Prevention Of Decline in Cognition After Stroke Trial (PODCAST): A factorial randomised controlled trial of intensive versus guideline lowering of blood pressure and lipids

Version 1.0, 24 July 2009

Short title:	Prevention Of Decline in Cognition After Stroke Trial
Acronym:	PODCAST
Trial Registration:	TBC
EUDRACT:	None – No Clinical Trials Authorisation required †
ISRCTN:	TBC
Research Ethics:	TBC
Trial Sponsor:	University of Nottingham
Funding Source:	The Stroke Association UK, Alzheimer's Society UK

† MHRA have confirmed that the trial is not within the scope of the Clinical Trials Directive.

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SYNOPSIS

Title	Prevention of decline in cognition after stroke trial: a factorial randomised controlled trial of blood pressure and lipid lowering
Short title	Prevention of Decline in Cognition After Stroke Trial (PODCAST)
Acronym	PODCAST
Chief Investigator	Professor Philip Bath
Objectives	Primary: To determine if 'intensive' blood pressure lowering therapy, and/or 'intensive' lipid lowering therapy, after stroke reduces cognitive decline and dementia. Secondary: To determine if 'intensive' blood pressure lowering therapy, and/or 'intensive' lipid lowering therapy, after stroke reduces poor quality of life, poor function, depression, stroke recurrence, vascular events, and death.
Trial Configuration	Prospective, randomised, open-label, blinded end-point, controlled, partial factorial, phase IV trial
Setting	Secondary care
Sample size estimate	Assuming overall significance α=5%, power 1-β=90%, rate of cognitive decline in 'guideline' BP group = 25% and 'intensive' BP group = 20% (absolute risk reduction 5%, relative risk reduction 20%) at 5 years, we estimate a sample size of 3,400 participants for the whole trial (start-up and main phase). The lipid factor will assume the same relative risk reduction (20 %) but will have a lower statistical power (~86 %), as it will only involve participants with ischaemic stroke (~3,060)
Number of participants	3,400 participants (1,700 per BP group, ~1,530 per lipid group), comprising a: Start-up phase: 600 participants (300 per BP group, ~270 per lipid group) Main phase: 2,800 participants (1,400 per BP group, ~1,260 per lipid group)
Eligibility criteria	Ischaemic stroke or primary intracerebral haemorrhage 3-7 months post stroke event Age >70 and normal cognition (Mini-Mental State Examination, MMSE >23), or Age 60-70 with MMSE 24-26
Description of interventions	1. BP lowering strategy: 'Intensive' group – target SBP <125 mmHg

	'Guideline' group – target SBP <140 mmHg 2. Cholesterol lowering strategy: 'Intensive' group – potent statin, add cholesterol absorption inhibitor if LDL-cholesterol >2.0 mmol/l (or total cholesterol >4.0 mmol/l if LDL-cholesterol cannot be calculated) 'Guideline' group – guideline statin 40 mg daily, with dose doubled if LDL-cholesterol >3.0 mmol/l (or total cholesterol >5.0 mmol/l if LDL-cholesterol cannot be calculated) Treatments will use licensed BP-lowering and lipid-lowering interventions (including life-style modification and drugs)
Duration of trial	8 years. The proposed start date is January 2010 Start-up phase: 3 years Main phase: 5 years
Randomisation and blinding	Randomisation over a secure internet site The trial is open-label with blinded end point
Outcome measures	Primary: Comparison of cognition (Addenbrooke's Cognitive Examination extended to include death) between 'intensive' and 'guideline' BP/lipid lowering groups Secondary: Other cognitive assessments; Quality of life; Vascular events; Functional outcome; Depression; Death
Statistical methods	Outcomes will be analysed by multiple regression, ordinal logistic regression and binary logistic regression, depending on the measure, with adjustment for baseline stratification and minimisation variables

ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Addenbrooke's Cognitive Examination
AE	Adverse Event
ALLHAT	Anti Hypertensive and Lipid Lowering Treatment to Prevent Heart Attacks Trial
ALT	Alanine transaminase
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
AVM	Arterio-venous malformation
BHS	British Hypertension Society
BP	Blood Pressure
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subacute infarcts and Leukoencephalopathy
CI	Chief Investigator
CT	Computer axial Tomography (scan)
CRF	Case Report Form
DMC	Data Monitoring Committee
ENOS	Efficacy of Nitric Oxide in Stroke
EMEA	European Medicines Agency
GCP	Good Clinical Practice
HR	Heart rate
HOT	Hypertension Optimal Treatment Trial
IQCODE	Informant Questionnaire on Cognition Decline in the Elderly
HDL	High Density Lipoprotein
LDL/LDL-c	Low Density Lipoprotein-cholesterol
MI	Myocardial Infarction
MMSE	Mini mental status examination
MR	Magnetic Resonance Imaging Scan
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute of Clinical Health and Excellence
NINDS	National Institute of Neurological Disorders and Stroke
OCSP	Oxford Community Stroke Project
Od	Once daily
On	At night
OAST	Optimising Analysis of Stroke Trials collaboration
OAST-Cog	Optimising Analysis of Stroke Trials-Cognition collaboration
P/GIS	Parent / Guardian Information Sheet
PI	Principle Investigator
PICH	Primary Intracerebral Haemorrhage
PIN	Postal Index Number
PIS	Participant Information Sheet
PP	Pulse Pressure
PRoFESS	Prevention regime for effectively avoiding second strokes Study
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study

REC	Research Ethics Committee
R&D	Research and Development department
RR	Relative Risk
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SHEP	Systolic Hypertension in Elderly Program
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
STU	Stroke Trials Unit
Syst-Eur	Systolic Hypertension in Europe Trial
TC	Total Cholesterol
TG	Triglycerides
TMC	Trial Management Committee
TOAST	Trial of Org 10172 in Acute Stroke Treatment Trial
TSC	Trial Steering Committee

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1 BACKGROUND INFORMATION AND RATIONALE

1.1 INTRODUCTION

Stroke and dementia are common, economically costly to society, and devastating to patients and their family. Hence, their combined effect is catastrophic. 30% of people develop dementia after stroke (post stroke dementia, PSD) and 50% of people with dementia have significant cerebrovascular disease, with UK annual care costs close to £30 billion. Despite this, the evidence base for the prevention of cognition decline and dementia post-stroke is negligible, perhaps because:

- People with stroke and dementia are a disadvantaged group who attract little medical interest
- Cognitive and physical disability reduces medication compliance

Elevated BP and cholesterol are common after stroke. There is good trial evidence and guideline support for blood pressure [1] and cholesterol [2] lowering treatment to prevent recurrent vascular events. As a result, most patients with a previous stroke need to receive life-style advice and have their BP lowered, and those with ischaemic stroke usually need a statin. Although BP-lowering post-stroke may reduce cognitive decline and dementia (PROGRESS, secondary outcomes [3, 4]) there is little evidence, so far, that lipid lowering is effective in preventing cognitive decline after stroke. Critically, it is unknown whether BP and cholesterol should be lowered intensively rather than more modestly as per guidelines.[5]

The PODCAST study will counter this negativity by:

- Actively seeking out people with stroke who are at risk of cognitive decline
- Aiming to reduce post stroke cognitive decline by ~20%
- Concentrating on ensuring compliance with management regimes
- Empirically testing the feasibility and applicability of therapeutic strategies for optimising BP and cholesterol control

The trial may offer the last opportunity to test these questions. Conclusive evidence that intensive BP/lipid lowering prevents cognitive decline would benefit patients, carers and society, and influence clinical management.

1.2 CURRENT MEDICAL LITERATURE

1.2.1 Blood pressure lowering

There are no definitive strategies for preventing post-stroke cognitive decline or dementia. High BP is a risk factor for stroke recurrence, and lowering BP, not just treating hypertension, reduces recurrence and other vascular events after ischaemic stroke and PICH.[1, 3] Midlife high BP is associated with dementia in later life.[6]

The results of those BP trials that studied cognition are confounded as:

- Cognition was only ever a secondary outcome
- Various cognitive outcome measures were used
- Most studies included patients at relatively low risk of developing cognitive decline
- Trials had relatively short follow-up (0.5-4.5 years) although observational studies suggest that treatment may be needed for >5 years

Figure 1: Effect of antihypertensive agents on cognitive decline; data from 3 randomised controlled trials: Syst-Eur, SCOPE and PROGRESS (MRC Older and SHEP did not provide appropriate data for inclusion).

