-scale trials managed by the ICC.[112, 113] The randomisation sequence will use a minimisation algorithm to achieve balance of study groups at each participating centre. Patients will be stratified according to:

1. time since stroke onset (≤4 vs. >4 hours);
2. hospital of recruitment;
3. country of recruitment

6. ALLOCATED STUDY TREATMENTS

All centres are required to adhere to the standard treatment regimes outlined in the protocol for all randomised patients. It is anticipated that there will be broad comparability of the regimens used in participating centres within each county. As the trial is an assessment of BP management policies, there is some flexibility in the use of particular BP lowering agents to achieve BP targets.

6.1 Early Intensive BP Lowering Group

The aim is to achieve a systolic BP level <140mmHg within one hour of treatment *and* to maintain this BP level for the next 7 days or hospital discharge should this occur earlier.

Patients allocated to early intensive BP lowering will commence immediate treatment with an intravenous BP lowering agent as soon as possible after randomisation. It is anticipated that treatment will be started in the emergency department and that patients will stay there until the target BP is achieved, and they are clinically stable. Intravenous bolus (or maintenance infusion) treatment would then be continued in an acute stroke unit or other monitored facility, although a high intensity nursing care and monitoring facility (ie an intensive care unit) is likely to be required for use of an intravenous infusion of a BP lowering agent in most centres.

It is expected that intravenous therapy will continue to be required during the initiation of oral anti-hypertensive therapy, in order to maintain the systolic BP levels of less than 140 mmHg. However, a systolic BP of 130 mmHg is considered to be the lower limit for the cessation of intravenous BP lowering therapy.

<u>Intravenous treatment protocol</u>

Intravenous treatment protocols, based on available medications, are provided in **Appendices 1A to 1D**. The intravenous treatment will be titrated against regular BP monitoring to achieve a target systolic BP (below 140 mmHg). It is anticipated that intravenous control of systolic BP will be continued for a minimum of 24 hours and possibly up to 48 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 1D**. 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[91] and established best practice for the long-term prevention of BP-related events in patients with cerebrovascular disease.[114]

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 of less than 140 mmHg for 7 days of hospital stay. If the patient is transferred to another hospital facility within 7 days, then attempts should be made to continue therapy to achieve the systolic BP target of 140 mmHg. 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.

6.2 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 1F** 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. Should control of systolic BP not be achieved via these routes, intravenous treatment may be started until the target systolic BP of 180 mmHg is achieved. The oral and intravenous agents used will be the same as in the intensive BP lowering group as detailed in **Appendices 1A to 1D**. 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.

6.3 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 (eg 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 BP MANAGEMENT POLICY

The investigator must not deviate from the protocol except the patient/surrogate chooses to withdraw consent to participation in the study. However, the BP management in either group should be discontinued 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 participants should be managed in an acute stroke, high dependency or intensive care unit, whilst receiving intravenous treatment for BP control. Regular non-invasive BP and heart rate monitoring as well as an adequate nurse/patient ratio must be available. BP will be monitored and recorded using digital sphygmomanometers as per the schedule outlined in **Appendices 1A to 1D**. All BP measurements should be taken from the non-paretic arm (or right arm in situations of coma or tetraparesis), with the patient resting in the supine position. In the case of ambulatory patients, measurements should be taken after the patient has been resting supine for a minimum of 3 minutes.

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).[70] [71] [72] [73] [74] [75] It is anticipated that background care may include significant use of treatments including drugs and surgical evacuation. Use of other therapies will be documented and compared between countries and should be balanced between randomised groups.

9. STUDY OUTCOMES

9.1 Primary Outcomes

The primary outcome is a binary indicator of the patient's death or dependency at 90 days, with dependency being defined by a score of 3 to 5 on the modified Rankin Score (mRS),

9.2 Secondary Outcomes

Key secondary outcome: will be to assess the effect of the treatment on the primary outcome in a subgroup of patients who receive treatment within 4 hours of ICH onset.

Other secondary outcomes relate to the specified objectives outlined below.

1. **Mortality** at 28 days and 90 days
2. **Dependency** (measured by mRS see Appendix 3) at 28 days and 90 days
3. **HRQoL** (measured by the EuroQuol 5D[115] see Appendix 3) at 28 days and 90 days.
4. **Recurrent stroke** defined as an acute disturbance of focal neurological function with symptoms lasting more than 24 hours due to new onset ICH or cerebral ischaemia, confirmed by neuro-imaging (or necropsy), that has occurred after an unequivocal period of neurological stability after 24 hours of the initial ICH.
5. **Acute myocardial infarction** (or sudden death) from a cardiovascular cause, according to standard definitions.
6. **Need for permanent residential care** (eg hostel or nursing home)
7. **Duration of initial hospital stay**

10. DATA COLLECTION AND FOLLOW-UP

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 BP 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 reports 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 encrypted 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, heart rate 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

Participating centres will keep a log of all patients presenting to their institution with a diagnosis of ICH. This will commence following activation of the centre until the end of recruitment and will include all patients whether randomised or not. The 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 (if applicable). 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.

Investigators at each site are required to submit the screening log to the ICC database by the last day of each month during the course of the study.

10.2 Patient 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 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 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 acute ICH will be assessed by the responsible physician for eligibility to the study using a checklist of the eligibility criteria described above.

10.4 Baseline Data

The following information is to be collected before randomisation:

- Medical history
- BP, temperature, heart rate (HR), and scores on the GCS and NIHSS
- CT findings to confirm the diagnosis of primary ICH

All baseline CT scans are to be copied in uncompressed DICOM format onto a CDROM and sent by courier to the regional coordinating centre at the end of each month (see Appendix 2).

10.5 Follow Up Data

Day 1 (from randomisation to 24 hours)

The primary goal of assessments within the first 24 hours will be to ensure adherence to the allocated BP management protocol. Accordingly, BP and administered medication will be recorded. HR will be recorded from an electrocardiographic monitor. BP will be recorded supine in the non-paretic arm from the automated, electronic device used at the Clinical Centre. BP will be recorded every 15 minutes for the first hour, every hour for the next 5 hours, and then 6 hourly for the next 18 hours. 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.

For those sites who have agreed to participate in the collection of a follow-up CT scan, a second CT scan should be undertaken at 24±3 hours after randomisation.

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
- GCS and NIHSS scores
- BP lowering medication
- Dependency assessed with the mRS
- 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. Number of BP lowering agents used 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 Log to assist in trial monitoring by the ICC.

Withdrawal of allocated BP management, 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 Case Report Form and the type(s) of consent obtained will also be recorded on the database.

Serious Adverse Events
All SAEs will be recorded on the SAE form and faxed or emailed 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	7(b)	28(c)	90(c)
Eligibility	**X**				
CT scan	**X**	**X***			
Fevers to be recorded	**X**		**X**		
BP/Heart rate	**X** BP x 2	**X** ** q 15 min 1 h hourly 2-6h 6 hourly 6-24h			
Consent (a)	**X**				
Clinical history prior medications	**X**				
Physical exam GCS/NIHSS	**X**	**X**	**X**		
Functional assessment with mRS			**X**	**X**	**X**
HRQoL assessment with EQ 5D				**X**	**X**
Standard care & routine blood tests	**X**	**X**			
BP lowering treatment		**X**	**X**	**X**	**X**
Standard stroke care		**X**	**X**	**X**	**X**
Hospitalised or not		**X**	**X**	**X**	**X**
Contact details for Follow-up		X	**X**		

* In the first 600 patients (300 Asian and 300 non-Asian) in site who have pre-specified agreement to provide a second CT scan undertaken at 24±3 hours, according to protocol.
** At any point where intravenous bolus drugs are administered, BP and HR should be recorded 5 and 15 minutes later.
(a) Consent may be obtained *after* randomisation.
(b) Or the day of discharge if prior to day 7,
(c) Information collected at a face to face consultation or through a telephone interview

11. SERIOUS ADVERSE EVENTS

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

11.2 Recording And Reporting

A 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 BP 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 may 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.

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 and Safety Monitoring Board (DSMB) for review outside of the planned interim analysis meetings.

12. QUALITY ASSURANCE

The study will be conducted in accordance with ICH-GCP, and all relevant local, national and international regulations.

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 an 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 existence of all randomised patients and deaths. A 10% of randomly selected study records and source documents will be reviewed for the verification of

participant details and data quality/completeness. A report of each visit will be prepared by the monitor and reviewed by the ICC.

In summary, the specific aims of the monitoring program will be to:

- confirm the existence of each patient
- confirm that the consent procedure has been documented
- confirm the diagnosis of ICH in every patient
- review source documents for 100% of the primary outcomes
- review 100 % of source data from a 10% of randomly selected of patients at each centre

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 by Government Regulatory Authorities

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

13. DATA MANAGEMENT

Randomisation and data entry will be performed at the participating centres via the password protected, encrypted 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 Clinical Endpoints Committee (CEC) will review information about every outcome reported in order to ensure that all endpoints meet the same diagnostic criteria. The CEC will comprise experts in cerebrovascular disease. The adjudication of every event will be made without knowledge of which randomised group the patient was allocated. The members of the CEC will be provided with explicit instructions about the adjudication of events and a manual detailing the criteria to be followed.

15. STATISTICAL CONSIDERATIONS

The sample size is 2,800. It is anticipated that patients will be accrued from approximately 140 Clinical Centres, with each site recruiting between 5 and 25 (average 15) patients annually over a 3 year recruitment period. It is expected that about 100 patients will be recruited from Australia and New Zealand, 1600 from China, 400 from other Asian countries, 500 from European countries and 200 from Canada. For an average-sized Clinical Centre, this will require that about one out of every five patients, who present with acute ICH, be enrolled over a 3-year recruitment period.

The proposed sample size of 2800 will provide at least 90% power (with alpha=0.05) to detect a 14% relative risk reduction in death or dependency in intervention compared to control treated patients. The assumptions in the power calculation are:

1. Primary outcome event rate will be of 50% in the control group, and will be reduced to 43% in the intervention group, which are similar to the INTERACT1 pilot study.
2. The 14% relative risk reduction is based upon the results of INTERACT1, whereby a 10-14 mmHg difference in systolic BP between randomised groups in the first 24 hours of treatment resulted in a 1.7ml absolute difference in haematoma growth. In a post-hoc analysis of patients randomized within 4 hours of ICH onset, however, the absolute

difference in haematoma growth increased to 3.4ml between groups. Other data from the rFVIIa trials [116] indicate a 7% relative increase in the risk of death or worsening of disability (1 point on mRS scale) at 90 days is associated with a 1 ml growth in haematoma. Thus, a difference in haematoma growth of 2ml (0-6 hours) and 3ml (0-4 hours) from BP lowering may result in at least 14% (7% absolute) and 21% (10% absolute) relative reduction, respectively, in the avoidance of a poor outcome in ICH

3. Non-adherence in the active treatment arm (drop-out) is 8% in INTERACT1, where 17 of the 203 patients in the treatment group did not receive any IV BP lowering treatment in the first 24 hours. It is expected that this figure will be 10% in INTERACT2.
4. Lost to follow up for the primary outcome is expected to be 3%, as seen in INTERACT1, where 11 (2.7%) patients were lost to follow up or did not have an assessment of their level of disability at 90 days.

A beneficial effect of early treatment on the primary outcome would equate to one or more cases of death or dependency prevented among approximately every 15 patients treated. This size of absolute benefit has been considered clinically valuable in other areas of neurology and is comparable to the magnitude of benefit seen with calcium channel blockers in subarachnoid haemorrhage and the use of stroke units for the management of acute stroke. The sample will expect to be balanced with 50% of patients randomized in 0-4 hour and 50% in 4-6 hour, time windows. This will provide more than 90% power to detect a relative risk reduction of 20% in those randomized within 4 hours for a pre-specified sub group analysis under the same assumptions on adherence and to follow-up, as outlined above.

16. STATISTICAL ANALYSES

All analyses will be conducted with patients allocated to the group to which they were assigned at randomisation, regardless of whether they used the study treatments (i.e. according to the principle of intention to treat). Baseline and demographic characteristics such as gender, ethnicity, medical history, etc, will be summarised by treatment group to assess comparability of treatment groups. No formal statistical analyses of these data other than descriptive statistics are planned. The primary endpoint of death or dependency at 90 days will be analysed by means of a chi-square test. If loss to follow-up is more substantial than in INTERACT1, some form of sensitivity analysis will be performed. A subgroup analysis of the primary endpoint for those patients treated within 4 hours of stroke onset will be conducted. Categorical secondary outcomes such as all cause and cause-specific, early neurological deterioration will preferably be analysed by means of a Chi-square. A Fisher test might be used if the numbers get too small.

The effect of treatment on any time-to-event type of outcome will be in principle tested by means of a log-rank test. This includes time to recurrent stroke and time to first event. For patients who are 'lost to follow-up', all information collected from randomisation to the time of the last contact will be included in these analyses. Continuous endpoints such as the HRQoL health utility score (ED-5D) at 28 or 90 days will all be summarised by means (SD) or medians (IQR). The effect of treatment will preferably be tested by a Wilcoxon test. If the data is not too skewed, mixed models will be used to describe the health utility score over time and assess the effect of BP lowering therapy.

The primary analysis will essentially be unadjusted but adjusted analyses can be carried out for the primary endpoint and key secondary outcomes. No adjustment for multiplicity is planned as a small number of pre-specified efficacy outcomes are investigated.

Descriptive statistics will be provided for safety data. The number of patients reporting any SAEs and AEs, the occurrence of specific SAEs and AEs, and discontinuation due to SAEs and AEs will be tabulated. Laboratory data will be listed and values outside the normal range will be noted where applicable. Tests of a treatment effect in specific SAE may be attempted by means of a Chi-square or Fisher test. The exact list of tests to be performed will be specified a priori in a blind review.

17. SUB-STUDIES (SELECTED SITES ONLY)

17.1 Genetics in ICH

There is some evidence that the ApoE4 genotype is associated with increased frequency of primary ICH, in particular those with a lobar location. INTERACT2, as one of the largest prospectively collected datasets of ICH, could provide a unique opportunity to test the hypothesis that the ApoE4 genotype, particularly patients who are homozygous, is an independent risk factor for lobar ICH. In centres participating in this sub-study, blood will be collected and stored for future genotyping.

17.2 Effects of treatment of haematoma growth in ICH

The effects of treatment on haematoma expansion and other indices including oedema will be evaluated in a sub-sample of 600 patients (300 Asian and 300 non-Asian) according to a similar protocol as used in INTERACT1. Apart from the CT scan at baseline**,** a repeat CT scan (24±3 hours) is required. The primary efficacy measure was proportional change ('growth') in haematoma volume at 24 hours. Clinical outcomes were assessed over 90 days.

The sites who wish to participate in this sub-study will be identified prior to site activation, and a per-patient loading of payments will be made to cover all extra costs required to undertake the 2nd CT. The 2nd CT images will be sent to the Regional Coordinating Centres in a similar manner to the CT scan that has been undertaken at the baseline and the outcome data will be analysed centrally by experts who will be kept blind to the treatment allocation.

18. PUBLICATIONS AND REPORTS

Publication of the main reports from the study will be in the name of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT2) Investigators. Full editorial control will reside with a Writing Committee approved by the EC.

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 EC. Investigators further agree to provide the EC 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 EC shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts. The EC 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 EC 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 "The INTERACT2 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.

19. ORGANISATION

INTERACT2 is an academic initiated and conducted study to be managed by an International Coordinating Centre (ICC) based at the George Institute for International Health, University of Sydney, Australia. The study will be overseen by an International Executive (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 140 participating hospitals in Australia/New Zealand, China, India, Europe and other countries.

19.1 Executive Committee (EC)

Responsibilities: Overall responsibility for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The EC 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 EC is given below:

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

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

A/Professor Bruce Neal, The George Institute, University of Sydney, Australia

Professor Richard Lindley, Westmead Hospital, University of Sydney, Australia

Dr Mark Parsons, John Hunter Hospital, Newcastle, Australia

Professor Lewis Morgenstern, Department of Neurology, University of Michigan, USA

Professor Wang Jiguang, Shanghai Institute of Hypertension, Shanghai, China

Professor Huang Yining, Department of Neurology, Peking University First Hospital

Professor Stephen Davis, Department of Neurology, University of Melbourne, Australia

Professor Jong Sung Kim, Asan Medical Center, Soeul, Korea

Professor Christophe Tzourio, INSERM U708 Neuroépidémiologie, Hospital de la Salpêtriére, Paris, France

Dr Christian Stapf, Department of Neurology, Hôsptial Larboisière, Paris, France

19.2 International Coordinating Centre (ICC)

The ICC is at The George Institute for International 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.

19.3 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. In the first instance, RCCs will be located in Beijing (for China) and Paris (for Europe)

19.4 Core Lab (CT Analysis)

Responsibilities: To measure haematoma volume on all de-identified and blinded CT scans (blinded by allocation group and timing of scan).

19.5 Clinical Events Committee

Responsibilities: Review blinded study outcomes to ensure endpoints meet the consistent diagnostic criteria in line with pre-determined criteria.

19.6 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 Graeme Hankey, Royal Perth Hospital, Perth, WA, Australia
Professor Konrad Jamrozik, University of Adelaide, Adelaide, SA, Australia
Professor S Claiborne Johnston, University of California, San Francisco, CA, United States
Professor Shunwei Li, Peking Union Medical College, Beijing, China

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.

19.7 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 the ICC in accordance with protocol.

20. FUNDING

INTERACT2 is supported by a project grant from the NHMRC of Australia.

21. TIMELINES

April – November 2008:		Site recruitment and activation, materials development, staff training
July 2008 to July 2011:		Patient recruitment
October 2011:		Final patient follow-up
April 2011 to November 2011		Data cleaning and site close-outs
February 2012:		Joint presentation and publication of results

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Appendix 1A - BP management protocol for centres WITHOUT Labetalol

Early intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP <140 mmHg** reached within 1 hour
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
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/Kg/min • OR start infusion of Nicardipine 5-15 mg/hour
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 <140 mmHg** reached within 1 hour
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
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/Kg/min • OR start infusion of Nicardipine 5-15 mg/hour
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 <140 mmHg** reached within 1 hour
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/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 <140 mmHg** reached within 1 hour
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 (< 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/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 Lowering 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.