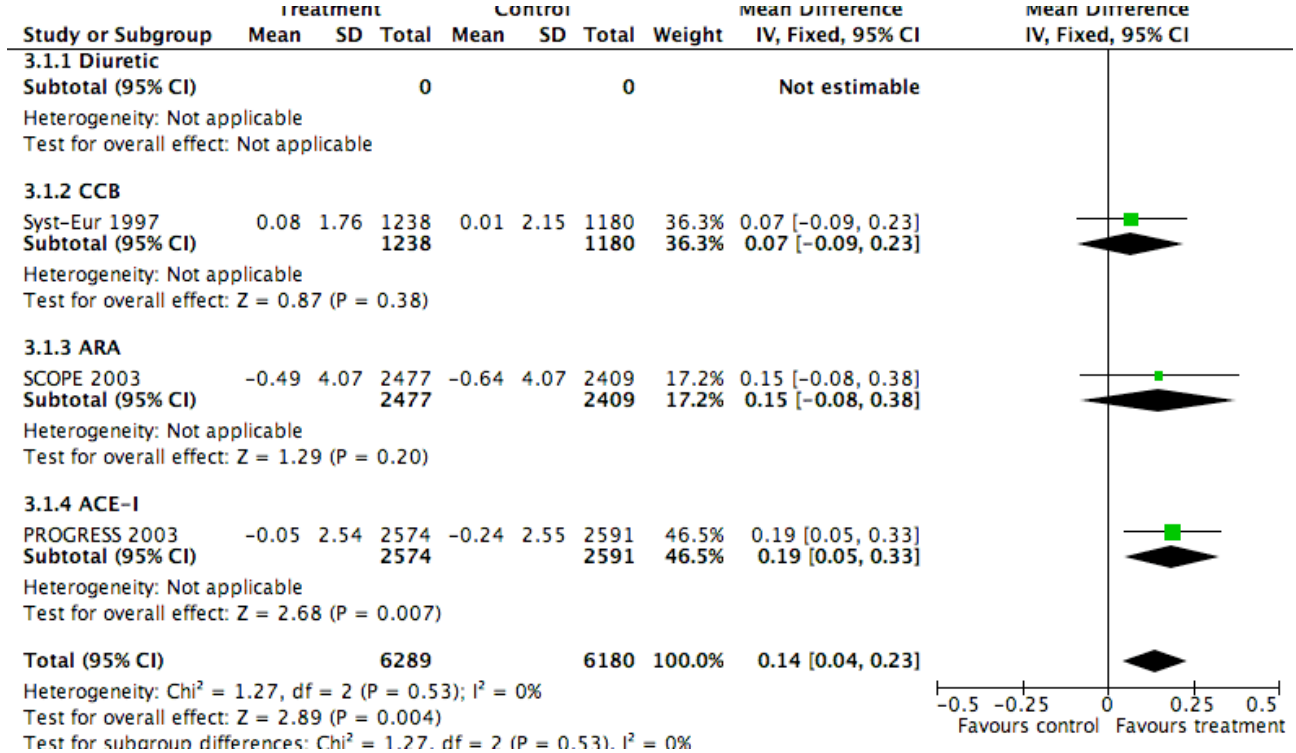
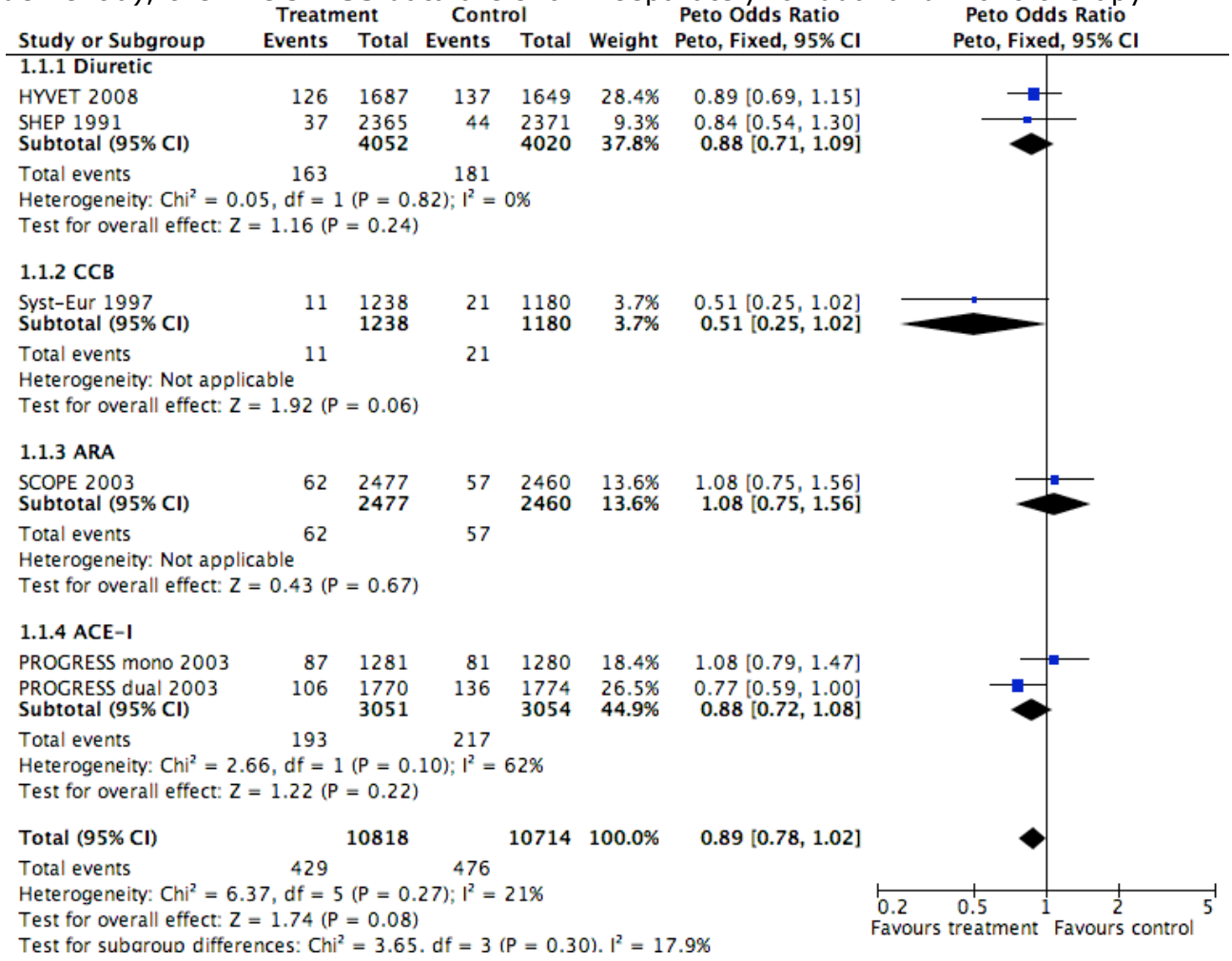