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 – 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 - CT imaging protocol

IF AT ALL POSSIBLE, ENSURE REPEAT SCAN IS PERFORMED ON THE SAME CT SCANNER

1. A digital scout radiograph in the lateral position should be obtained.
2. Scanning plane is axial and approximately 30 degrees to infraorbital meatal line.
3. Scan from level of foramen magnum to high vertex.
4. Correct obliquity.
5. Recommended Parameters:
   a. Perform acquisition in conventional mode.
   b. Slice thickness: 5-8 mm throughout posterior fossa and remaining brain (if 5-8 mm not possible, maximum of 10 mm slice thickness). Slice thickness should be the same for follow-up scans.
   c. Kilo voltage: 100-140kV.
   d. mA: 100-300 mA.
   e. Matrix size: 512 by 512.
   f. Scanning time: At least 300 mAs for 5 mm.
   g. FOV: 20-25 cm.
6. Recommended window width and level settings:
   a. Posterior fossa: Window width 100-120 and level 35-45.
   b. Supratentorial: Window width 80-100 and level 35-45.
7. Sites should submit digital images. The digital images should be submitted in DICOM format (**MUST BE UNCOMPRESSED**). One patient per CD-ROM is recommended. The digital images must be saved to CD-ROM without patient identifiers (study subject number can be saved digitally or written on the CD-ROM).
8. Place CD-ROM in free-post envelope and post to the RCC who will forward data to the ICC in Sydney, Australia. CT 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 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.	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 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).	

Assessment	Response	Score
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).	
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 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.	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 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 stroke care protocol

Airway Management:
Objectives: Normal SpO2 (≥ 92%)

- Monitor oxygen saturation continuously
- Oxygen supplementation is recommended only if patients de-saturate
- Intubate patients, **with precautions for prevention of elevated intracranial pressure** (ICP), 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 sub-cutaneous heparin (5000 U subcutaneous twice daily) **72 hours after** symptom onset in patients with poor mobilization

Elevated ICP Management
Objectives: Treat elevated ICP in patients with clinical deterioration associated with mass effect seen on CT scan

- Mannitol 20% (0.25–0.5 g/kg every 4 hours); do **NOT** use prophylactically
- Steroids are **NOT** recommended
- Consider mannitol 1 g/kg acutely and intubation with hyperventilation (PCO2 30-35 mmHg) for false localizing signs/acute loss of consciousness.

Management of Warfarin Related Coagulopathy:
Objectives: Rapid reversal of coagulopathy

- Fresh Frozen Plasma 2-4 units and repeat INR; treat until INR is normal (<1.3)
- Vitamin K 10 mg intravenously

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
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association 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 only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. 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 on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, 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. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

26. 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. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Page back to paragraph 29.

Note: **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Page back to paragraph 30.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

9.10.2004

THE SECOND INTENSIVE BLOOD PRESSURE REDUCTION IN ACUTE CEREBRAL HAEMORRHAGE TRIAL

An international randomised controlled trial to establish the effects of early intensive blood pressure lowering in patients with intracerebral haemorrhage

STUDY PROTOCOL

(Version 1.0 – 24 April 2008)

CONTACT DETAILS
INTERACT2 International Coordinating Centre
The George Institute for International Health
University of Sydney
PO Box M201, Missenden Road
NSW 2050, Australia

Tel +61 2 9993 4561
Fax +61 2 9993 4502
Email Interact@george.org.au

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.

_____

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

_____

Name of Investigator (Printed)

_____

Name of Institution (Printed)

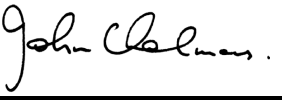
Principal Investigator
Craig Anderson PhD FRACP
Professor of Stroke Medicine
Director,
Neurological and Mental Health Division,
The George Institute for International Health,
University of Sydney
Royal Prince Alfred Hospital

24 April 2008
Date

Signature

Chair, Executive Committee
John Chalmers ACC PhD FRACP
Professor of Medicine
Head of Research Office,
The George Institute for International Health,
University of Sydney

24 April 2008
Date



Signature

Trial Statistician
Dr Stephane Heritier PhD
The George Institute for International Health,
University of Sydney

24 April 2008
Date

Signature

Protocol Version History and Amendments

Date	Version Number
24 April 2008	1.0

List of abbreviations and definition of terms

ACE-I	Angiotensin Converting Enzyme Inhibitor
AE/SAE	Adverse Event/ Serious AE
AHA	American Heart Association
ANZ	Australia and New Zealand
ARCOS	Auckland Regional Community Stroke Study
BP	Blood Pressure
CEC	Clinical Endpoints Committee
CHF	Congestive Heart Failure
CI	Confidence Interval
CRF/eCRF	Case record form /Electronic CRF
CT	Computerised tomography
CV	Curriculum Vitae
CVD	Cardiovascular Disease
DAP	Data Analysis Plan
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
EC	Executive Committee
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GI	The George Institute for International Health
HR	Heart Rate
HREC	Human Research Ethics Committee
HRQoL	Health Related Quality of Life
ICC	International Co-ordinating Centre
ICH	Intracerebral Haemorrhage
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intention to Treat
MI	Myocardial infarction
mRS	Modified Rankin Scale
NB	Note
NHMRC	National Health and Medical Research Council
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio
PI	Principal Investigator
SAH	Subarachnoid Haemorrhage
SAP	Statistical Analysis Plan
SD	Standard Deviation
TIA	Transient Ischaemic Attack
WHO	World Health Organisation

CONTENTS

SUMMARY PROTOCOL

THE SECOND INTENSIVE BLOOD PRESSURE REDUCTION IN ACUTE CEREBRAL HAEMORRHAGE TRIAL

The main phase of an academic lead and conducted, international, multi-centre, open label, blinded endpoint, randomised controlled trial to establish the balance of benefits and risks of a treatment strategy of early intensive lowering of blood pressure (BP) compared to a conservative BP lowering policy in patients with acute primary intracerebral haemorrhage (ICH) and co-existing elevated BP without any definite indication or contraindication to treatment.

Background and rationale

Intracerebral haemorrhage (ICH) is one of the most serious subtypes of stroke, affecting over a million people worldwide each year, most of whom live in Asia. About one third of people with ICH die early after onset and the majority of survivors are left with major long-term disability. Despite the magnitude of the disease burden and cost on healthcare resources, there remains uncertainty about the role of surgery for ICH and no acute medical therapies have been shown to definitely alter outcome in ICH. Although administration of activated recombinant human Factor VII (ie rFVIIa; NovoSeven®) has been shown to limit haematoma expansion, a recent clinical trial failed to show that this effect translated into improved survival and less major disability in ICH. Moreover, future use of this agent will be limited by its short therapeutic time window, contraindication in patients at risk of thromboembolism, and high cost. The management of ICH, therefore, contrasts sharply with that of acute ischaemic stroke, where there is now strong evidence to support the routine use of thrombolysis in carefully selected patients, and aspirin in the majority.

Blood pressure (BP) levels are strongly and positively associated with the incidence of first and recurrent stroke, and there is definitive evidence that BP lowering reduces stroke risk. Although BP levels are commonly elevated early after the onset of stroke, particularly in ICH, 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 the setting of acute ICH. While these provide an indication of perceived harm associated with 'very high' BP levels (>220mmHg), they also highlight persisting clinical uncertainty about what comprises optimal management of BP in this patient group.

The adverse effect of high BP levels on outcome in ICH is likely to involve a number of different mechanisms: elevated hydrostatic pressure at the site of bleed is likely to result in a larger initial bleed and early haematoma expansion, while elevated BP increases the likelihood of early re-bleeding, more severe oedema and early recurrent stroke. The first of these mechanisms is likely to be most relevant in the first several hours after onset, as haematoma expansion is most frequent in the first several hours after onset. Reduction of BP may also be important sub-acutely, as peri-haematomal oedema, which appears to be plasma derived, increases in volume over several days. Against this background of processes is the increased risk of early stroke recurrence from elevated BP levels.

The INTERACT2 study follows the recently completed initial pilot study (vanguard phase) which established the feasibility of the protocol, safety of early intensive BP lowering, and effects on haematoma expansion within 6 hours of onset of ICH. Having established 'proof-of-concept' that BP lowering may improve outcome by reducing haematoma expansion, INTERACT2 aims to establish the effects of the treatment on major clinical endpoints in patients with ICH recruited from an expanding clinical network around the world.

Aims

To establish the effects of a management policy of early intensive BP lowering on death and disability in patients with acute spontaneous, primary, ICH and co-existing elevated BP compared to a more conservative BP management policy that is based on a commonly used guideline for the management of high BP in this clinical setting. The study uses a similar design to the pilot study - INTERACT1 - undertaken in 44 sites in Australia, China and South Korea during 2005-2007. All patients will contribute to assessment of the mortality/dependency endpoint at 90 days follow-up post-randomisation.

Design

A multi-centre, prospective, open label, blinded outcome, randomised, controlled, trial involving 2800 patients with acute ICH recruited from approximately 140 sites in the world.

Patient recruitment

Patients with CT-confirmed acute ICH within 6 hours of onset are potentially eligible if they have a sustained elevated systolic BP level (≥150 to ≤220 mmHg) and where an intensive BP lowering management strategy and active ancillary care are available. Exclusion criteria include: (a) clear indication to BP lowering (eg very high BP >220 mmHg or hypertensive encephalopathy); (b) a contraindication to intensive BP lowering (eg known severe carotid stenosis or uncontrolled heart failure); (c) the attending clinician considers the patient to be unlikely to benefit from any therapy due to existing severe illness or medical condition (eg advanced dementia, known serious pre-stroke disability) or because they have a very high likelihood of death within 24

hours (ie GCS score 3-5) or massive ICH with major cerebral midline shift; (d) there is concomitant medical illness that would interfere with outcome assessments and follow-up; and (e) arrangements have been made for early surgical removal of the haematoma. .

Randomised interventions
Patients will be randomised via a 24-hour central internet-based randomisation system (or IVRS system, currently in development) to either (a) intensive or (b) conservative management of BP. Treatment is to start as soon as possible after randomisation (eg in the emergency department) and will be continued in a monitored facility (ie intensive care unit, high dependency unit, or stroke unit) for all randomised patients.

Intensive BP lowering - patients allocated to the intensive BP lowering group will be started on a standardised treatment regime commencing with intravenous and then changed when feasible to oral (or via a nasogastric tube) agent(s). The treatment goal is to achieve a systolic BP goal (<140 mmHg) within one hour of commencing the randomised treatment. The second goal will be to maintain the systolic BP to 140 mmHg or less or at least 7 days in hospital, and subsequently on discharge and for 90 days post-randomisation. Specific treatment protocols are developed for each participating region/centre based on the availability of BP lowering agents for routine use.

Conservative BP lowering - patients allocated to this group will receive BP management that is based on American Heart Association (AHA) guidelines. In this group, the threshold to be considered for the initiation of treatment will be a systolic BP ≥180 mmHg.

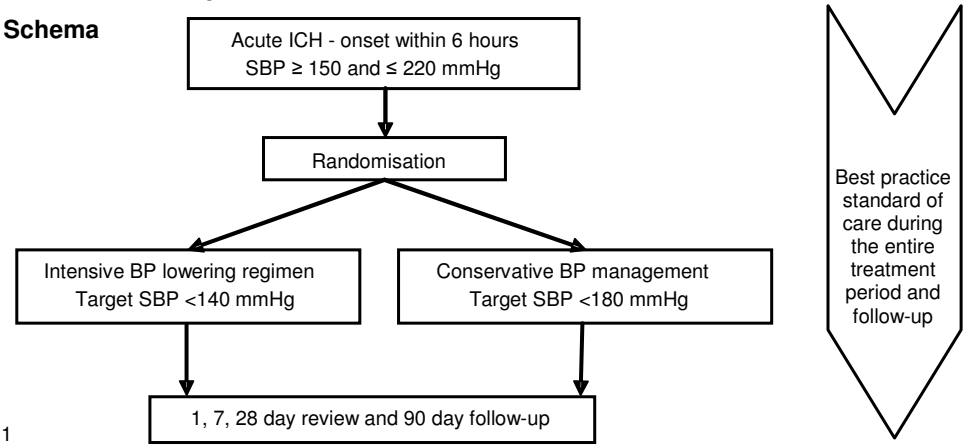
For both groups, patients must be on an oral anti-hypertensive agent by day 7 or discharge from acute care hospital, with a long-term target systolic BP of 140 mmHg, as per secondary stroke prevention guidelines.

Data collection and follow-up
Key baseline information will be collected at the time of randomisation. Follow-up data will be collected on four occasions: 24 hours and 7 days (or at the time of death or hospital discharge, if this should occur before day 7), and 28 days and 90 days, with the latter two assessments able to be carried out either in-person or over the telephone. The clinical assessments are to be undertaken by a person who was not involved in the initial treatment of the patient and kept blind to the treatment allocation. Data collection and trial management will be facilitated by an established internet-based system.

Outcomes
Primary outcome: the efficacy of the treatment regime will be evaluated on the combined endpoint of death and dependency at the end of follow-up. Key secondary outcome: to assess efficacy of the primary outcome in those patients treated within 4 hours of ICH onset. Other secondary outcomes: to determine effects of treatment on (a) physical function, health-related quality of life, recurrent stroke and other vascular events, days of hospitalisation, and requirement for permanent residential care, and (b) other serious adverse events.

Statistical power
The sample size of 2,800 provides at least 90% power (alpha=0.05) to detect a beneficial effect of early treatment on the primary outcome, which equates to one or more cases of death or dependency prevented among every 14 patients treated. This assumes primary outcome event rates of about 50% in the control group and 43% in the active group, a 14% difference in relative risk between the groups, a 10% non-adherence (drop-out) to treatment, and a 3% loss to follow-up. This sample size also provides 90% power to detect a 20% relative risk reduction on the primary endpoint among those patients treated within 4 hours of ICH onset, expected to be about half (1400) of the study population. This size of absolute benefit of the treatment has been considered clinically valuable in other areas of neurology and is comparable to the magnitude of benefit seen with calcium channel blockers in acute subarachnoid haemorrhage and the use of stroke units for the management of acute stroke.

Study Schema



INTRODUCTION

Primary ICH, defined as the spontaneous rupture of an intraparenchymal blood vessel, affects over a million people worldwide each year.[1] Of these, around one third will die within one month, while the majority of survivors will be left with significant long-term disability.[2 3] ICH is associated with very high medical and socio-economic costs.

Despite the magnitude of the disease burden, there are currently no routine acute therapies for ICH that have been proven beyond doubt to improve outcomes. This contrasts sharply with the management of acute ischaemic stroke where thrombolysis has been shown to be highly effective in certain subgroups of patients. There is increasing evidence to suggest that early intensive BP lowering therapy is a safe and effective treatment, but a large-scale clinical trial is required to reliably determine the overall balance of risks and benefits of such an intervention.

INTERACT2 has been designed to resolve an area 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. The results of the study will have significant impact on future clinical practice in ICH management.

BACKGROUND

1. EPIDEMIOLOGY

Stroke accounts for around 5 million deaths in the world every year and according to projections by the World Health Organisation (WHO), will remain the second leading cause of death in both developed and developing countries for at least the next few decades.[4] Among the major pathological stroke subtypes, ICH accounts for approximately 10-15% of all strokes in Western countries,[5] but this figure is up to 20-30% in African and Asian populations.[6, 7] The incidence of ICH varies by country; results from the International Stroke Incidence Collaboration estimate the standardised annual incidence of ICH in the 45-84 year age group to be between 26 and 60 per 100,000 population.[8] In the USA, this equates to about 70,000 cases of ICH annually,[9] and in China, the number is estimated to be 300,000.[10]

ICH is associated with very high early mortality and morbidity, with case fatality ratios of between 30% and 50%,[11 12-14 15-18 19, 20 21] and about one half of survivors being dependent on long-term care.[14, 21, 22] Thus, between 65% and 75% of all ICH patients will either die or be permanently disabled by the disease. In 2004, the estimated direct and indirect cost of stroke in the US is approximately $54 billion.[9]

Elevated BP or 'hypertension' is well established as the major risk factor for ICH, with several large-scale observational studies demonstrating that BP levels are positively and continuously associated with risks of ICH.[23, 24] The association between hypertension and ICH risk appears to be much stronger than that for ischaemic stroke.[23, 24] There is also evidence that BP levels are strongly and positively associated with the long-term risks of recurrent stroke for both haemorrhagic[25] and ischaemic events.[26, 27] In a systematic review, systolic BP elevations of 10 mmHg were associated with a 42% (95% confidence interval [95% CI] 39-44%) increase in the risk of haemorrhagic stroke.[24] The relative risk of ICH in hypertensive individuals is 2-3 times that of non-hypertensive individuals.[28] In addition, among hypertensive individuals, those who have ceased taking medication appear to be at significantly greater risk of ICH.[29]

The other major modifiable risk factor for ICH is high alcohol intake, with intake greater than 56 g/day being associated with crude odds ratio (OR) of 3.36 (95% CI 2.21-5.12).[28] The data for hypercholesterolemia as a risk factor are conflicting, with cohort studies showing a clear association for decreasing risk of ICH with increasing serum cholesterol levels.[28] Diabetes may be a weak risk factor (OR 1.27; 95% CI 0.99-1.62), whilst data for physical activity are inconclusive.[28] Certain genetic factors such as the presence of an apolipoprotein E2 or E4 allele and a first degree relative with ICH have also been shown to be significant independent risk factors for ICH.[30]

2. PATHOPHYSIOLOGY

ICH usually results from spontaneous rupture of a small penetrating artery or arteriole deep in the brain. The most common sites are the basal ganglia (lentiform nucleus, caudate and thalamus), cerebral hemispheres (lobar), cerebellum and pons. Modern neuro-imaging studies indicate that continued bleeding and expansion of the haematoma of ICH occurs in up to one third of patients within several hours of onset, and probably over 3 to 24 hours in another 10%.[31-34] Further neurological deterioration may occur over several days secondary to the adverse effects of oedema[35-37] and inflammation[38-41] in the peri-haematomal region.

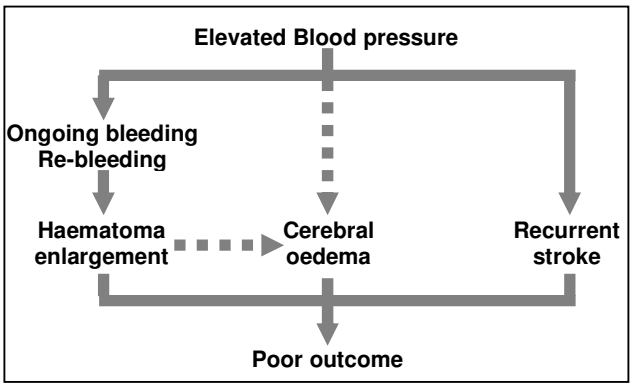


Figure 1. The mechanism by which higher blood pressure levels may lead to a poor clinical outcome in patients with intracerebral haemorrhage

High BP levels in acute ICH have been shown to be associated with poor outcome.[42] The adverse effect of high BP levels on outcome in patients with ICH are likely to involve a number of different mechanisms (**Figure 1**): an elevated hydrostatic pressure at the site of the haemorrhage is likely to result in a larger initial bleed and early haematoma expansion,[43-48] while elevated BP levels increase the likelihood of early re-bleeding, more severe oedema,[35, 36] and early stroke recurrence.[25]

The first of these mechanisms resulting from elevated BP level is considered to be the result of persistent bleeding or re-bleeding from the ruptured vessel. Several observational studies have reported the frequency of early haematoma expansion **(Table 1)**. In the only prospective study, Brott et al. performed a baseline CT scan within 3 hours of onset and found a haematoma expansion (>33% volume expansion) in 26% of patients within the subsequent hour.[31] An additional 12% of patients exhibited expansion by 20 hours post-ictus. Most haematoma expansion appears to occur within the first several hours after onset, although continued growth up to 24 hours in a limited number of patients is suggested by retrospective studies.[34] CT angiographic studies also suggest that bleeding may continue for up to 24 hours in some patients.[43] In patients taking anticoagulants, haematoma expansion appears to persist even longer.[49]

Table 1 Frequency of early haematoma expansion*

Interval from symptom onset to first CT (hours)	Prospective	Retrospective		
	Brott et al.[31] (n=103)	Fujii et al[32] (n=627)	Kazui et al[34] (n=204)	Takizawa et al[33] (n=369)
0 to 3	38%	18%	36%	14%
3 to 6	N/A	8%	16%	4%
0 to 6	N/A	17%	29%	12%
6 to 24	N/A	2%	10%	0%

*Haematoma expansion defined as >33% increase in volume by Brott et al, >50% (or 20ml) increase by Fuji et al, and >40% (or 12.5ml) increase by Kazui et al. No expansion criteria specified by Takizawa et al. N/A = data not available.

Although haematoma expansion is an important predictor of poor outcome in patients with ICH,[31, 34, 43, 47, 50-54] other mechanisms may also contribute to overall morbidity and mortality. Early re-bleeding occurs in a substantial proportion of patients in the first 12 hours. However, peri-haematomal oedema persists in the majority for at least several days.[35-37] The effect of BP reduction on oedema development is unknown. Elevated BP levels also increase the risk of early stroke recurrence through similar mechanisms responsible for the primary ICH event.[25] Thus, BP lowering has potential to reduce ICH related morbidity within a wide therapeutic time window.

3. CLINICAL PRESENTATION AND ACUTE MANAGEMENT

Time of presentation to hospital of patients with all forms of acute stroke varies widely **(Table 2)**. However, many patients arrive at hospital within 6 hours after onset of symptoms in Australia and New Zealand (ANZ), China, the United Kingdom (UK), and the USA. Thus, it appears feasible to evaluate the effects of early BP lowering treatment in ICH.

Table 2 Time from onset to hospital presentation in acute stroke

	n	Time of hospital presentation (hours)		
		0 to 3	0 to 6	0 to 12
Australia and New Zealand				
ICH in the Auckland, ARCOS study of 2002-03 (C Anderson, personal communication)	112	64%	82%	87%
China				
Cheung et al.[55]	71	N/A	56%	N/A
UK				
Salisbury et al.[56]	128	37%	52%	75%
Harraf et al.[57]	729	37%	50%	62%
USA				
Barsan et al.[58]	1159	59%	N/A	N/A
Smith et al.[59]	1334	50%	65%	80%
Kothari et al.[60]	119	30%	50%	N/A
Willmot et al[61]	553	46%	61%	70%

*N/A = data not available

Elevated BP occurs commonly after the onset of stroke, and is more frequent in patients with ICH compared to patients with ischaemic stroke.[62 63 64] Hypertension has been reported in up to 90% of patients presenting with acute ICH.[62 63 64] Although BP levels decline spontaneously in most patients, they remain elevated in a substantial proportion.[62 63] Observational studies have shown a clear association between high BP levels in ICH and subsequent death or dependency.[42] Other factors such as reduced level of consciousness,[12 13, 43] continued bleeding suggested by extravasation,[43] haematoma expansion,[31, 53] large haemorrhage size,[12 14-16, 44 54 65 66, 67] intra-ventricular extension[12 14, 16 43 54 66] and older age,[17, 43] have also been associated with poor outcome.

The goals of treatment of ICH, as with other forms of stroke and brain injury, are firstly to prevent or reverse acute brain injury; and secondly to prevent future neurological impairment and disability. A meta analysis of all randomised controlled trials has shown that treatment of patients in stroke units reduces mortality, dependency and the need for institutional care.[68] An observational study has also shown benefit of semi-intensive monitoring.[69] Although very high BP levels are generally considered to require treatment, the effects of BP lowering treatment in the acute phase of stroke are less well established. Despite there being an indication of harm associated with high BP levels, there are wide ranging recommendations for the management of BP expressed in current guidelines **(Table 3)**, which highlight the persisting clinical uncertainty surrounding what comprises 'optimal management' for acute ICH patients. In particular, there is uncertainty over the level at which BP lowering should commence, how quickly the BP should be lowered, and the ultimate target BP level to be reached.

Table 3 Guideline recommendations for BP lowering treatment in patients with acute ICH

	Start medication	Target
ICH		
American Heart Association[70]	>180 mmHg	160/95 mmHg
International Society of Hypertension[71]	>220/120 mmHg	Up to 20% reduction
Stroke Foundation of New Zealand[72]	Mean BP ≥ 130 mmHg	Mean BP <130 mmHg
Any stroke		
European Stroke Initiative[73]	>220/120 mmHg	Hypertensive - 180/100-105 mmHg Non-hypertensive - 160-180/90-100 mmHg
National Stroke Foundation (Australia)[74]	≥200/110 mmHg	Up to 20% reduction
Royal Collage of Physicians (UK)[75]	If complications are apparent	Not described

There are a small number of randomised controlled trials of other medical treatments (steroid, haemodilution and glycerol) in ICH.[76-78] None of these treatments have shown to be effective.

Most recently, evidence has emerged of potential benefit of use of activated recombinant human factor VII (rFVIIa/NovoSeven®) when administered within 4 hours after the onset of ICH.[79,80] Although rFVIIa has been shown to reduce haematoma expansion, it has not been demonstrated to clearly improve clinical outcome. The reason for this is not entirely clear but may be due to the benefit being offset by major thromboembolic events (eg ischaemic stroke and myocardial infarction), imbalances in stroke severity at baseline favouring the placebo group in the first clinical trial, and ancillary care attenuating any modest treatment effect. Even if the rFVIIa was approved for clinical use, it seems that it will have limited applicability due to the restricted therapeutic time window, the risk of thromboembolic complications, and high cost.

Despite the completion of a large-scale international study (the Surgical Trial in ICH [STICH] trial with a neutral overall result of treatment)[81] and several smaller trials,[82] the decision about whether and when to operate on patients with ICH remains controversial. However, guideline recommendations for surgical treatment are mainly based on severity, clinical course and size and location of the haematoma.[70 72 75] The proportion of patients treated surgically varies considerably, both between and within countries around the world, but is probably less than 10% in Australia, New Zealand, the US, and China.[83] BP lowering treatment has been shown to be associated with lower re-bleeding after surgical treatment,[84] and patients who undergo surgery usually receive intensive BP lowering treatment.

4. EVIDENCE FOR BP LOWERING IN ICH

a) Observational studies

A number of studies have also examined the short-term effects of BP with prognosis of acute ICH.[12-15 18-20, 44, 54, 65-67, 85-88] Most have shown that higher BP levels are associated with worse outcomes.[13-15, 18-20, 54 66, 67, 86 87, 88] In the largest of these studies,[67] the mean arterial pressure was 134 mmHg on admission in patients who died, compared with 124 mmHg in those that survived ($p<0.01$). In the second largest study,[13] the risk of early death was greatest among the quartile of patients with the highest BP levels at presentation, and risks declined progressively in each of the other three groups **(Figure 2)**.

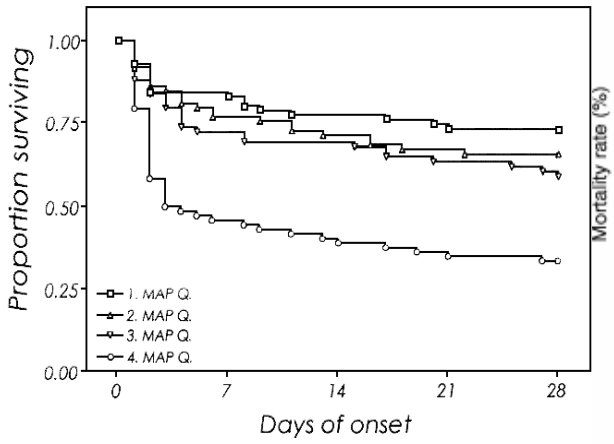


Figure 2. Twenty-eight day survival of patients with acute intracerebral haemorrhage in four groups defined by mean arterial pressure (MAP) quartiles (Q)
From Fogelholm et al.[13]

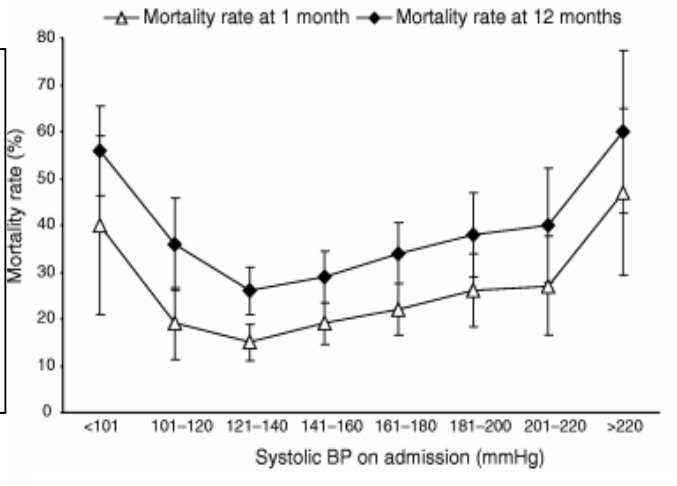


Figure 3. Proportion of patients who died at 1 (triangle) and 12 months (circle) by baseline systolic blood pressure
From Vemmos et al.[85]

A systematic review of these observational studies has also shown a clear association between high BP and subsequent death or dependency in acute ICH.[42] Only one study has suggested a J-shaped association between BP levels and outcome, with both the highest and lowest BP levels being associated with increased risks of adverse outcomes **(Figure 3)**.[85] In this study, however, it is uncertain whether the low BP level is a cause of adverse outcomes. It could be reverse causation that low BP levels and death are caused by the most severe haemorrhages.

It is clear that if there is any adverse effect of low BP on outcome, it does not seem to be apparent until systolic BP levels reach 140 mmHg or less, which is well below the level observed in most acute ICH patients and the level recommended for intervention in current guidelines.

b) Randomised trials

Randomised trials have clearly demonstrated that BP lowering reduces the risk of initial stroke, both ischaemic and haemorrhagic.[89, 90] Clear evidence from PROGRESS[91] has also shown that BP lowering reduces the risk of recurrent stroke. PROGRESS recruited approximately 6,000 patients from 172 collaborating centres in 9 countries (Australia, Belgium, China, France, Japan, New Zealand, Sweden, the United Kingdom and Ireland) during 1995-2001. This study showed that a regimen based on an angiotensin converting enzyme (ACE) inhibitor significantly reduced the risk of recurrent stroke by 28% (95% CI 17 to 38%).

In PROGRESS, subsidiary analyses suggested that the benefits of treatment were particularly large among patients with a history of ICH at baseline.[91, 92] In this subgroup, treatment reduced the risk of a recurrent stroke by 49% (95% CI 18 to 68%) compared to a reduction of 17% (95% CI 12 to 38%) among patients with an ischaemic stroke. The overall reduction in the risk of ICH (50%; 95% CI 26 to 67%) appeared to be greater than the reduction in the risk of ischaemic events (24%; 95% CI 10 to 35%) and tracking of stroke subtypes within individuals appears to explain much of the additional benefit observed in patients with a baseline history of haemorrhage. Subsidiary analyses of PROGRESS which examined the effects of BP lowering in a third of the study population defined by time between qualifying event and randomisation,[91] showed no evidence of any difference in the benefits of treatment between patients commenced within an average of 1.5, 7.2, or 30 months of the first stroke registered in the study (p homogeneity = 0.3). However, this study did not provide any information about the effects of BP lowering commenced in the acute phase of either ischaemic or haemorrhagic stroke subtypes, and there remains great uncertainty about the overall balance of risks and benefits of BP lowering in this scenario.[93, 94]

Several small clinical trials have examined the effects of BP lowering in the acute phase of stroke, but these included predominantly patients with cerebral ischaemia.[95-97 98-100] Systematic overviews summarise the findings for BP lowering treatment in general,[100] and of calcium channel antagonists specifically.[99] No individual study or overview has conclusively identified significant beneficial (or harmful) effects of BP lowering treatment in acute stroke. Overall, the studies suggest blood pressure reduction is associated with lower mortality rates **(Figure 4)** but the 95% CIs for the estimates are wide.

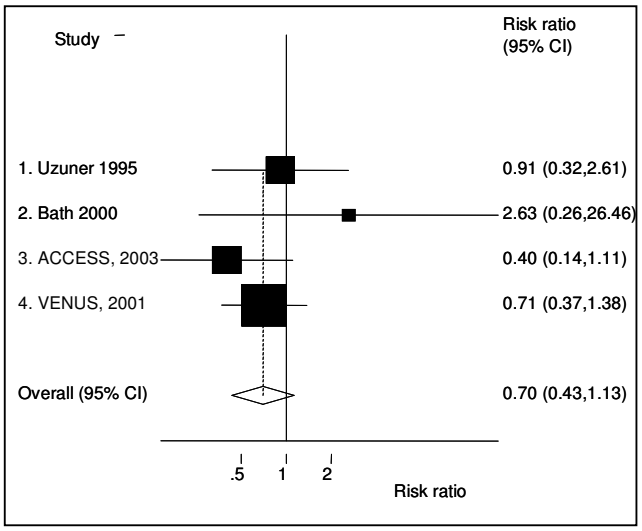


Figure 4. Summary of studies of acute blood pressure lowering on mortality after acute stroke.[98,100,101]

Adapted from the Blood Pressure in Acute Stroke Collaboration.[101]

To date, the largest randomised blood pressure treatment trial conducted in the acute phase of stroke is the Acute Candesartan Cilexitil Evaluation in Stroke Survivors (ACCESS) study,[98] which included 339 patients with acute ischaemic stroke. Patients were randomised to receive candesartan cilexitil (an angiotensin II receptor blocker) or placebo, within 48 hours of stroke onset. The study was stopped early due to a significant reduction in the frequency of a composite secondary endpoint (combining death, cerebrovascular and cardiovascular events at 12 months) in the actively treated group compared to control group (OR 0.48; 95% CI 0.25 to 0.90).

The ACCESS results are difficult to interpret, since the secondary outcome could be due to chance, and there was no significant effect on the primary outcome (the Barthel Index at 3 months). Thus, although the study certainly provides some reassurance that use of a BP lowering agent in the acute phase of ischaemic stroke is unlikely to be seriously harmful, the study does not

provide the level of evidence required to recommend the routine use of BP lowering in acute ischaemic stroke and does not appear to have resulted in widespread change in clinical practice. In addition, even when the ACCESS mortality data are combined with the results for all the other completed trials of BP lowering in acute stroke,[96, 98, 100] the effect of BP lowering on mortality remains unclear **(Figure 4).**

There has been only one study that has reported separately the effects of early BP lowering in patients with acute ICH.[96] This trial enrolled a total of 296 patients, 35 of whom had suffered an acute primary ICH. The trial evaluated the effects of the calcium antagonist nimodipine orally commenced within 6 hours of stroke onset and showed no effect (relative risk 1.0, 95% CI 0.6 to 1.7) on the primary study outcome of death or dependency after 3 months. However, no BP differences were observed between the oral nimodipine and placebo groups. Furthermore, there were few events recorded and the wide CIs around the point estimate make the trial of little clinical relevance. This trial does, however, provide further reassurance that early BP lowering is unlikely to be seriously harmful for the majority of ICH patients.

Aside from this randomised trial, there are some prospective non-randomised studies[86, 101] which have sought to determine the effects of early BP lowering in hypertensive patients with ICH. One early study of 167 individuals with hypertensive ICH, were divided into three groups that were 'untreated', 'inadequately treated' or 'adequately treated' with the antihypertensive agent reserpine.[86] A poor outcome was most frequently observed in the group that received no BP lowering treatment, and least common in those that received effective BP lowering. In another study of 27 ICH patients, aggressive BP reduction was associated with a lower rate of neurological deterioration and haematoma expansion.[102] In another observational study,[101] 76 individuals with hypertensive acute ICH were treated with different systolic BP targets.

A target systolic BP of less than 160 to 170 mmHg was associated with haematoma enlargement more frequently than those patients in whom BP was reduced to less than 140 to 150 mmHg. In another study of 369 ICH patients,[33] intensive BP lowering treatment to a target systolic BP of 140 to 160 mmHg (systolic BP levels were reduced to 140 mmHg in most patients) was associated with less frequent haematoma enlargement than other studies **(Table 1)**.[31, 32, 34, 53] These prospective studies suggest that intensive BP lowering treatment with target systolic BP to less than 140 mmHg, which is 20 to 40 mmHg lower than that of present guideline recommendations,[70 71 72, 73, 75 74] is associated with reduced haematoma expansion in acute ICH. However, just as the randomised trials were too small to reliably determine the effects of BP lowering, the non-randomised design of these studies makes it impossible to know whether the observed beneficial effects were due to the different BP lowering strategies or other factors.