Figure 2: Effect of antihypertensive agents on all dementia; data from 4 randomised controlled trials: SHEP, Syst-Eur, SCOPE and PROGRESS (MRC Older did not report dementia); the PROGRESS data are shown separately for dual and mono therapy.



Older trials (SHEP, MRC Older [7, 8]) were neutral and newer ones (Syst-Eur, SCOPE, PROGRESS [4, 9, 10]) positive for cognitive outcomes.[11]. Overall, lowering BP was associated with reduced cognitive decline (weighted mean difference 0.14, 95% CI 0.04-0.23, p=0.004, 3 trials; Bath, unpublished, figure 1) and a trend to reduced dementia (RR 0.89%, 95% CI 0.77-1.04, p=0.13, figure 2).

The likely driver for reductions in cognitive impairment is the magnitude of fall in BP as the relative risk reduction (RRR) for dementia was associated with the difference in diastolic BP between active and control treatment groups (rs=0.95, p=0.014; Bath, unpublished); a similar relationship exists for reductions in systolic BP and secondary stroke.[1]

In the 2008 PRoFESS trial (n=20,332), final cognition (MMSE 27.3 vs. 27.4) and post stroke dementia (PSD, 4.7 vs. 4.7%), as well as stroke and vascular events, did not differ between telmisartan and placebo; however, BP difference was small (3/2 mmHg) and follow-up short (2.5 years). BP lowering (indapamide with/without perindopril) was associated with trends to reduced cognitive decline (MMSE, HR 0.93, 95% CI 0.82-1.05) and dementia (HR 0.86, 95% CI 0.67-1.09) in the 2008 HYVET trial in the very elderly (n=3,845).[7] Although BP difference was large (15/6 mmHg);

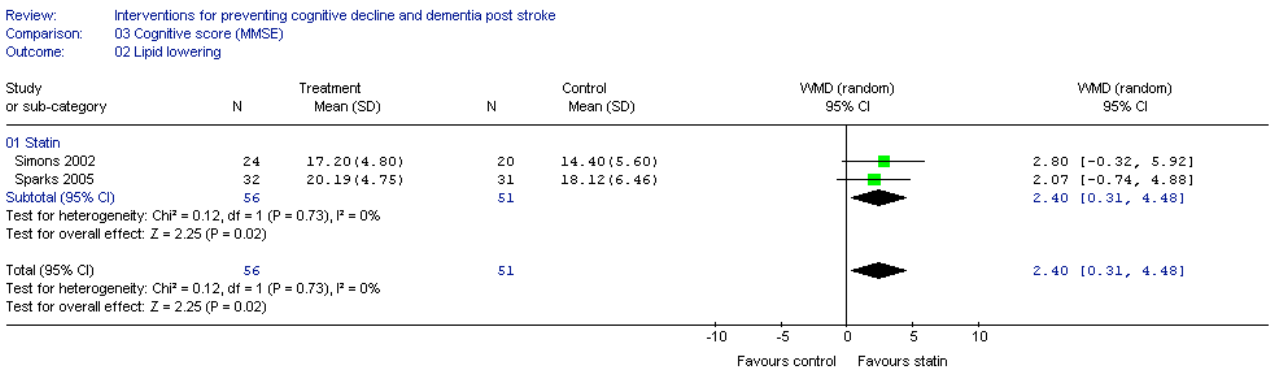
follow-up was, again, short at 2 years so that effects on cognition were probably under-estimated.