Some further indirect evidence to support the safety and potential benefit of BP lowering in acute ICH is provided by the results of trials of calcium antagonists in patients with subarachnoid haemorrhage. In these trials there is clear evidence of benefit associated with the use of calcium antagonist-based regimens, with overall reductions in the rate of poor outcome at 3 to 6 months of 18% (95% CI 7% to 28%).[103] While the aetiology of subarachnoid haemorrhage is different to that of ICH,[104, 105] BP is an important determinant of risk in both,[104 105 106] and there is some evidence of associations of early high BP levels with the risk of haemorrhage extension.[107]

5. CHOICE OF BP LOWERING AGENT

There are a number of different drug classes that may be used to lower BP in acute stroke,[100] 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.[108, 109] 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 ICH 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 of action	Duration of action	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

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,[71] and profound BP lowering effects.

Guidelines only recommend use of sodium nitroprusside in patients with extremely high BP levels.[70] 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.

6. FINDINGS OF THE PILOT STUDY – INTERACT1

The results of INTERACT1 have been published in Lancet Neurology, May 2008.[110] The study enrolled 404 patients from 44 hospitals in Australia, China and Korea from November 2005 to April 2007. Eligible patients were aged ≥18 years with CT-confirmed ICH and elevated systolic BP (≥150 and ≤220 mm Hg), with the capacity to commence randomly assigned BP lowering treatment within 6 hours of ICH in a monitored environment. A central randomization system was used to assign patients, either to a treatment strategy of intensive BP lowering (target systolic BP of 140 mm Hg) based on a stepped protocol of routinely available intravenous agents, or to previous version AHA guidelines for BP lowering (target systolic BP of 180 mm Hg). Digital images of baseline and repeat CT (24±3 hours) performed using standardized techniques were analysed centrally. The primary efficacy measure was proportional change ('growth') in haematoma volume at 24 hours. Clinical outcomes were assessed over 90 days.

At baseline, the characteristics of patients were similar between groups, but mean haematoma volumes were slightly smaller in the control group (12.7, SD 11.6) compared to the intensive group (14.2, SD 14.5). From randomisation to 1 hour, mean systolic BP was 153 mmHg and 167 mmHg in the intensive and guideline groups, respectively (difference 13.3 mmHg, $p<0.0001$), and from 1 to 24 hours, levels were 146 and 157 mmHg, respectively (difference 10.8 mmHg, $p<0.0001$).. Mean proportional haematoma growth was 36.3% in the guideline group and 13.7% in the intensive group, a significant difference of 22.6% (95% CI 0.6-44.5%; $p=0.04$) at 24 hours. After adjustment for initial haematoma volume and time from onset to CT, the difference was borderline significant (adjusted $p=0.06$). Likewise, 'substantial' haematoma growth (i.e. >33% or >12.5 ml) was 36% (95% CI 0-59%, $p=0.05$) lower in the intensive group. Intensive BP lowering treatment did not alter the risks of adverse events nor clinical outcomes at 90 days.

The study has shown that early intensive BP lowering treatment is well tolerated and appears to attenuate the growth of haematoma in ICH. These data provide the basis for proceeding with the main phase of the study with project grant funding from the National Health and Medical Research Council (NHMRC) of Australia during 2008-2011.

7. SUMMARY OF RATIONALE FOR A TRIAL OF BP LOWERING IN ICH

There is currently insufficient evidence to recommend a specific management strategy for BP in the acute phase of stroke.[93, 94] However, on the basis of available evidence, there is a strong rationale to expect beneficial effects of early intensive BP lowering in acute ICH. While ongoing trials will provide new information about the effects of BP lowering in acute ischaemic stroke, there are no other corollary large-scale studies in ICH yet being undertaken. As the basis for anticipating a beneficial effect of BP lowering in patients with acute ICH is strong INTERACT2 has been designed as a large-scale study to determine the overall balance of risks and benefits associated with the use of BP lowering in patients with acute ICH and co-existing elevated BP with no definite indication or contraindication to the treatment.

AIMS AND OBJECTIVES

The primary null hypothesis to be tested is that there is no effect of early intensive BP lowering compared with a conservative BP treatment policy, on death and dependency in patients with acute spontaneous ICH.

1. PRIMARY AIM

To determine the effects of the randomised BP management on all-cause mortality and dependency at 90 days.

2. KEY SECONDARY AIM

To evaluate the clinical benefit in those patients treated within 4 hours of onset of ICH.

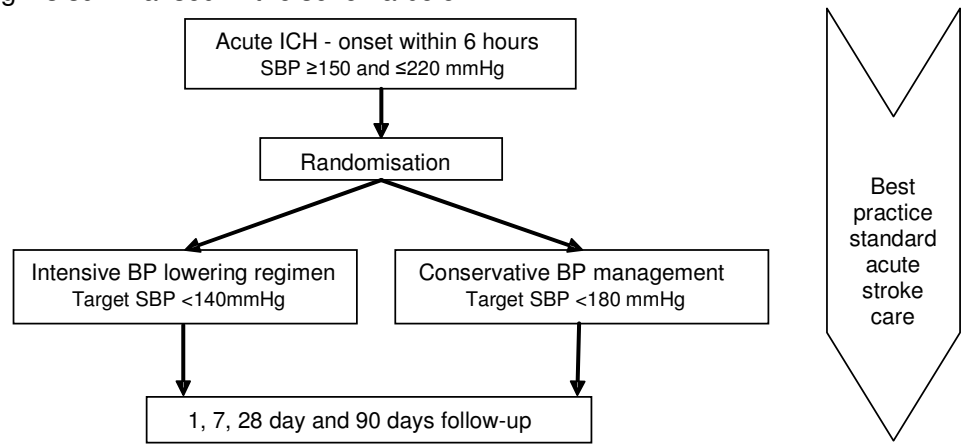
3. OTHER SECONDARY AIMS

To determine the effects of the treatment separately on death and dependency, as well as on physical function, health-related quality of life (HRQoL), recurrent stroke and other vascular events, days of hospitalisation, and requirement for permanent residential care.

METHODS

1. OVERALL DESIGN

This study is an open label, prospective, randomised, controlled, multi-centre trial that, will involve 2800 patients with acute primary ICH recruited from approximately 140 Clinical Centres from Asia, Europe and other regions of the world. Endpoint assessment will be blinded to treatment. The study design is summarised in the schema below.



2. STUDY POPULATION

All patients presenting to participating centres with suspected acute ICH 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:

(1) Completion of CT scan;

(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 ARE to satisfy all of the following criteria:

a. Aged 18 years or above.

b. Acute stroke syndrome due to spontaneous ICH, defined as the sudden occurrence of bleeding into the parenchyma of the brain that may extend into the ventricles and, in rare cases, into the subarachnoid space, confirmed by clinical history and CT scan. (NB Patients with ICH secondary to medical treatment, eg antiplatelet or antithrombotic therapy, are eligible, but ICH secondary to thrombolysis are ineligible).

c. At least two systolic BP measurements of ≥150 mmHg and ≤220 mmHg, recorded 2 or more minutes apart. (NB Patients with initial systolic BP levels outside this range, eg <150 or >220 mmHg, may be randomised should the BP levels fulfil entry criteria on re-checking up to 6 hours. Moreover, patients with systolic BP >220 mmHg may receive initial BP lowering and then randomised, provided systolic BP is <220 mmHg within 6 hours of symptom onset).

d. Able to commence randomly assigned BP lowering regimen within 6 hours of stroke onset. (NB If the precise timing of the first symptoms or signs of the qualifying event are unknown then the time of onset will be taken as the last time at which the patient was known to be well).

e. Able to be 'actively' treated and admitted to a monitored facility, such as an acute stroke unit, high dependency unit or intensive care unit. It is recognized that many ICH patients are designated 'Not For Resuscitation' or 'Do Not Resuscitate' after appropriated consultation with family members. This in itself is not a contraindication to enrolment in the trial, as long as management is otherwise active.

Patients will **NOT** be eligible if there is one or more of the following:

a. Known definite *contraindication* to an intensive BP lowering regimen (eg severe carotid, vertebral or cerebral arterial stenosis, known Moya Moya disease or Takayasu's arteritis, high-grade stenotic valvular heart disease, or severe renal failure).

b. Known definite *indication* for an intensive BP lowering regimen that is similar or more intensive than the active treatment arm of this study (eg very high systolic BP >220 mmHg, hypertensive encephalopathy, or aortic dissection).

c. Definite evidence that the ICH is secondary to a structural abnormality in the brain (eg an AVM, intracranial aneurysm, tumour, trauma, or previous cerebral infarction) or previous thrombolysis.

d. Previous ischaemic stroke within 30 days.

e. A very high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria (eg massive haematoma with mid-line shift of hemisphere or deep coma on presentation, defined by Glasgow Coma Scale Score of 3-5), (NB seizures occur commonly after the onset of ICH, so a reduction in the level of consciousness that is

disproportionate to the size of the haematoma may be secondary to epilepsy rather than mass effect from the ICH).

f. Known advanced dementia or significant pre-stroke disability (eg modified Rankin Score [mRS][111] of 3 or more).
g. Concomitant medical illness that would interfere with outcome assessments and follow-up (eg advanced cancer or respiratory disease).
h. Already booked for surgical evacuation of haematoma.
i. Previous participation in this trial or current participation in another investigational drug trial.
j. A high likelihood that the patient will not adhere to the study treatment and follow-up regimen.

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

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 (ie 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 ICH require emergency care. One aspect of this care is the 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 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.

Surrogate 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 next of kin or surrogate will be approached to provide informed consent on his or her behalf. 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 dieing or is still unable to record their personal consent by the time of completed follow up on the study, the consent given by their next of kin or surrogate 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 next of kin or surrogate 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.

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 surrogate is not available or cannot be contacted, clinicians may enrol eligible patients and inform the patient or their surrogate 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 surrogate 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 surrogate 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 National Health and Medical Research Council also give 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 BP management in the medical profession and the current guidelines. Moreover, the INTERACT1 study has shown that there is no major hazard associated with the treatments under investigation in INTERACT2.

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 International Coordinating Centre (ICC) at The George Institute for International 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 eligibility to the study has been confirmed, the responsible clinician will access a 24-hour password protected, internet-based randomisation system. This will be done by connecting the study centre (eg emergency department or stroke unit) to the server at the ICC where the patient will be registered and the randomised BP management will be assigned for that particular patient. This system has been used successfully in other large-scale trials managed by the ICC.[112, 113] The randomisation sequence will use a minimisation algorithm to achieve balance of study groups at each participating centre. Patients will be stratified according to:

1. time since stroke onset (≤4 vs. >4 hours);
2. hospital of recruitment;
3. country of recruitment

6. ALLOCATED STUDY TREATMENTS

All centres are required to adhere to the standard treatment regimes outlined in the protocol for all randomised patients. It is anticipated that there will be broad comparability of the regimens used in participating centres within each county. As the trial is an assessment of BP management policies, there is some flexibility in the use of particular BP lowering agents to achieve BP targets.

6.1 Early Intensive BP Lowering Group

The aim is to achieve a systolic BP level <140mmHg within one hour of treatment *and* to maintain this BP level for the next 7 days or hospital discharge should this occur earlier.

Patients allocated to early intensive BP lowering will commence immediate treatment with an intravenous BP lowering agent as soon as possible after randomisation. It is anticipated that treatment will be started in the emergency department and that patients will stay there until the target BP is achieved, and they are clinically stable. Intravenous bolus (or maintenance infusion) treatment would then be continued in an acute stroke unit or other monitored facility, although a high intensity nursing care and monitoring facility (ie an intensive care unit) is likely to be required for use of an intravenous infusion of a BP lowering agent in most centres.

It is expected that intravenous therapy will continue to be required during the initiation of oral anti-hypertensive therapy, in order to maintain the systolic BP levels of less than 140 mmHg. However, a systolic BP of 130 mmHg is considered to be the lower limit for the cessation of intravenous BP lowering therapy.

<u>Intravenous treatment protocol</u>

Intravenous treatment protocols, based on available medications, are provided in **Appendices 1A to 1D**. The intravenous treatment will be titrated against regular BP monitoring to achieve a target systolic BP (below 140 mmHg). It is anticipated that intravenous control of systolic BP will be continued for a minimum of 24 hours and possibly up to 48 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 1D**. 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[91] and established best practice for the long-term prevention of BP-related events in patients with cerebrovascular disease.[114]

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 of less than 140 mmHg for 7 days of hospital stay. If the patient is transferred to another hospital facility within 7 days, then attempts should be made to continue therapy to achieve the systolic BP target of 140 mmHg. 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.

6.2 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 1E** 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. Should control of systolic BP not be achieved via these routes, intravenous treatment may be started until the target systolic BP of 180 mmHg is achieved. The oral and intravenous agents used will be the same as in the intensive BP lowering group as detailed in **Appendices 1A to 1D**. 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.

6.3 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 (eg 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 BP MANAGEMENT POLICY

The investigator must not deviate from the protocol except the patient/surrogate chooses to withdraw consent to participation in the study. However, the BP management in either group should be discontinued 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 participants should be managed in an acute stroke, high dependency or intensive care unit, whilst receiving intravenous treatment for BP control. Regular non-invasive BP and heart rate monitoring as well as an adequate nurse/patient ratio must be available. BP will be monitored and recorded using digital sphygmomanometers as per the schedule outlined in **Appendices 1A to 1C**. All BP measurements should be taken from the non-paretic arm (or right arm in situations of coma or tetraparesis), with the patient resting in the supine position. In the case of ambulatory patients, measurements should be taken after the patient has been resting supine for a minimum of 3 minutes.

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).[70] [71] [72] [73] [74] [75] It is anticipated that background care may include significant use of treatments including drugs and surgical evacuation. Use of other therapies will be documented and compared between countries and should be balanced between randomised groups.

9. STUDY OUTCOMES

9.1 Primary Outcomes

The primary outcome is a binary indicator of the patient's death or dependency at 90 days, with dependency being defined by a score of 3 to 5 on the modified Rankin Score (mRS),

9.2 Secondary Outcomes

Key secondary outcome: will be to assess the effect of the treatment on the primary outcome in a subgroup of patients who receive treatment within 4 hours of ICH onset.

Other secondary outcomes relate to the specified objectives outlined below.

1. **Mortality** at 28 days and 90 days
2. **Dependency** (measured by mRS see Appendix 3) at 28 days and 90 days
3. **HRQoL** (measured by the EuroQuol 5D[115] see Appendix 3) at 28 days and 90 days.
4. **Recurrent stroke** defined as an acute disturbance of focal neurological function with symptoms lasting more than 24 hours due to new onset ICH or cerebral ischaemia, confirmed by neuro-imaging (or necropsy), that has occurred after an unequivocal period of neurological stability after 24 hours of the initial ICH.
5. **Acute myocardial infarction** (or sudden death) from a cardiovascular cause, according to standard definitions.
6. **Need for permanent residential care** (eg hostel or nursing home)
7. **Duration of initial hospital stay**

10. DATA COLLECTION AND FOLLOW-UP

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 BP 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 reports 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 encrypted 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, heart rate 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

Participating centres will keep a log of all patients presenting to their institution with a diagnosis of ICH. This will commence following activation of the centre until the end of recruitment and will include all patients whether randomised or not. The 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 (if applicable). 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.

Investigators at each site are required to submit the screening log to the ICC database by the last day of each month during the course of the study.

10.2 Patient 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 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 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 acute ICH will be assessed by the responsible physician for eligibility to the study using a checklist of the eligibility criteria described above.

10.4 Baseline Data
The following information is to be collected before randomisation:

- Medical history
- BP, temperature, heart rate (HR), and scores on the GCS and NIHSS
- CT findings to confirm the diagnosis of primary ICH

All baseline CT scans are to be copied in uncompressed DICOM format onto a CDROM and sent by courier to the regional coordinating centre at the end of each month (see Appendix 2).

10.5 Follow Up Data
Day 1 (from randomisation to 24 hours)
The primary goal of assessments within the first 24 hours will be to ensure adherence to the allocated BP management protocol. Accordingly, BP and administered medication will be recorded. HR will be recorded from an electrocardiographic monitor. BP will be recorded supine in the non-paretic arm from the automated, electronic device used at the Clinical Centre. BP will be recorded every 15 minutes for the first hour, every hour for the next 5 hours, and then 6 hourly for the next 18 hours. 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.

For those sites who have agreed to participate in the collection of a follow-up CT scan, a second CT scan should be undertaken at 24±3 hours after randomisation.

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
- GCS and NIHSS scores
- BP lowering medication
- Dependency assessed with the mRS
- 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. Number of BP lowering agents used 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 Log to assist in trial monitoring by the ICC.

Withdrawal of allocated BP management, 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 Case Report Form and the type(s) of consent obtained will also be recorded on the database.

Serious Adverse Events
All SAEs will be recorded on the SAE form and faxed or emailed 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	7(b)	28(c)	90(c)
Eligibility	**X**				
CT scan	**X**	**X***			
Fevers to be recorded	**X**		**X**		
BP/Heart rate	**X** BP x 2	**X** ** q 15 min 1 h hourly 2-6h 6 hourly 6-24h	**X**		
Consent (a)	**X**				
Clinical history prior medications	**X**				
Physical exam GCS/NIHSS	**X**		**X**		
Functional assessment with mRS			**X**		
HRQoL assessment with EQ 5D				**X**	**X**
Standard care & routine blood tests	**X**	**X**			
BP lowering treatment		**X**	**X**	**X**	**X**
Standard stroke care		**X**	**X**	**X**	**X**
Hospitalised or not		**X**	**X**	**X**	**X**
Contact details for Follow-up		X	**X**		

* In the first 600 patients (300 Asian and 300 non-Asian) in site who have pre-specified agreement to provide a second CT scan undertaken at 24±3 hours, according to protocol.
** At any point where intravenous bolus drugs are administered, BP and HR should be recorded 5 and 15 minutes later.
(a) Consent may be obtained *after* randomisation.
(b) Or the day of discharge if prior to day 7,
(c) Information collected at a face to face consultation or through a telephone interview

11. SERIOUS ADVERSE EVENTS

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

11.2 Recording And Reporting

A 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 BP 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 may 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.

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 and Safety Monitoring Board (DSMB) for review outside of the planned interim analysis meetings.

12. QUALITY ASSURANCE

The study will be conducted in accordance with ICH-GCP, and all relevant local, national and international regulations.

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 an 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 existence of all randomised patients and deaths. A 10% of randomly selected study records and source documents will be reviewed for the verification of

participant details and data quality/completeness. A report of each visit will be prepared by the monitor and reviewed by the ICC.

In summary, the specific aims of the monitoring program will be to:

- confirm the existence of each patient
- confirm that the consent procedure has been documented
- confirm the diagnosis of ICH in every patient
- review source documents for 100% of the primary outcomes
- review 100 % of source data from a 10% of randomly selected of patients at each centre

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 by Government Regulatory Authorities

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

13. DATA MANAGEMENT

Randomisation and data entry will be performed at the participating centres via the password protected, encrypted 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 Clinical Endpoints Committee (CEC) will review information about every outcome reported in order to ensure that all endpoints meet the same diagnostic criteria. The CEC will comprise experts in cerebrovascular disease. The adjudication of every event will be made without knowledge of which randomised group the patient was allocated. The members of the CEC will be provided with explicit instructions about the adjudication of events and a manual detailing the criteria to be followed.

15. STATISTICAL CONSIDERATIONS

The sample size is 2,800. It is anticipated that patients will be accrued from approximately 140 Clinical Centres, with each site recruiting between 5 and 25 (average 15) patients annually over a 3 year recruitment period. It is expected that about 100 patients will be recruited from Australia and New Zealand, 1600 from China, 400 from other Asian countries, 500 from European countries and 200 from Canada. For an average-sized Clinical Centre, this will require that about one out of every five patients, who present with acute ICH, be enrolled over a 3-year recruitment period.

The proposed sample size of 2800 will provide at least 90% power (with alpha=0.05) to detect a 14% relative risk reduction in death or dependency in intervention compared to control treated patients. The assumptions in the power calculation are:

1. Primary outcome event rate will be of 50% in the control group, and will be reduced to 43% in the intervention group, which are similar to the INTERACT1 pilot study.
2. The 14% relative risk reduction is based upon the results of INTERACT1, whereby a 10-14 mmHg difference in systolic BP between randomised groups in the first 24 hours of treatment resulted in a 1.7ml absolute difference in haematoma growth. In a post-hoc analysis of patients randomized within 4 hours of ICH onset, however, the absolute

difference in haematoma growth increased to 3.4ml between groups. Other data from the rFVIIa trials [116] indicate a 7% relative increase in the risk of death or worsening of disability (1 point on mRS scale) at 90 days is associated with a 1 ml growth in haematoma. Thus, a difference in haematoma growth of 2ml (0-6 hours) and 3ml (0-4 hours) from BP lowering may result in at least 14% (7% absolute) and 21% (10% absolute) relative reduction, respectively, in the avoidance of a poor outcome in ICH

3. Non-adherence in the active treatment arm (drop-out) is 8% in INTERACT1, where 17 of the 203 patients in the treatment group did not receive any IV BP lowering treatment in the first 24 hours. It is expected that this figure will be 10% in INTERACT2.
4. Lost to follow up for the primary outcome is expected to be 3%, as seen in INTERACT1, where 11 (2.7%) patients were lost to follow up or did not have an assessment of their level of disability at 90 days.

A beneficial effect of early treatment on the primary outcome would equate to one or more cases of death or dependency prevented among approximately every 15 patients treated. This size of absolute benefit has been considered clinically valuable in other areas of neurology and is comparable to the magnitude of benefit seen with calcium channel blockers in subarachnoid haemorrhage and the use of stroke units for the management of acute stroke. The sample will expect to be balanced with 50% of patients randomized in 0-4 hour and 50% in 4-6 hour, time windows. This will provide more than 90% power to detect a relative risk reduction of 20% in those randomized within 4 hours for a pre-specified sub group analysis under the same assumptions on adherence and to follow-up, as outlined above.

16. STATISTICAL ANALYSES

All analyses will be conducted with patients allocated to the group to which they were assigned at randomisation, regardless of whether they used the study treatments (i.e. according to the principle of intention to treat). Baseline and demographic characteristics such as gender, ethnicity, medical history, etc, will be summarised by treatment group to assess comparability of treatment groups. No formal statistical analyses of these data other than descriptive statistics are planned. The primary endpoint of death or dependency at 90 days will be analysed by means of a chi-square test. If loss to follow-up is more substantial than in INTERACT1, some form of sensitivity analysis will be performed. A subgroup analysis of the primary endpoint for those patients treated within 4 hours of stroke onset will be conducted. Categorical secondary outcomes such as all cause and cause-specific, early neurological deterioration will preferably be analysed by means of a Chi-square. A Fisher test might be used if the numbers get too small.

The effect of treatment on any time-to-event type of outcome will be in principle tested by means of a log-rank test. This includes time to recurrent stroke and time to first event. For patients who are 'lost to follow-up', all information collected from randomisation to the time of the last contact will be included in these analyses. Continuous endpoints such as the HRQoL health utility score (ED-5D) at 28 or 90 days will all be summarised by means (SD) or medians (IQR). The effect of treatment will preferably be tested by a Wilcoxon test. If the data is not too skewed, mixed models will be used to describe the health utility score over time and assess the effect of BP lowering therapy.

The primary analysis will essentially be unadjusted but adjusted analyses can be carried out for the primary endpoint and key secondary outcomes. No adjustment for multiplicity is planned as a small number of pre-specified efficacy outcomes are investigated.

Descriptive statistics will be provided for safety data. The number of patients reporting any SAEs and AEs, the occurrence of specific SAEs and AEs, and discontinuation due to SAEs and AEs will be tabulated. Laboratory data will be listed and values outside the normal range will be noted where applicable. Tests of a treatment effect in specific SAE may be attempted by means of a Chi-square or Fisher test. The exact list of tests to be performed will be specified a priori in a blind review.

17. SUB-STUDIES (SELECTED SITES ONLY)

17.1 Genetics in ICH

There is some evidence that the ApoE4 genotype is associated with increased frequency of primary ICH, in particular those with a lobar location. INTERACT2, as one of the largest prospectively collected datasets of ICH, could provide a unique opportunity to test the hypothesis that the ApoE4 genotype, particularly patients who are homozygous, is an independent risk factor for lobar ICH. In centres participating in this sub-study, blood will be collected and stored for future genotyping.

17.2 Effects of treatment of haematoma growth in ICH

The effects of treatment on haematoma expansion and other indices including oedema will be evaluated in a sub-sample of 600 patients (300 Asian and 300 non-Asian) according to a similar protocol as used in INTERACT1. Apart from the CT scan at baseline**,** a repeat CT scan (24±3 hours) is required. The primary efficacy measure was proportional change ('growth') in haematoma volume at 24 hours. Clinical outcomes were assessed over 90 days.

The sites who wish to participate in this sub-study will be identified prior to site activation, and a per-patient loading of payments will be made to cover all extra costs required to undertake the 2nd CT. The 2nd CT images will be sent to the Regional Coordinating Centres in a similar manner to the CT scan that has been undertaken at the baseline and the outcome data will be analysed centrally by experts who will be kept blind to the treatment allocation.

18. PUBLICATIONS AND REPORTS

Publication of the main reports from the study will be in the name of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT2) Investigators. Full editorial control will reside with a Writing Committee approved by the EC.

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 EC. Investigators further agree to provide the EC 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 EC shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts. The EC 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 EC 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 "The INTERACT2 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.

19. ORGANISATION

INTERACT2 is an academic initiated and conducted study to be managed by an International Coordinating Centre (ICC) based at the George Institute for International Health, University of Sydney, Australia. The study will be overseen by an International Executive (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 140 participating hospitals in Australia/New Zealand, China, India, Europe and other countries.

19.1 Executive Committee (EC)

Responsibilities: Overall responsibility for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The EC 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 EC is given below:

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

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

A/Professor Bruce Neal, The George Institute, University of Sydney, Australia

Professor Richard Lindley, Westmead Hospital, University of Sydney, Australia

Dr Mark Parsons, John Hunter Hospital, Newcastle, Australia

Professor Lewis Morgenstern, Department of Neurology, University of Michigan, USA

Professor Wang Jiguang, Shanghai Institute of Hypertension, Shanghai, China

Professor Huang Yining, Department of Neurology, Peking University First Hospital

Professor Stephen Davis, Department of Neurology, University of Melbourne, Australia

Professor Jong Sung Kim, Asan Medical Center, Soeul, Korea

Professor Christophe Tzourio, INSERM U708 Neuroépidémiologie, Hospital de la Salpêtriére, Paris, France

Dr Christian Stapf, Department of Neurology, Hôsptial Larboisière, Paris, France

19.2 International Coordinating Centre (ICC)

The ICC is at The George Institute for International 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.

19.3 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. In the first instance, RCCs will be located in Beijing (for China) and Paris (for Europe)

19.4 Core Lab (CT Analysis)

Responsibilities: To measure haematoma volume on all de-identified and blinded CT scans (blinded by allocation group and timing of scan).

19.5 Clinical Events Committee

Responsibilities: Review blinded study outcomes to ensure endpoints meet the consistent diagnostic criteria in line with pre-determined criteria.

19.6 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 Graeme Hankey, Royal Perth Hospital, Perth, WA, Australia
Professor Konrad Jamrozik, University of Adelaide, Adelaide, SA, Australia
Professor S Claiborne Johnston, University of California, San Francisco, CA, United States
Professor Shunwei Li, Peking Union Medical College, Beijing, China

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.

19.7 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 the ICC in accordance with protocol.

20. FUNDING

INTERACT2 is supported by a project grant from the NHMRC of Australia.

21. TIMELINES

April – November 2008:		Site recruitment and activation, materials development, staff training
July 2008 to July 2011:		Patient recruitment
October 2011:		Final patient follow-up
April 2011 to November 2011		Data cleaning and site close-outs
February 2012:		Joint presentation and publication of results

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Appendix 1A - BP management protocol for centres WITHOUT Labetalol

Early intensive BP lowering group	TREATMENT PROTOCOL
INITIAL therapy	
BP Target	**SBP <140 mmHg** reached within 1 hour
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
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/Kg/min • OR start infusion of Nicardipine 5-15 mg/hour
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 <140 mmHg** reached within 1 hour
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
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/Kg/min • OR start infusion of Nicardipine 5-15 mg/hour
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 Urapadil (China)

Early intensive BP lowering group	**TREATMENT PROTOCOL**
INITIAL therapy	
BP Target	**SBP <140 mmHg** reached within 1 hour
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
Urapadil (IV)	• Urapadil 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 urapadil infusion following an initial bolus.</u>** • Urapadil infusion 5-30 mg/hour • If target still not reached, ADD infusion of hydralazine 50-150 µg/min OR glyceryl trinitrate 1-100 µg/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 Urapadil (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 130-140mmHg, Urapadil 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: urapadil 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

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 <140 mmHg** reached within 1 hour
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 (< 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/Kg/min
MAINTENANCE therapy	
BP Target	Maintenance of SBP <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 130-140mmHg, 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

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 Lowering 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.

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 – 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 - CT imaging protocol

IF AT ALL POSSIBLE, ENSURE REPEAT SCAN IS PERFORMED ON THE SAME CT SCANNER

1. A digital scout radiograph in the lateral position should be obtained.
2. Scanning plane is axial and approximately 30 degrees to infraorbital meatal line.
3. Scan from level of foramen magnum to high vertex.
4. Correct obliquity.
5. Recommended Parameters:
   a. Perform acquisition in conventional mode.
   b. Slice thickness: 5-8 mm throughout posterior fossa and remaining brain (if 5-8 mm not possible, maximum of 10 mm slice thickness). Slice thickness should be the same for follow-up scans.
   c. Kilo voltage: 100-140kV.
   d. mA: 100-300 mA.
   e. Matrix size: 512 by 512.
   f. Scanning time: At least 300 mAs for 5 mm.
   g. FOV: 20-25 cm.
6. Recommended window width and level settings:
   a. Posterior fossa: Window width 100-120 and level 35-45.
   b. Supratentorial: Window width 80-100 and level 35-45.
7. Sites should submit digital images. The digital images should be submitted in DICOM format (**MUST BE UNCOMPRESSED**). One patient per CD-ROM is recommended. The digital images must be saved to CD-ROM without patient identifiers (study subject number can be saved digitally or written on the CD-ROM).
8. Place CD-ROM in free-post envelope and post to the RCC who will forward data to the ICC in Sydney, Australia. CT 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 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.	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 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).	

Assessment	Response	Score
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).	
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 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.	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 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 stroke care protocol

Airway Management:
Objectives: Normal SpO2 (≥ 92%)

- Monitor oxygen saturation continuously
- Oxygen supplementation is recommended only if patients de-saturate
- Intubate patients, **with precautions for prevention of elevated intracranial pressure** (ICP), 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 sub-cutaneous heparin (5000 U subcutaneous twice daily) **72 hours after** symptom onset in patients with poor mobilization

Elevated ICP Management
Objectives: Treat elevated ICP in patients with clinical deterioration associated with mass effect seen on CT scan

- Mannitol 20% (0.25–0.5 g/kg every 4 hours); do **NOT** use prophylactically
- Steroids are **NOT** recommended
- Consider mannitol 1 g/kg acutely and intubation with hyperventilation (PCO2 30-35 mmHg) for false localizing signs/acute loss of consciousness.

Management of Warfarin Related Coagulopathy:
Objectives: Rapid reversal of coagulopathy

- Fresh Frozen Plasma 2-4 units and repeat INR; treat until INR is normal (<1.3)
- Vitamin K 10 mg intravenously

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
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association 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 only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. 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 on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, 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. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

26. 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. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

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Note: **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

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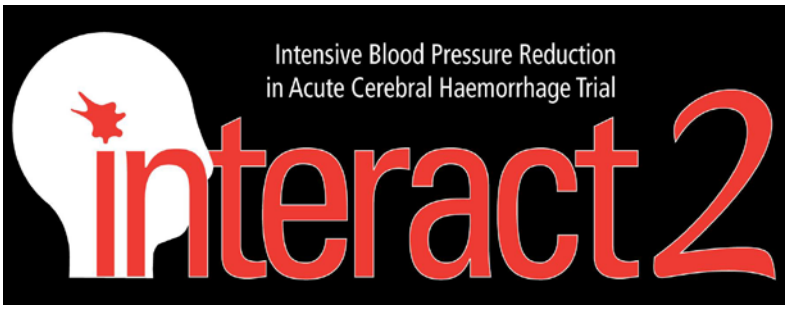
The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

9.10.2004



Article type: Special Report

STATISTICAL ANALYSIS PLAN

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Contents

List of abbreviations and definition of terms

ACE-I	Angiotensin converting enzyme inhibitor
AE/SAE	Adverse event / serious adverse event
AHA	American Heart Association
AVM	Arteriovenous malformation
BP	Blood pressure
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF/eCRF	Case record form / electronic CRF
CT	Computerised tomography
DICOM	Digital Imaging and Communications in Medicine
DSMB	Data Safety Monitoring Board
EC	Executive Committee
ECG	Electrocardiogram
GCP	Good clinical practice
GCS	Glasgow coma scale
TGI	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
INTERACT	INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial
IRB	Institutional Review Board
IQR	Interquartile range
IST3	The third International Stroke Trial
ITT	Intention to treat
IVRS	Interactive Voice Randomisation System
MedDRA	Medical Dictionary for Regulatory Authorities
Mins	Minutes
mmHg	Millimetres of mercury
MIStar	MIStar® is a multi-modality, multi-module and multi-purpose software package with a broad spectrum of functionalities developed by Apollo Medical Imaging Technology Pty. Ltd., Melbourne, Australia.
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NFR	Not For Resuscitation, similar to ‘Do Not Resuscitate’ (DNR) orders.
NHMRC	National Health and Medical Research Council of Australia
NIHSS	National Institutes of Health Stroke Scale
NNT	Number Needed to Treat
OC	Operations Committee
OR	Odds ratio
PI	Principal Investigator
PROBE	Prospective, randomised, open assessor-blinded end-point study design
PROGRESS	Perindopril protection against recurrent stroke study
PT	Preferred Term
RCC	Regional Coordinating Centre
rFVIIa	Recombinant activated clotting Factor VII
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Standard deviation
SOC	System-Organ Class

Abstract

Background: The second (main phase) INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT2) is a large-scale investigation of the benefits and risks of early intensive blood pressure (BP) lowering in patients with acute stroke due to primary spontaneous intracerebral haemorrhage (ICH).

Objective: To outline in detail and make public the pre-determined statistical analysis plan (SAP) for the main analyses of INTERACT2 for the primary report of the trial results, and outline subsequent key publications. The SAP was finalised before completion of data collection and is what investigators will adhere to in analysing data on two management regimes, targeting either a lower ('intensive') or higher ('standard') systolic BP level, in patients who present within 6 hours of onset of ICH.

Methods: All data collected by participating researchers will be reviewed and formally assessed. Information pertaining to the baseline characteristics of patients will be selected and for each item; statistically relevant descriptive elements are described. Information relevant to the BP lowering treatment and the process of care and delivery of other treatments is classified and, for each item, descriptive statistical analyses are planned for comparisons between randomised groups. Finally, for the trial outcomes that are classified as primary, secondary or tertiary, the most appropriate statistical comparisons to be made between groups are described.

Results: A SAP has been developed for the results of the INTERACT2 study. This plan will allow a comprehensive description of baseline characteristics, features of the process of care, and trial treatments, along with pre-determined statistical assessment of relevant outcome measures in a way that is transparent, available to the public, verifiable and pre-determined before completion of data collection.

Conclusions: We have developed a pre-determined SAP for the INTERACT2 study which is to be followed, once data are complete, to avoid analysis bias arising from prior knowledge of the study findings.

Trial registration: NCT00716079, ISRCTN73916115, and ACTRN12608000362392.

1. Introduction

The INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT2) study is the largest study to date of an acute treatment for stroke due to primary spontaneous intracerebral haemorrhage (ICH). Planning for INTERACT2 began in 2003 following release of the PROGRESS trial results demonstrating the greatest benefit of long-term blood pressure (BP) lowering for secondary stroke prevention was in patients with prior ICH.[1] The aim was to design a trial that would not only provide a definitive answer to longstanding controversy over the most appropriate management of elevated BP in the hyperacute phase of ICH, but also for it to have pragmatic features so that the results could be widely generalisable. More specifically, INTERACT2 was designed to have good power to provide a reliable estimate of a minimum clinically worthwhile beneficial effect of the treatment strategy of early intensive BP lowering in ICH of a sufficient degree to influence clinical practice.[2] An initial pilot phase (INTERACT1), undertaken between 2005 and 2007, demonstrated the feasibility of the study protocol, safety of the treatment regime of early intensive BP lowering, and beneficial effects of the treatment regime on the important surrogate biomarker endpoint of haematoma expansion within 6 hours of onset of ICH.[3]

The main phase (INTERACT2) uses a similar design, randomisation, data collection and follow-up systems as used in INTERACT1, in an expanded global network. The sample size calculations for the primary outcome were based on estimates of the difference between randomised groups on the traditional fixed dichotomous measure of poor outcome in acute stroke: that is, defined by any score between 3 and 5 (indicating 'dependency' or 'significant disability') or 6 (death) on the modified Rankin Scale (mRS).[2]

Here we describe the statistical analysis plan (SAP) for INTERACT2, which was finalised prior to completion of patient recruitment and data collection, and represents our pre-specified analyses of the study. The SAP was approved by the study's Executive Committee on 25 July 2012.