However, the intensity of lowering BP on cognition has not been studied. HOT (n=18,790) did not achieve its 5 mmHg differences in target diastolic BP (3 treatment groups).[8] In the PROGRESS trial, patients with previous stroke who took 2 BP agents (perindopril, indapamide) rather than 1 (perindopril) had larger reductions in BP (-12/-5 vs. -5/-3 mmHg), stroke risk (primary outcome, RRR 43 vs. 5 %) and 'all dementia' (secondary outcome, RRR 23% vs. RRR -8%), as compared with control.[3, 4] However, patients were not assigned randomly to dual/mono therapy so treatment intensity was not compared directly. Critically, no large antihypertensive trial has set out to assess the effect of BP lowering on cognition as the primary outcome. Intensive BP lowering may have additional benefits, e.g. improved well-being,[9] and appears to be safe and effective in preventing recurrence.[10]

1.2.2 Lipid lowering

High cholesterol is a risk factor for ischaemic stroke. Lowering cholesterol with a statin prevents stroke in patients with vascular disease (pravastatin, simvastatin) [11] or an elevated C-reactive protein (rosuvastatin), vascular events in patients with prior stroke (simvastatin),[12, 13] and stroke recurrence (atorvastatin).[2] Lowering cholesterol could reduce cognitive decline and dementia, in part by preventing stroke, but the evidence to date is limited; cross-sectional, prospective and case control studies are conflicting.[14] Of 3 small trials of statins in patients with Alzheimer's Disease (AD), 2 suggested efficacy [15, 16] (figure 3) and one found no effect (LEADe, n=600). The results of large randomised control trials have not found significant effects of statins on cognition (HPS, PROSPER);[12, 17, 18] however, these studies involved individuals with modest high cholesterol and low risk of developing cognitive decline. ALLHAT-LLA, ASCOT-LLA & SPARCL did not assess lipids and cognition.[2, 19]

Figure 3: Effect of statins on cognition (MMSE) in 2 small randomised controlled trials. The varied reporting of cognition/dementia (absolute score, change scores, z-scores, differing scales, qualitative results) mean that it is not possible to assess all the trials together.



1.3 ONGOING TRIALS

Few ongoing trials are addressing blood pressure and lipid management on cognition. A PRoFESS [20] sub-study with detailed cognitive assessment in 600 patients will be published in 2009 (Chief Investigator=Ford). SPS3 is assessing anti-platelet and BP-lowering strategies (SBP<130 vs. <150 mmHg) on stroke recurrence in patients with sub-cortical infarcts (n=2,500); cognition over 3 years is a secondary outcome and patients with cortical infarcts or haemorrhage are excluded (http://clinicaltrials.gov/ct/show/NCT00059306).[21] A small statin (simvastatin) trial has recently been completed in Alzheimer's disease (CLASP, n=400) (http://clinicaltrials.gov/ct2/show/NCT00053599). We are not aware of ongoing BP/lipid trials aiming to prevent cognitive decline as the primary outcome.

2 TRIAL OBJECTIVES AND PURPOSE

2.1 PURPOSE

Develop interventions to prevent cognitive decline and dementia after stroke.

2.2 PRIMARY OBJECTIVE

To determine if 'intensive' blood pressure lowering therapy, and/or 'intensive' lipid lowering therapy, after stroke reduces cognitive decline and dementia.

2.3 SECONDARY OBJECTIVES

To determine if 'intensive' blood pressure lowering therapy, and/or 'intensive' lipid lowering therapy, after stroke reduces poor quality of life, poor function, depression, stroke recurrence, vascular events, and death.

3 TRIAL DESIGN

3.1 TRIAL CONFIGURATION

PODCAST is a multi-centre, prospective, randomised, open-label, blinded end-point, controlled, partial-factorial, phase IV trial. It will be performed in two phases: start-up and main.