2. Background

There is no proven effective medical therapy for ICH, which affects over 1 million people in the world each year,[4] most of whom either die or are left seriously disabled. The burden of ICH is disproportionately greater in 'non-white' ethnic groups, where there are higher frequencies (20-50% of strokes) and greater rates (i.e. higher risks) of ICH due mainly to high population-wide BP levels. Among the various prognostic factors for ICH, which include increasing age, large initial haematoma volume, major neurological deficit, intraventricular extension and infra-tentorial location,[5-11] haematoma growth is an attractive therapeutic target as it is a potentially modifiable factor that is present in nearly all patients.[9-11]

To date, however, medical treatments targeting haematoma growth in ICH have failed to demonstrate any benefits. In particular, the pivotal Factor VII for Acute hemorrhagic Stroke Trial (FAST)[12] failed to show an improvement in clinical outcomes despite a consistent effect on reducing haematoma growth with early use of the potent haemostatic agent, recombinant activated clotting Factor VII (rFVIIa).

Elevated BP is common after ICH, often to very high levels, and is well established as another key prognostic factor related to haematoma growth.[9-11,13] The pilot phase INTERACT1 study demonstrated that the size of the treatment effect of early intensive BP lowering on reducing haematoma growth is dependent on both the timing and degree of achieved level of BP.[14,15] Any

potential clinical benefit of early BP lowering is therefore likely to be most evident in patients in whom the management strategy is commenced early and where the BP lowering target is reached rapidly after the onset of ICH. As patients with major cerebral mass effect, as determined by having a large haematoma volume and major neurological deficit, have the worst prognosis, the INTERACT2 protocol allows the attending clinician to exclude patients who are considered unlikely to benefit from such a treatment.

3. Study design

3.1 Overview

The INTERACT2 study is an international, multicentre, prospective, parallel group, randomised, open assessor-blinded end-point (PROBE) clinical trial that compares the effects of two management regimes, targeting either a relatively low or high systolic BP level, in patients presenting within 6 hours of onset of primary spontaneous ICH. The study is registered and the protocol has been published.[2] Project grant funding was obtain in 2008 and the first patient was randomised in October of that year.

The primary aim of the INTERACT2 study is to compare the effects of an early intensive BP lowering management regime against the more conservative guideline-recommended level of BP management on the poor outcome of the combination of death or dependency at 90 days after the onset of ICH. The treatment targets are a systolic BP level of 140 mmHg within 1 hour of the randomisation ('intensive') and a guideline-recommended systolic BP level of 180 mmHg ('standard'), achieved with locally available intravenous antihypertensive agents according to pre-defined site-specific dose-escalation treatment protocols. *The null hypothesis is that there is no difference in the risk of a poor outcome between patients assigned to an early intensive treatment regime (target systolic BP of 140 mmHg) and those assigned to a standard control treatment regime (target of systolic 180 mmHg).*

3.2 Patient population

There is no upper age limit for inclusion in the study and all participating patients are required to receive national guideline-recommended medical treatment and levels of care. However, the protocol allows the attending clinician to exclude patients in deep coma or with massive haematomas who are expected to die early irrespective of any treatment. In addition, patients who are assessed to require early surgical evacuation of the haematoma are also excluded, as this would complicate assessment of the study treatments. Patients are also excluded if the outcome assessments are likely to be confounded by major co-morbid medical illness or poor adherence to the follow-up procedures. However, the inclusion/exclusion criteria are kept simple and broad to allow the inclusion of patients with a wide range of characteristics. This not only facilitates recruitment and data collection in a large number of patients as part of routine care, but it also improves the external validity ('generalisability') of the results.

3.2.1 Inclusion criteria

Patients are eligible for inclusion in the study if all of the following criteria are met.

- Age is ≥18 years.
- Presentation with an acute stroke syndrome due to primary spontaneous ICH, defined as the sudden occurrence of bleeding into the parenchyma of the brain that may extend into the ventricles and/or in rare situations the subarachnoid space, that is confirmed by a

computerised tomography (CT) scan (or magnetic resonance imaging [MRI]) of the brain. Patients with ICH whilst on antithrombotic treatment (antiplatelet agents or anticoagulation) are eligible.

- There are at least 2 systolic BP measurements of ≥150 and ≤220 mmHg, recorded 2 or more minutes apart. Patients with initial systolic BP levels outside of this range (<150 or >220 mmHg) may be randomised should the BP levels fulfil entry criteria on re-checking up to 6 hours after the onset of ICH. Patients with an initial systolic BP >220 mmHg may receive initial BP lowering and then be randomised, provided that the systolic BP is ≤220 mmHg within 6 hours of symptom onset.
- The randomly assigned BP lowering regimen is able to be commenced within 6 hours after the onset of ICH. If the precise timing of the onset of symptoms or signs of the qualifying event is unknown, then the time of onset will be taken as the last time the patient was known to be well.
- Active treatment and care will be provided to the patient in a suitable monitored facility (e.g. high dependency unit or intensive care unit) even if they are assigned with 'Not For Resuscitation (NFR)' or 'Do Not Resuscitate' (DNR) orders.
- Written informed consent is able to be obtained directly from the patient, or an appropriate surrogate based on local ethics committee recommendations

3.2.2 Exclusion criteria

Patients are excluded from the study if one or more of the following criteria are present.

- Known definite contraindication to intensive BP lowering (e.g. known severe carotid, vertebral or cerebral arterial stenosis, Moya Moya disease or Takayasu's arteritis, high-grade stenotic valvular heart disease, or severe renal failure).
- Known definite indication to intensive BP lowering (e.g. very high systolic BP >220 mmHg, hypertensive encephalopathy, or aortic dissection).
- Definite evidence that the ICH is secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation [AVM], intracranial aneurysm, tumour, or trauma), cerebral infarction within the last 30 days, or recent use of thrombolysis for ischaemic stroke (or other vascular condition).
- A high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria (e.g. massive haematoma with mid-line shift of a hemisphere or deep coma on presentation, defined by score of 3-5 on the Glasgow Coma Scale [GCS]).
- Known existing dementia or pre-stroke disability (e.g. score 3-5 on the mRS).
- Concomitant medical illness that would interfere with the outcome assessments and/or follow-up (e.g. advanced cancer or respiratory disease).
- Patients considered for early surgical evacuation of the haematoma.
- Patients who have previously participated in INTERACT2 or are currently participating in another investigational drug trial.
- Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen.

3.3 Randomisation

Eligible patients are randomised using a minimisation algorithm[16] to either intensive BP lowering (intensive) or guideline-based (standard) management of BP. Randomisation is stratified by country, hospital, and time since ICH onset (≤4 and >4 hours). Twenty one countries are included in the study: Argentina, Australia, Austria, Belgium, Brazil, Chile, China, Finland, France, Germany, Hong Kong, India, Italy, Netherlands, Norway, Pakistan, Portugal, Spain, Switzerland, United Kingdom, and the United States. Central randomisation is achieved via a password-protected web-based program operated from The George Institute for Global Health in Sydney, Australia. In China, investigators had the option of using a customised 24 hour digital Interactive Voice Response System connected to the central server to allow patients to be randomised at sites where rapid access to the internet is not possible.

3.4 BP lowering treatments and background care

Intensive group Patients allocated to the intensive BP lowering group are commenced on a standardised treatment regime commencing with intravenous and then changed - when feasible - to oral (or via a nasogastric tube) agent(s). The treatment goal is to achieve a systolic BP level of 140 mmHg within 1 hour of randomisation. The second goal is to maintain this level of systolic BP for at least 7 days in hospital. Specific treatment protocols were developed for each participating region/centre based on the availability of different BP lowering agents for routine use prior to participation in the study. When administering BP lowering treatment, care is required to ensure that hypotension is avoided in patients by first checking for potential dehydration and providing intravenous fluids. BP lowering treatment is titrated by repeat intravenous bolus or continuous infusion, with a systolic BP of 130 mmHg is considered the safety threshold for cessation of such treatment. It is anticipated that intravenous BP lowering agents will be required for the first several hours in most cases; the clinician's decision to introduce/switch from intravenous to oral BP lowering is made according to BP control and patient status.

Standard group Patients allocated to the standard group receive BP management according to American Heart Association (AHA) guidelines.[17] The threshold for the initiation of intravenous treatment is more conservative (systolic >180 mmHg) than in the intervention group.

Both groups Oral BP lowering agents are allowed when patients are deemed medically stable by the attending physician. Patients are given oral antihypertensive agents by day 7 or discharge from acute care hospital if sooner, with a long-term target systolic BP of <140 mmHg as per secondary stroke prevention guidelines. Since the study seeks to assess the impact of BP lowering management, and not of a specific agent, and so as to ensure the trial result is maximally generalisable to existing routine practice, there is flexibility in the protocol to allow use of locally available agents (e.g. urapidil, labetolol, hydralazine, metoprolol, and nitrates). However, all other aspects of BP lowering treatment are standardised across sites including continuation of prior oral BP lowering where possible. Investigators are to adhere to study protocols and provide active care, but are free to modify a patient's treatment if it is deemed to be necessary according to their clinical judgment.

3.5 Baseline and follow-up assessments

All responsible investigators receive training in the data collection systems and Good Clinical Practice (GCP), and training in the assessment scales if they have had no certification prior to participation. Each collaborating site is required to complete the online screening log, for a randomly assigned calendar month in each participating year, of all patients presenting with a

diagnosis of ICH who are considered for the study but are subsequently excluded. The screening log records each patient's initials and date of admission together with a brief description of the main reason as to why he or she was not randomised. The log is used to monitor recruitment and identify specific barriers to randomisation of eligible patients.

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

The 28 and 90 day evaluations are to be conducted either in-person or by telephone, by a trained staff member at the local site who is not directly involved with the acute treatment of the subject and is blind to the treatment allocation.

The hospital coordinator at each collaborating site ensures that all data are completed in a timely manner. Investigators receive modest reimbursement for their time involved in data collection and for local expenses (e.g. printing, internet connection, purchase of medications, copying of CT scans). Patients who do not receive the allocated randomised treatment or do not follow the protocol are still followed up and analysed as per the 'intention to treat' (ITT) principle. Data collection is kept to a minimum to ensure rapid enrolment and follow-up of patients within the context of routine clinical practice.

3.6 Brain imaging

CT scans (or MRIs if no CT scan) are conducted according to standardised techniques at baseline (i.e. for confirmation of the diagnosis) in all patients, and at 24±3 hours in a subset of patients where such repeat scanning is either part of routine practice or where patients provide consent for an additional scan for research. The 24 hour scans are used to assess the treatment effects on haematoma growth. In China, the collection of 24 hour CT scans was stopped after a target of approximately 400 consecutive patients was reached in 2009. The rationale for stopping China earlier than the other regions is that follow-up CT scanning for ICH is generally not routine and is an additional cost of medical care. However, combining these data with >300 repeat CT scans from China in INTERACT1 will provide >700 repeat CT scans specifically in Chinese patients, and an even larger number of patients overall in the INTERACT studies for examination of the treatment effects on haematoma growth.

Uncompressed digital CT images are collected in DICOM format on a CD-ROM identified only with the patient's unique study number and are analysed centrally for measurement of haematoma volumes and other parameters at The George Institute for Global Health. Haematoma volumes with and without inclusion of any intraventricular component are calculated independently by one of several trained imaging scientists who are kept blind to clinical data, treatment, and date and sequence of scan. This calculation is done with computer-assisted multi-slice planimetric and voxel

threshold techniques in MIStar software (version 3.2). Inter-reader reliability is checked by re-analysis of 15% of the scans by a single neurologist using intra-class correlation with and without removing outliers. Where some brain images are received as digital pictures or plain films, haematoma volume is measured manually by the (AxBxC)/2 formula.[18]

3.7 Sample size considerations

The sample size was set at 2800 to provide at least 90% power to detect a 14% relative risk reduction in the primary outcome for patients in the intensive BP lowering group compared to those in the standard control group, using a two-sided significance test with 5% type I error. The following assumptions have been made: a primary outcome of 50% in the control group will be reduced to 43% in the intensive group (i.e. 7% absolute decrease); and there will be 10% non-adherence to the intensive treatment and 3% overall loss to follow-up, as seen in INTERACT1. The 14% relative risk reduction is extrapolated from INTERACT1 where differences in systolic BP between randomised groups of 13 mmHg and 11 mmHg in the first 1 and 24 hours of treatment, respectively, resulted in approximately 2 ml absolute difference in haematoma growth at 24 hours. Further analysis of INTERACT1 cohort[19] confirmed results of a meta-analysis of the rFVIIa studies[7] to indicate a 2-4 ml reduction in haematoma growth could translate into 10-20% better outcome in ICH. The expected magnitude of absolute benefit in terms of cases of death or dependency prevented being considered, which equates to a number needed-to-treat (NNT) of 15, is considered a minimum clinically worthwhile benefit of the treatment, which could be applied widely as a standard care.

Secondary analysis of INTERACT1 indicates that the treatment effect is likely to be greater in patients randomised <4 hours of ICH onset, where the absolute difference in haematoma growth was 3-4 ml between randomised groups.[15] This is estimated to translate into a 21% (10% absolute) relative reduction (and a 10% absolute reduction) in the risk of a poor outcome. Assuming that the sample size is balanced with regard to patients being randomised into the 0–4 and the 4–6 hour time epochs, the study will also have 90% power to detect a relative risk reduction of 20% in those patients treated <4 hours of ICH onset.

3.8 Unblinding

Only the Data and Safety Monitoring Board (DSMB) and associated statisticians responsible for writing the reports have access to the interim data/results. The first drafts of the SAP were written by the principal investigator, two independent statisticians, and two other investigators, who are blind to the treatment allocations and study results. Treatment allocations are stored securely in a separate location for that purpose. Statisticians not involved in the writing of the DSMB reports remain blinded and work on dummy datasets until the statistical computer code is validated, which is done in accordance with the Standard Operating Procedures of The George Institute for Global Health.

3.9 Definitions of the outcomes

3.9.1 Primary outcome

The primary measure of outcome is the occurrence of a poor outcome at 90 days after randomisation. This outcome is measured using the mRS,[20] the most widely used instrument for grading the impact of stroke treatments on daily functioning through the categorisation of levels of disability (or 'dependency'; sometimes equated to 'handicap').[21,22] The broad mRS scaling is: 0 = no symptoms at all; 1 = no significant disability despite symptoms, but able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities but able to look

after own affairs without assistance; 3 = moderate disability requiring some help, but able to walk without assistance; 4 = moderate-severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability, bedridden incontinent, and requiring constant nursing care and attention; 6 = dead. The protocol states that scores of 3–6 (i.e. dead or significant disability) is defined as a poor outcome. The primary analysis of the mRS will be unadjusted and undertaken using the traditional dichotomous (i.e. 0-2 versus 3-6) separation of the mRS. As loss to follow-up is expected to be minimal, missing values will not be imputed for the primary analysis. However, if there are >5% missing values in the primary outcome, we will undertake a secondary analysis with imputed data (section 5.10). A sensitivity analysis will also be undertaken of the primary outcome adjusted by key prognostic covariates, which are defined below. Where appropriate, data will be summarised by an odds ratio (OR) and 95% confidence intervals (CI).

3.9.2 Key secondary outcome

During the course of the trial, several novel ordinal approaches to analysis of the categorical outcome data provided by the mRS were developed, validated and gained greater acceptance in allowing enhanced statistical power and broader interpretation of the results of acute treatment trials in stroke.[23-25] However, there are several different approaches to these analyses and they each require various specific statistical assumptions to be satisfied. Whether or not they are cannot be known until the data for each treatment group are known. The trial Executive Committee therefore decided to include an ordinal approach or 'shift analysis' as a key secondary analysis of the mRS using unadjusted ordinal logistic regression for the assessment of functional recovery across all 7 levels of the mRS.[25,26] Data will be summarised by the OR and its 95% CI. A sensitivity analysis will be undertaken of this analysis, adjusted adjusting for several prognostic covariates. Another sensitivity analysis will reduce the mRS from 7 to 5 levels, where levels 0, 1, 2 and 3 are analysed separately to the combined levels 4, 5 and 6 (poor outcome) as a single level. This approach was used in the IST3 study.[26] Additional sensitivity analyses using different cut points for the mRS will also be conducted to allow comparison with the measures used in another major stroke trial where levels 0-1 ('favourable outcome') were compared to levels 4-6.[27]

3.9.3 Other secondary outcomes

Secondary outcomes will include the following.

- Death, from the time of randomisation.
- Cause-specific mortality within the 90-day follow-up period. The primary cause of death will be categorised as:
  - *Death from direct effects of initial ICH*, defined as death ≤7 days after the onset of the randomised ICH event with any of the following: baseline brain scan shows haematoma with mass effect or midline shift, or follow-up scans show significant extension of initial haematoma with mass effect or midline shift.
  - *Death from recurrent cardiovascular event*, defined by clear clinical evidence of a recurrent stroke (i.e. a new stroke event occurring after a period of at ≥24 hours of stability with clear clinical, biological, and if applicable, CT brain scan findings), a coronary vascular event, or sudden death, according to standard definitions;
  - *Death due to other causes*, defined by clear evidence of death due to a non-neurological cause, including pneumonia, sepsis, or injury.

- Health-related quality of life (HRQoL), as assessed on the EuroQoL, as an overall health utility score (ED5D) at Day 90.
- Need for living in a residential care facility at day 90.
- Duration of initial hospitalisation in days.
- Poor outcome at day 7 and day 28.
- Haematoma growth at 24 hours

3.9.4 Tertiary outcomes

Tertiary outcomes will include the following.

- Place of death (in initial hospital, another hospital or institutional facility, at home).
- Neurological function on the NIHSS at 24 hours and day 7 (or hospital discharge).
- Physical functioning at days 7 and 28.
- Duration of stay in an intensive care unit.
- Requirement for surgical intervention.
- Separate components of the EQ5D: mobility, self care, usual activities, pain/discomfort, and anxiety/depression at days 28 and 90.