The start-up phase will assess feasibility in the UK:

- Delivering the protocol
- Recruiting 30+ centres and 600 participants
- Achieving and maintaining differences in systolic BP (≧10 mmHg) and LDL-cholesterol (≧1 mmol/l) between the 'intensive' and 'guideline' treatment groups
- Performing clinic and telephone follow-up of outcome measures
- Assess the sensitivity of ACE to change
- Tolerability and safety of interventions

The main phase will assess efficacy with recruitment from both UK and international centres. Participants enrolled in the start-up phase will continue to be followed during the main phase. The trial is being discussed with other countries (including those taking part in the ongoing ENOS trial,[22] as well as France). Separate ethical review and permission will be sought in each participating country.

3.2 TRIAL OVERVIEW

The aim of the proposed trial is to determine if routine BP and lipid lowering therapy after stroke should be based on 'intensive' rather than 'guideline' interventions. The trial will run for 8 years with the start-up phase running for 3 years (recruitment in the first 2 years) and the main phase for a further 5 years.

The start-up phase will recruit 600 participants from 30+ UK Stroke Research Network Centres. Assuming a 'go' decision at 34 months based on start-up feasibility, as assessed by data collected from the start-up phase, the trial will seamlessly proceed into the main phase with the same design for a further 5 years. The main phase will aim to recruit a further 2,800 participants from across 100 sites internationally. Separate permission for funding from the appropriate bodies will be sought for the second phase (as done in the ENOS trial ISRCTN 99414122 with funding moving from BUPA Foundation to MRC).

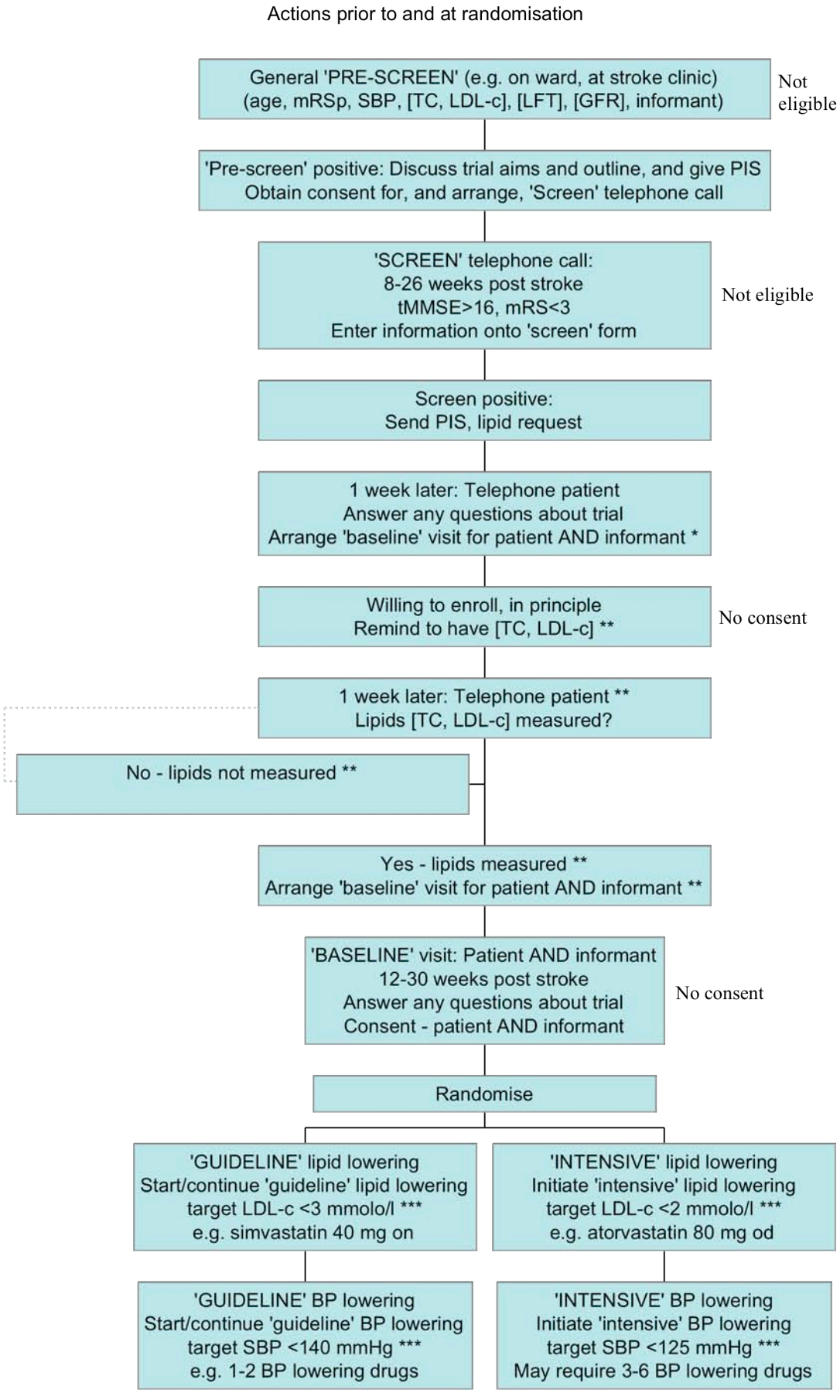
Participants with confirmed ischaemic stroke or PICH 3-7 months post event who satisfy the inclusion and exclusion criteria will be randomised to the 'intensive' or 'guideline' BP management group over a secure internet web site after informed consent is taken. Participants with an ischaemic stroke (but not PICH) will be randomised to the 'intensive' versus 'guideline' lipid-lowering arm as well.

Algorithms, which will take account of NICE stroke, hypertension, and lipid and type 2 diabetes guidelines, will aid investigators so that participants are treated as randomised. The 'intensive' BP lowering regime will aim for a SBP <125 mmHg, and the 'guideline' regime a SBP <140 mmHg. The 'intensive' cholesterol-lowering group will aim for a target LDL cholesterol <2.0 mmol/l (or total cholesterol <4.0 mmol/l if LDL-cholesterol cannot be calculated), and the 'guideline' group a target LDL-cholesterol of <3.0 mmol/l (or total cholesterol <5.0 mmol/l if LDL-cholesterol cannot be calculated). The number of drugs and/or doses in the 'intensive' group will be escalated on review at the hospital research; moderate care group will be managed as per current standard care by their GPs.

Cognition and other outcome data will be collected at baseline and in the research clinic annually. An interim analysis will be performed at the end of the start-up phase. Separate funding will be sought to perform systematic neuro-imaging in a subset of participants. CT/MR images from the index stroke will be adjudicated using a derivative of the MRC NeuroGrid system.[23]

If the overall trial is positive for one or both 'intensive' interventions, then they can be implemented readily and inexpensively in the UK since the treatments are available and will be off patent.

3.2.1 Trial Flow Chart



3.2.1.1 Trial Flow Chart Key

Acronyms		Inclusion criteria
BP	Blood pressure	-
GFR	glomerular filtration rate	>60
LDL-c	LDL-cholesterol (fasting)	-
LFT	liver function test	ALT≤60
mRS	modified Rankin Scale	<3
mRSp	pre-morbid modified Rankin Scale	<3
PIS	Patient Information Sheet	-
SBP	systolic blood pressure	125-170 mmHg
TC	total cholesterol (fasting)	3-8 mmol/l
tMMSE	telephone Mini Mental State Examination	>16/22

*	Only applies to patients with primary intracerebral haemorrhage
**	Only applies to patients with prior ischaemic stroke
***	See management algorithms

3.3 OUTCOMES

3.3.1 Primary outcome measure

For each of BP-lowering and lipid-lowering arms, comparison between 'intensive' and 'guideline' groups, of cognition assessed using the Addenbrooke's Cognitive Examination[24], (a superset of the Mini-Mental State Examination, MMSE [25]).

3.3.2 Secondary outcome measures

For each of BP-lowering and lipid-lowering arms, comparison between 'intensive' and 'guideline' groups:

1. Dementia
    a. Using AD - NINCDS/ADRDA [26] and VaD - NINDS-AIREN [27]
    b. With/without recurrent stroke
2. Cognition
    a. Global – MMSE, tMMSE,[28] TICS [29]
    b. Association – trail making A/B [30, 31]
    c. STROOP test [31]
    d. Cognitive decline with/without recurrent stroke
    e. Ordinal cognition (MMSE>28/23-28/10-22/<10/dementia/dead)
    f. Informant (IQCODE) [32]
3. Quality of life – EuroQoL[33], informant (DEMQoL) [34]
4. Depression (Zung) [35, 36]
5. Dependency (modified Rankin Scale, mRS) [37, 38]
6. Disability (Barthel Index, BI) [38, 39]
7. Stroke recurrence
8. Myocardial infarction
9. Composite vascular events (non-fatal stroke, non-fatal MI, fatal vascular)

10. Stroke: fatal/severe non-fatal/mild/TIA/none[40]
11. Myocardial infarction: fatal/non-fatal/angina/none[40]
12. Vascular: fatal/non-fatal/none [40]
13. New diabetes
14. New atrial fibrillation
15. Residence (home, institution), care package, informal family support
16. Blood pressure (systolic BP, diastolic BP, pulse pressure, rate-pressure product)
17. Lipids (TC, TG, HDL, calculated LDL)
18. Neuroimaging (in a subset of participants)