3.9.5 Safety variables

Although there are a number of different agents to rapidly lower BP, each with potential advantages and disadvantages, it is uncertain which class of BP lowering agent is the most desirable in the acute phase of stroke. As the effect of oral antihypertensive agents is dependent on absorption and distribution times, the oral route of administration is less desirable for achieving rapid and intensive BP lowering. Moreover, such treatment cannot be guaranteed during the acute phase of stroke due to dysphagia and/or reduced consciousness, and an early insertion of a nasogastric tube may not be possible or practicable. Administration of a nitroglycerine transdermal patch may be useful[28] but it is not widely used in routine emergency department or critical care settings. Intravenous treatment is the optimal route of administration of BP lowering (i.e. hypotensive) agents during the hyperacute phase of ICH to allow rapid and titratable BP lowering.

Hypotension is the main adverse event and safety issue of early intensive BP lowering that can affect the cardiovascular system resulting in death, acute cardiovascular events, or acute renal failure. The study protocol recommends close monitoring of BP levels in patients to avoid hypotension; this is best accomplished within a high dependency or intensive care unit setting. Amongst the various agents, sodium nitroprusside is arguably the least desirable for routine use outside of an intensive care unit because of its potent antiplatelet effects, ability to increase intracranial pressure, and profound BP lowering effects.

All deaths, cardiovascular events and recurrent strokes are adjudicated by blinded clinical experts through review of source data in their local language. Discrepancies between reports of the serious adverse event (SAE) by clinician and expert adjudicator are reviewed and resolved by a central expert committee, on review of all available data. Since all patients had ICH, deaths are classified as due to this condition unless an unequivocal non-cerebral cause was established. SAEs are reported according to standard definitions and coded using terminology of the Medical Dictionary for Regulatory Authorities (MedDRA). However, as this is a classification by System-Organ Class

(SOC) and Preferred Term (PT) that is not necessarily relevant for this study, the following categories of SAEs derived from MedDRA and follow-up assessments are were defined:

- Neurological deterioration where declines from the baseline to 24 hours assessment of either ≥4 on the NIHSS or ≥2 on the GCS are reported;
- Clinician-reported episode of severe hypotension with clinical consequences which required corrective therapy;
- Acute coronary event according to standard definitions consistent with a typical clinical presentation, abnormal electrocardiogram, or abnormally elevated enzymes;
- Acute renal failure as reported by the clinician confirmed by elevation of biochemistry with or without the need for dialysis;
- Other sequelae as reported by clinicians.

The exact link between the MedDRA codes and the SAE categories is available upon request. All SAEs will be categorised into fatal and non-fatal SAEs with a similar structure.

4. Funding

The study was funded by the National Health and Medical Research Council (NHMRC) of Australia (Program Grant number 571281 and Project Grant numbers 512402 and 1004170). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author will have full access to all the data in the study and the final responsibility of the decision to submit for publication.

5. Statistical analysis

5.1 Analysis principles

- Analyses will be conducted on an intention-to-treat (ITT) basis. No per-protocol analysis will be carried out as a clear definition of such a dataset is extremely difficult.
- All tests are two-sided and the nominal level of type I error will be 5%.
- The primary analysis of the effect of treatment on the primary outcome will be unadjusted. All other statistical analyses will be unadjusted, except where indicated.
- Subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcome.
- There will be no imputing of missing values, unless specified. Where the number of missing observations is substantial, the number of observations used in an analysis will be reported. Last observations will not be carried forward. Multiple imputation will be used if >5% of patients have missing data on the primary outcome at 90 days.
- Analyses will be conducted primarily using SAS software.

5.2 Data sets analysed

- The randomised data set (*Rand set*) will be constituted of all patients randomised in the study without exclusion and the analysis conducted according to the ITT principle. This will be used to assess both efficacy and safety.

- The CT scan data set (*CT set*) will be constituted of all randomised patients with a baseline CT scan in a format that could be analysed for volumetric measurements.
- The Haematoma growth data set (*Haem set*) will be constituted of the subset of randomised patients with both a baseline and 24 hour CT scan in a format that could be analysed for volumetric measurements. This will be used to assess the treatment effect on haematoma growth.

5.3 Interim analyses

An independent DSMB, chaired by Professor John Simes of the Clinical Trials Centre (CTC) at the University of Sydney, and consisting of clinicians and biostatisticians, reviews unblinded data from the INTERACT2 study at twice-yearly intervals during its conduct. The DSMB is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the intervention during the trial, and for monitoring the overall conduct of the clinical trial. The DMSB members have as their mission to review recruitment, BP separation, dropout and event rates, monitor safety endpoints, and examine the effects of treatment on the efficacy outcomes. They are also charged with informing the study Executive and Operational Committees if at any time there emerges either evidence beyond reasonable doubt of a difference between randomised groups in the primary outcome, or evidence that is likely to change clinical practice in the context of current knowledge. Two formal interim analyses after approximately 30% and 60% of the patients were followed up for 30 days were planned and actually conducted. The Haybittle-Peto stopping rule (i.e. where a difference of 3 standard errors is considered as clear evidence of a treatment effect) was used. The study was not terminated early and the DSMB did not request any additional analyses of the data. The final last level of significance with 3 looks will consequently be 0.0482. Although naïve estimates can theoretically be slightly biased when a stopping rule is used, there will be no correction of the estimates on termination, as the bias is likely to be negligible with this design.

5.4 Dates, vital status and consent-related issues

The study is conducted at sites with experience in acute stroke care. Regionally-based experienced clinical research monitors performed online and on-site data verification. Site monitoring was undertaken, initially after the first few patients were randomised at a site, and thereafter according to number of patient recruited during the course of the trial. As this 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 should improve the accuracy of the data obtained. Site monitoring aims to confirm: (i) eligibility; (ii) demographic and consent details on all randomised patients; (iii) details of all SAEs against source documents; (iv) collect/correct any outstanding/missing data; and (v) check selected variables against source medical documents in a 10% random selection of patients.

Inconsistencies in key data points, vital status at final follow-up, dates and details of any deaths are queried by the ICC or RCC to limit the number of errors and missing values. Due to the specific circumstances surrounding emergency care research it may not always be possible to obtain consent from either the patient or next of kin without delaying the initiation of treatment. 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, and with approval of the local ethics committee, 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 follow up period, the next of kin or

person responsible should be approached to obtain delayed consent. In the case of a patient's death, the site Principal Investigator will 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 documented in the patients file.

Two important situations can lead to cessation of the study treatment: a patient, next of kin or legal surrogate may withdraw consent; or they may refuse continuation of the study treatment when delayed consent is sought. In both cases, the study treatment will cease and the patient will receive appropriate treatment as determined by the attending clinician. The information sheet provided to the patient and/or the next of kin or surrogate clearly states that the patient can be withdrawn from the study at any time without prejudice and explanation. Such withdrawal is documented in the patient's file. If withdrawal of consent relates to the BP management alone, data collection can continue on documentation of this fact in the patient's files. If consent for use of all data is withheld, the patient's data will be removed from the analysis, except for data related to consent. If consent for future study inclusion is withdrawn, the patient's data will be included up to the date the consent was withdrawn. Censoring dates will be used only in case of 'real' loss to follow-up, such that the date of censoring will be the last day of contact, or the date of hospital discharge if no other information is available.

5.5 Trial profile

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

5.6 Patients characteristics and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data is available. If missing values are ≥5%, the denominator will be added in a footnote in the corresponding summary table. In some instances, frequencies and percentage of patients in the category will be reported as further indicated in the tables. Continuous variables will be summarised by use of standard measures of central tendency and dispersion, either mean and standard deviation (SD) for variables identified with #, or median and interquartile range (IQR) with †. Durations will also be summarised by medians and IQR.

Baseline measures for all patients will be tabulated for the following variables: age #, sex, ethnicity (Chinese vs other), geographical region (Asia/Australia, Europe, and Americas), systolic BP #, diastolic BP #, heart rate #, temperature #, weight #, NIHSS score #, GCS score #, medical history (prior stroke, hypertension, coronary heart disease, atrial fibrillation, diabetes, and smoking status), time between onset and randomisation †, medications at time of admission, key biochemistry variables #, location of the haematoma, size of the haematoma †, and presence of intraventricular extension.

5.7 BP lowering details in the first 24 hours

BP lowering details will be summarised by treatment arm and period in the first 24 hours and details of BP lowering agents. Similar data will also be obtained for days 2-7. Counts and percentages will be displayed for all categorical items. Continuous outcomes will be summarised

by either means (SD) or medians (IQR) as further detailed in the same table. A figure will be used to describe systolic BP differences between groups.

5.8 Process measures of background management and treatments

Counts and percentages will be calculated per treatment arm for key items of standard stroke care. The period covers day 0 (randomisation) to day 7. A p-value corresponding to a χ^2 test or Fisher test will also be reported. The default analysis is based on the χ^2 test unless the expected number per cell is too small (<5), in which case a Fisher test will be used.

5.9 Primary outcome and key secondary outcomes

The primary analysis of the effect of treatment on the primary measure of poor outcome will be undertaken using the traditional dichotomous (i.e. 0-2 versus 3-6) separation of the mRS. A standard χ^2 test will be used as the primary test of statistical significance on the effect of treatment allocation on poor outcome. Frequencies and percentages per arm, and an OR measuring the treatment effect and its 95% CI will also be reported. We will also perform an adjusted analysis for sensitivity purposes, based on a multivariable logistic regression analysis adjusted for randomisation strata and key prognostic covariates: age (continuous); baseline score on the NIHSS (<15 and ≥15 score); time from the onset of symptoms to randomisation (minutes); haematoma volume (<15 and ≥15 ml); location of the haematoma (lobar and deep [including brainstem/cerebellum]), and the presence of intraventricular haemorrhage.

The key secondary outcome will be analysed using an unadjusted ordinal logistic regression model across all levels of the mRS at 90 days. This analysis assumes a common OR across all cut points of the mRS. An adjusted analysis will be presented for sensitivity purposes, with adjustment for the same covariates as defined above. A secondary analysis will be undertaken using all levels of good functional outcome (i.e. 0, 1, 2, and 3) compared to a single combined poor outcome (i.e. 4, 5 and 6 levels grouped together), as used in the IST3 trial.[25] A shift figure will be presented to illustrated the change distribution across each treatment arm. If the proportional-odds assumption is violated in either of these analyses (i.e. significant p-value for the Brant test of a common OR) the effect of treatment across categories will be tested using a standard χ^2test and a model with non-proportional odds will be fitted. Additional sensitivity analyses using different cut points for the mRS will be unadjusted odds ratios for 0-1 ('favourable outcome') compared to 4-6.[27]

The absolute risk of a poor outcome, for each treatment group, and corresponding 95% CI will be estimated by fitting a log-binomial regression model. If this model cannot be fitted, due to numerical problems, a bootstrap method will be substituted to compute the CI from logistic regression.

5.10 Missing values in the primary and key secondary endpoints

The percentage of missing data for the mRS is expected to be small. However, if it exceeds 5%, a sensitivity analysis based on multiple imputation by chained equations (MICE)[29] will be performed. Should this suggest substantial bias for the complete case analysis, the MICE approach will become the chosen method of analysis.

5.11 Secondary outcomes

All binary secondary outcomes will be preferably analysed by means of a χ^2 test. A Fisher test will be used if the numbers are ≤5. These data will be summarised by an OR and its 95% CI. The effect of treatment on survival time or any time-to-event type of outcome will be tested by a log-rank test. Skewed continuous endpoints, such as the health utility score (ED-5D) at 90 days, will all be

summarised by medians (IQR). The effect of treatment will be tested by a Wilcoxon test. A difference between medians and its 95% CI will be imputed if deemed useful. Rates of death by treatment group will also be presented as Kaplan-Meier curves. Length of stay in hospital (and in an intensive care unit) will be censored due to early deaths or stays longer than 90 days. They will then be analysed with a log-rank test.

5.12 Haematoma-related endpoints

The effects of randomised treatment on haematoma growth will be evaluated in the Haem data set, a subgroup of patients with baseline and a repeat CT scan (24±3 hours) according to a similar protocol that was used in INTERACT1. The proportional growth in haematoma volume will be analysed by analysis of covariance after transformation, adjusted by key prognostic factors. As INTERACT1 revealed that this variable is highly skewed with small negative values, proportional growth will be log-transformed to remove skew after addition of constant (e.g. 1.1) to eliminate negative values, thus achieving a roughly normal distribution for the analysis. The analysis will be adjusted for the baseline haematoma volume, haematoma location, and time from stroke onset to CT scan.

When several measurements are available the rating made first by the main rater (not the neurologist who conducted the quality control) will be used unless a gross error has been identified. If the number of CT scans at 24 hours that are outside the ±3 hour time window is more than 10%, a sensitivity analysis will be carried out for the primary endpoint. The absolute haematoma change will not be transformed. A similar strategy in terms of adjustment will be performed for the absolute haematoma change. The analysis of 'substantial' haematoma growth, defined as an increase in volume of ≥33% (relative) or >12.5 ml (absolute) in the first 24 hours, will be carried out by means of logistic regression adjusted again in a similar fashion as above. A similar strategy will be used for the change in haematoma volume plus intraventricular haemorrhage for all its derivations (relative, absolute change and substantial growth) (Appendix 1, Table 5). Haematoma-related endpoints will be summarised by the adjusted medians (or means) per treatment arm, their difference, and 95% CI and p value. A sensitivity analysis will be carried out by adding a random effect for raters.

5.13 Safety endpoints

Counts and percentages per treatment arm will generally summarise all specific pre-defined SAE categories. They generally represent the number of patients experiencing a specific SAE (at least once), the fatal ones, and the breakdown by subcategory (when appropriate). This includes evidence of an early neurological deterioration within 72 hours, the various forms of recurrent stroke, other vascular events, renal failure, non-vascular events (pneumonia, sepsis, fracture and so forth), and severe hypotension. The exact definitions based on MedDRA codes have been established prior to unblinding and are available upon request. If possible a global χ^2 or Fisher test of a treatment effect will be carried out and its p value reported. A Fisher exact test will be performed only when the χ^2test is thought to be unreliable due to small expected numbers per cell (Appendix 3, Table 3). . A measure of treatment effect (i.e. a relative risk and its 95% CI) might be reported if its computation is possible (Appendix 1, Table 4)None of the above analyses will be adjusted. All deaths occurring during the first 7 days will be considered as stroke deaths unless otherwise specified. The same rules for the tests, relative risk and 95% CI apply.

5.14 Subgroup analysis

All subgroups will be defined by the presence or absence of a pre-randomisation variable; we will not select any subgroups based on post-randomisation criteria. Seven subgroup analyses will be carried out for the primary outcome. Unadjusted p values will be reported but the number of declared subgroups analyses will be specified in all publications. Categorisation is as follows:

- Age category: <65 and ≥65 years
- Ethnicity: China and other
- Time to randomisation: <4 and ≥ 4 hours
- Systolic blood pressure at baseline: <180 and ≥180 mmHg
- History of hypertension: yes/no
- Baseline NIHSS score: <15 and ≥15
- Haematoma volume at baseline: <15 and ≥15 ml
- Haematoma location: cortical and deep (including brainstem/cerebellum)

The main analysis for each subgroup will be an interaction test in a logistic regression model to determine whether the effect of treatment differs significantly across categories for that particular subgroup. The primary analysis will be unadjusted but for consistency, an adjusted analysis will also be carried out. Summary measures will include counts, percentages and a measure of effect (OR) with its 95% CI obtained in a stratified analysis, and reported with a p-value for the interaction test. The cut points for continuous variables will be chosen with reference to the distribution of the baseline characteristics (both treatment groups combined) in the first 30% of randomised patients. Forest plots will be constructed to illustrate subgroup analyses, with p values for heterogeneity for each pair of subgroups.

5.15 Tables and figures for main paper

The proposed tables and figures for the main results are presented in Appendix 1 and 2. Appendix 3 includes supplementary data tables. Table 1 will report key collected baseline characteristics of the participants by treatment group. Table 2 will report on the different approaches to BP lowering treatment, the number of patients treated with BP lowering, and the number of types of agents used to control BP. A figure will be used to display levels of achieved systolic BP at different time points in the first 24 hours. Table 3 will report on process measures and concomitant treatments. Table 4 will report the primary and secondary outcomes, selected tertiary outcomes, and major adverse events. Supplementary Table 3 (Appendix 3) will report all non-fatal serious adverse events to the end of follow-up. In addition, the following figures will be prepared:

- A CONSORT diagram illustrating the flow of patients through the study (Appendix 2; Figure 1)
- A diagram showing mean and standard error bar for systolic BP pressure levels in each randomised group from before and after the time from randomisation to follow-up at day 90.
- A bar chart displaying each grade on the mRS in each treatment group (Appendix 2, Figure 2)
- A Forest plot of the treatment effect on the primary outcome among different subgroups, with a P value displayed as a p value for a test of interaction (based on the data provided in Appendix 1; Table 6).
- Kaplan-Meier survival analysis of intensive versus standard BP lowering.

A more extensive list of tables and figures used to report additional information on the INTERACT2 has been written and is available upon request.

5.16 Systematic reviews and meta-analysis

The estimated effects of treatment on the components of the primary outcome, key secondary outcome and haematoma growth parameters will be pooled across the INTERACT1 and INTERACT2 studies to provide a more comprehensive assessment of the effects of early intensive BP lowering in ICH than is available from INTERACT2 alone.

5.17 Proposed content of primary and subsequent publications

Appendix 4 provides an outline of the publication plan for the INTERACT2 study, alone and when combined with data from INTERACT1.

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Appendix 1: Proposed format of data tables in the main results publication

Table 1: Baseline characteristics of the study participants

Characteristic	Standard BP control (n=xxxx)	Early intensive BP lowering (n=xxxx)
ICH onset to randomisation (hrs:mins), median (IQR)	xx:xx (xx:xx – xx:xx)	xx.xx (xx.xx – xx.xx)
Demographic and clinical		
Age (yr), mean (SD)	xx (xx)	xx (xx)
Male, n (%)	xxx (xx)	xxx (xx)
Chinese, n (%)	xxx (xx)	xxx (xx)
Systolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)
Diastolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)
Heart rate (beats per minute), mean (SD)	xxx (xx)	xxx (xx)
NIHSS score		
Median (IQR)	xx (xx - xx)	xx (xx - xx)
≥14 n (%)	xxx (xx)	xxx (xx)
GCS score		
Median (IQR)	xx (xx - xx)	xx (xx - xx)
Severe (3-8) n (%)	xxx (xx)	xxx (xx)
Hypertension, n (%)	xxxx (xx)	xxxx (xx)
Current antihypertensive use, n (%)	xxxx (xx)	xxxx (xx)
Previous ICH, n (%)	xxx (xx)	xxx (xx)
Previous ischaemic stroke, n (%)	xxx (xx)	xxx (xx)
Previous acute coronary event, n (%)	xxx (xx)	xxx (xx)
Other heart disease, n (%)	xxx (xx)	xxx (xx)
Diabetes mellitus, n (%)	xxx (xx)	xxx (xx)
Warfarin anticoagulation use, n (%)	xxx (xx)	xxx (xx)
Aspirin or other antiplatelet agent use, n (%)	xxx (xx)	xxx (xx)
Statin or other lipid lowering agent use, n (%)	xxx (xx)	xxx (xx)
Haematoma characteristics		
Baseline volume, mL, median (IQR)	xx (xx - xx)	xx (xx - xx)
Location		
Lobar, n (%)	xxx (xx)	xxx (xx)
Basal ganglia/thalamic, n (%)	xxx (xx)	xxx (xx)
Brainstem/cerebellum, n (%)	xxx (xx)	xxx (xx)
Left hemisphere site, n (%)	xxx (xx)	xxx (xx)
Intraventricular extension, n (%)	xxx (xx)	xxx (xx)

Table 2: Blood pressure lowering treatment details in first 24 hours

	Standard BP control (n=xxxx)	Early intensive BP lowering (n=xxxx)
Any BP lowering treatment, n (%)	xxx (xx)	xxx (xx)
Any intravenous BP lowering treatment, n (%)	xxx (xx)	xxx (xx)
Time from ICH onset to BP lowering treatment, mins		
median (IQR)	xxx (xx - xx)	xxx (xx - xx)
<4 hrs, n (%)	xxx (xx)	xxx (xx)
≥4 hrs, n (%)	xxx (xx)	xxx (xx)
Method of intravenous treatment, n (%)		
Bolus	xxx (xx)	xxx (xx)
Infusion	xxx (xx)	xxx (xx)
Number of intravenous agents, n (%)		
1	xxx (xx)	xxx (xx)
2	xxx (xx)	xxx (xx)
≥3	xxx (xx)	xxx (xx)

Table 3: Management details from randomisation to day 7: number (%)

	Standard BP control (n=xxx)	Early intensive BP lowering (n=xxx)	P value*
Intubation	xxx (xx)	xxx (xx)	
Admission to intensive care unit	xxx (xx)	xxx (xx)	
Deep vein thrombosis prevention	xxx (xx)	xxx (xx)	
Intravenous mannitol	xxx (xx)	xxx (xx)	
Any surgical intervention	xxx (xx)	xxx (xx)	
Evacuation/decompression	xxx (xx)	xxx (xx)	
Ventricular drain inserted	xxx (xx)	xxx (xx)	
Haemostatic therapy	xxx (xx)	xxx (xx)	
Decision to withdrawal active care	xxx (xx)	xxx (xx)	

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

Table 4: Clinical endpoints at 90 days

Outcome	Standard BP control (n=xxxx)	Early intensive BP lowering (n=xxxx)	Treatment effect (95% CI)	P value
Primary endpoint				
Death or dependency (3 + 4 + 5 + 6)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Secondary endpoints				
Death, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)[#]	0.xxx
Primary cause of death, n (%)				0.xxx
Direct effects of primary ICH event n (%)	xxx (xx)	xxx (xx)		
Recurrent cardiovascular event n (%)	xxx (xx)	xxx (xx)		
ICH	xxx (xx)	xxx (xx)		
Ischaemic/undifferentiated stroke	xxx (xx)	xxx (xx)		
Acute MI/coronary event/other	xxx (xx)	xxx (xx)		
Other causes	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
ED5D score – median (IQR)	xx (xx - xx)	xx (xx - xx)	xxx (xxx-xxx)†	0.xxx
Living in residential care facility n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Duration of hospitalisation, days, median (IQR)	xx (xx-xx)	xx (xx-xx)	xxx (xxx-xxx) †	0.xxx
Poor outcome at day 7, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Poor outcome at day 28, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Safety				
Total number of serious adverse events (SAE), n (%)‡	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Number of patients with at least one SAE, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Neurological deterioration, n (%)‖	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Severe hypotension, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx

*Odds ratio, [#] Hazard ratio for time to death, using log rank test, † Median difference, ‡A patient could have more than one event

‖Neurological deterioration where declines from the baseline to 24 hours assessment of either ≥4 on the NIHSS or ≥2 on the GCS are reported

Table 5: Effects of early intensive blood pressure lowering on haematoma volume

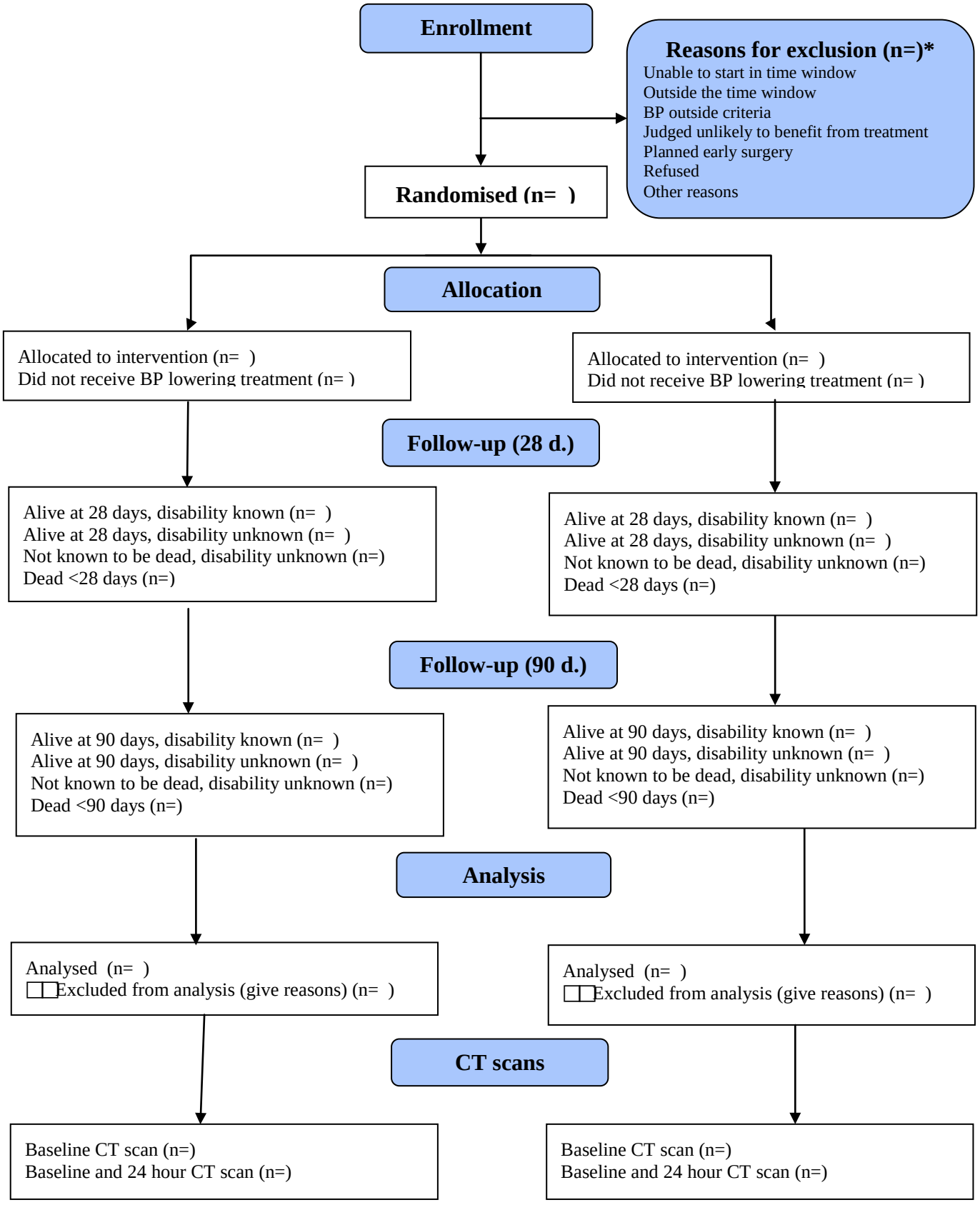
	Standard BP Group (n = xxxx)		**Early intensive Group (n = xxxx)**		**Absolute (mls) / proportional (%) less in intensive group**	
					(95% CI)	P Value
Haematoma volumes, baseline to 24 hours	Baseline	24 hours	Baseline	24 hours		
Haematoma (ml), mean unadjusted (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Haematoma + ICH (ml), mean unadjusted (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)		
Haematoma growth						
Growth (ml), mean unadjusted (95%CI)	x.x (x.x-x.x)		x.x (x.x-x.x)		x.x (x.x-x.x)	x.xxx
Growth (ml), mean adjusted (95% CI)	x.x (x.x-x.x)		x.x (x.x-x.x)		x.x (x.x-x.x)	x.xxx
Growth (%), mean unadjusted (95% CI)	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx (xx-xx)	x.xxx
Growth (%), median adjusted (95% CI)	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx (xx-xx)	x.xxx
Haematoma + IVH growth						
Growth (ml), mean unadjusted (95%CI)	x.x (x.x-x.x)		x.x (x.x-x.x)		x.x (x.x-x.x)	x.xxx
Growth (ml), mean adjusted (95% CI)	x.x (x.x-x.x)		x.x (x.x-x.x)		x.x (x.x-x.x)	x.xxx
Growth (%), mean unadjusted (95% CI)	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	x.xxx
Growth (%), median adjusted (95% CI)	xx (xx.x-xx.x)		xx.x (xx.x-xx.x)		xx (xx-xx)	x.xxx
Proportion of patients who experienced substantial haematoma growth						
Haematoma volume	xx (xx)		xx (xx)		xx (xx-xx)	x.xxx
Haematoma + IVH volume	xx (xx)		xx (xx)		xx (xx-xx)	x.xxx

Table 6: Forest plot of key subgroups

	Standard (n=xxx)	Intensive (n=xxx)	Odds ratio (95% CI)	p-value for interaction
Age n (%)				0.xxx
<65 years	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
65+ years	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Ethnicity n (%)				0.xxx
Chinese	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Non-Chinese	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Time to randomisation n (%)				0.xxx
< 4 hours	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
≥ 4 hours	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Baseline systolic BP n (%)				0.xxx
<180 mmHg	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
≥180mmHg	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
History of hypertension n (%)				0.xxx
Yes	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
No	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Baseline NIHSS				0.xxx
<15 score	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
≥15 score	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Baseline haematoma volume				0.xxx
<15 ml	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
≥15 ml	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Baseline haematoma location n (%)				0.xxx
Cortical	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Deep	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	

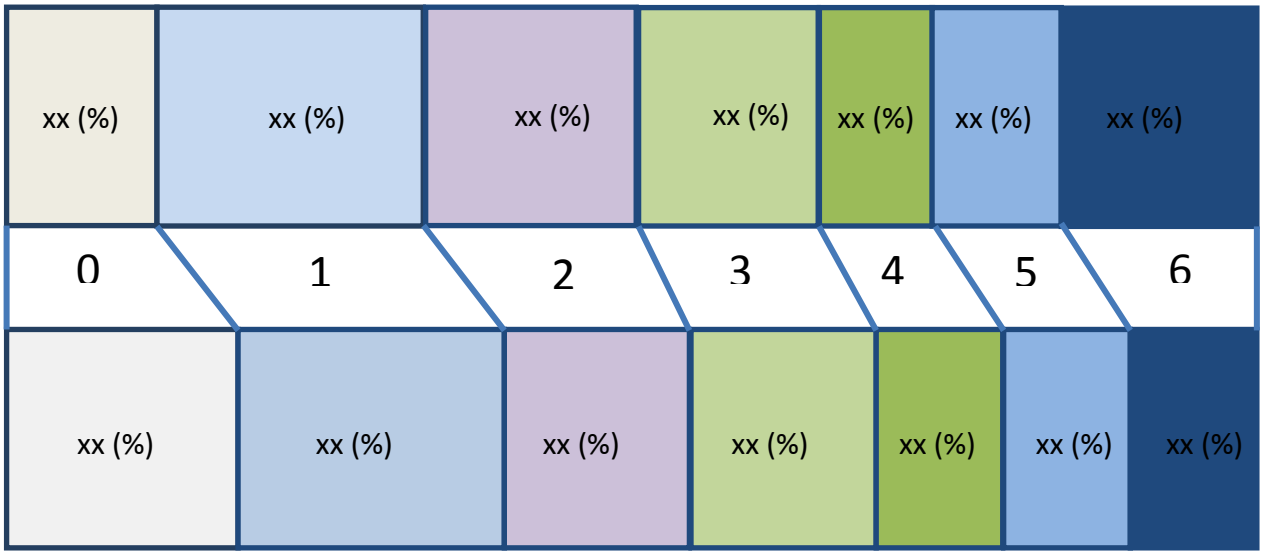
Appendix 2: Figures for the main results paper

Figure 1: INTERACT2 Flow Diagram based on CONSORT 2010



*Screening logs collected at each site 1 month per year

Figure 2: mRS outcome at 90 days by treatment group



The ordinal logistic regression analysis across all mRS levels gave an overall odds ratio of x.xx (95% CI x.xx-x.xx, p= x.xx) and x.xx (95%CI x.xx-x.xx,p=x.xx), and overall odds ratio of x.xx (95% CI x.xx-x.xx, p= x.xx) and x.xx (95%CI x.xx-x.xx,p=x.xx) when adjusted for age, National Institutes of Health Stroke Scale (NIHSS), time from ICH onset to randomisation, haematoma volume, location, and presence intraventricular extension.

Appendix 3: Proposed format of data tables in subsequent publications

Table 1b: Baseline characteristics of the study participants

Characteristic	Standard BP control (n=xxxx)	Early intensive BP lowering (n=xxxx)
Treatment times (hrs:mins), median (IQR)		
Onset to hospital arrival ('door')	xx:xx (xx:xx–xx:xx)	xx.xx (xx.xx–xx.xx)
Door to CT scan	xx:xx (xx:xx–xx:xx)	xx.xx (xx.xx–xx.xx)
Door to treatment	xx:xx (xx:xx–xx:xx)	xx.xx (xx.xx–xx.xx)
Demographic and clinical		
Age (yr)	xx (xx)	xx (xx)
<35		
35-44		
45-64		
65-74		
75-84		
85+		
Region of recruitment, n (%)	xxx (xx)	xxx (xx)
China		
Aust/India/Pakistan		
Europe/UK		
South America/USA		
Ethnic origin		
White		
Oriental		
Other		
Patients recruited per centre, n (%)	xxx (xx)	xxx (xx)
1-20		
21-50		
50-99		
≥100		
Systolic BP (mmHg), n (%)	xxx (xx)	xxx (xx)
150-169		
161-179		
180-199		
200-219		
Temperature (°C), >38 n (%)	xxx (xx)	xxx (xx)
Elevated blood glucose, >8 mmol/L n (%)	xxx (xx)	xxx (xx)
Medications on presentation		
ACE-I or ARB		
Diuretic		
Calcium channel blocker		
Beta blocker		
Other antihypertensive agent		
≥2 antihypertensive agents		

Table 2b: BP lowering treatment

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

Table 3: Non-fatal serious adverse events at 90 days, number (%)

	Standard BP control (n=xxxx)	Early intensive BP lowering (n=xxxx)	P value*
Non fatal SAEs	n (%)	n (%)	
*Total events***	xxx (xx)	xxx (xx)	0.xxx
Number of patients	xxx (xx)	xxx (xx)	0.xxx
Direct effects of primary ICH event	xxx (xx)	xxx (xx)	0.xxx
Recurrent cardiovascular event	xxx (xx)	xxx (xx)	
ICH	xxx (xx)	xxx (xx)	
Ischaemic/undifferentiated stroke	xxx (xx)	xxx (xx)	
Acute MI/coronary event/other	xxx (xx)	xxx (xx)	0.xxx
Other vascular	xxx (xx)	xxx (xx)	0.xxx
Neurological deterioration	xxx (xx)	xxx (xx)	0.xxx
Acute renal failure	xx (xx)	xx (xx)	0.xxx
Non-vascular	xxx (xx)	xxx (xx)	0.xxx
Pneumonia	xxx (xx)	xxx (xx)	
Sepsis	xxx (xx)	xxx (xx)	
Fracture	xx (xx)	xx (xx)	
Other non-vascular	xxx (xx)	xxx (xx)	
Severe hypotension	xxx (xx)	xxx (xx)	0.xxx
Other SAE	xxx (xx)	xxx (xx)	0.xxx

Counts correspond to the number of patients who experienced at least one specific SAE with the exception of the first row. Denominators are all patients randomised.

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

**A patient could have more than one event

Appendix 4: Proposed content of primary and key subsequent publications

	Content / overview of analytic approach
1	*Main results paper 1:* Effects of early intensive blood pressure lowering on death and dependency in acute intracerebral haemorrhage: the INTERACT2 randomised trial
2	*Main results paper 2:* Effects of early intensive blood pressure lowering according to the timing and degree of blood pressure lowering, and key patient and haematoma characteristics: individual patient meta-analysis of the INTERACT trials
3	Further subgroup analysis of the primary outcome and exploratory analysis of the secondary outcome in relation to the degree of reduction in 24-hour haematoma growth
4	Descriptive analysis of how intracerebral haemorrhage differs between Chinese and non-Chinese patients? a pooled analysis of the INTERACT trials
5	Descriptive analysis of the relation of regional differences in clinical management practice and outcome from intracerebral haemorrhage in the INTERACT2 study
6	Descriptive analysis of the type of blood pressure lowering agent and outcomes

Appendix 5: Statement of contribution of the authors

CA and EH participated in writing the first draft and all revisions of the SAP. SH and MW participated in revisions of the SAP. All other authors participated in critical reviews of the SAP. The final version of the SAP was approved by the INTERACT2 Executive Committee on 25 July 2012. The SAP was prepared without knowledge of the unblinded data. The unblinded study statisticians prepared tabulations of the baseline characteristic as grouped data for reports during the course of the study, which were used to inform the authors in selection of cut-points to define subgroups and aspects of the overall analysis plan. The SAP was prepared independent of the key funding agency for the trial, the Australian National Health and Medical Research Council (NHMRC).