3.3.3 Safety outcome measures

Comparison between 'intensive' and 'guideline' BP/lipid lowering groups:
1. Death
2. Falls (leading to fracture or hospitalisation)
3. Postural hypotension
4. Myositis
5. SAEs

3.4 RANDOMISATION AND BLINDING

3.4.1 Randomisation

All participants eligible for inclusion and for whom consent has been obtained will be randomised centrally using a secure internet site in real-time. Randomisation will be performed using:
1. Stratification on stroke type (ischaemic stroke/PICH) and country
2. Minimisation on key prognostic/logistical baseline factors:
    a. Age (<70/$\geq$70 yrs)
    b. Sex (female/male)
    c. Stroke side (left/right)
    d. Dysphasia, mild (no/yes)
    e. MMSE (>28/$\leq$28)
    f. SBP (<140/$\geq$140 mmHg)
    g. Total cholesterol (<5.0/$\geq$5.0 mm)
    h. Diabetes (diet-tablets/insulin)
    i. Function/dependency (mRS<1/$\geq$1)
    j. Imaging method (CT/MR)
    k. Brain region (subcortex/cortex)
    l. Leukoaraiosis (no/yes)
    m. Time since index stroke (<4/$\geq$4 months)
    n. Number of antihypertensive drugs (<2/$\geq$2)
    o. Already on a statin (no/yes)

This approach ensures concealment of allocation, minimises differences in key baseline variables, and slightly improves statistical power.[41]

In the event that the website cannot be accessed, participants may be randomised by telephoning one of a series of emergency telephone numbers. These participants will be randomised without stratification or minimisation.

3.4.2 Blinding

PODCAST is a trial of BP and lipid management post-stroke. Hence, it is not placebo-controlled and neither participants nor investigators will be blinded to treatment. However, outcome assessment will be assessed blinded to treatment assignment.

3.5 DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

Centre identification, national/local approvals and development of trial materials will be obtained before funding for the start-up phase commences to allow early recruitment. During the 3 year start-up phase, participants will be recruited over 2 years (300 participants per annum from 30 UKSRN sites = 1 participant/site/month) with average follow-up 2 years (minimum 1 year). The start-up phase will demonstrate the trial feasibility (protocol, centre/participant recruitment, intervention tolerability, and effects on BP and lipids, clinic and central follow-up, early safety – see section 3.2). Main phase funding will sought at 18 months. Assuming a 'go' decision at 34 months (based on start-up feasibility and funding), the trial will seamlessly run into the main phase with centre expansion and increased recruitment rate). The trial, including both start-up and main phases, will run for 8 years. Participant involvement in the trial will range from 1-8 years depending on the time of recruitment (long follow-up is essential in trials of cognition since cognitive impairment may take many years to develop)

3.5.1 Timelines

3.5.1.1 *Start-up phase*

Time (months)	-6-0	0-2	3-6	7-18	19-24	25-30	31-36
Protocol	<>						
Approvals	<>						
Trial materials	<>						
Site identification	<	=	>				
Funding, TSA/AS		<	=	=	=	=	>
Recruit participants		<	=	=	>		
DMC reviews			<	=	=	=	>
Feasibility reviews				<	=	=	>
Interim analysis (blinded)							<>

3.5.1.2 *Main phase*

Time (months)	37-42	43-48	49-54	55-60	61-66	67-72	73-78	79-84	85-90	91-96
Further site identification	<	=	=	=	>					
Funding (source to be identified		<	=	=	=	=	>			
Recruit participants	<	=	=	=	>					
DMC reviews	<	=	=	=	=	=	=	=	>	
Final data cleaning								<	=	>
Analysis										<>

Nb; Participants enrolled in the start-up phase will continue to be followed up in the main phase.

3.5.1.3 *Participant measures*

Time (months)	Screen	0	1	3	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Inclusion	+																			
Consent		+																		
Randomise		+																		
CT/MR	†									‡										
Clinic																				
BP	+	+	+	+	+		+		+		+		+		+		+		+	+
ABPM ‡		+			+		+													
Lipids	+	+		+	+		+		+		+		+		+		+		+	+
Cognition	+	+			+		+		+		+		+		+		+		+	+
Stroke, MI					+		+		+		+		+		+		+		+	+
SAEs		+	(+)	(+)	+		+		+		+		+		+		+		+	+
Informant		+			+		+		+		+		+		+		+		+	+
Telephone																				
Cognition						+		+		+		+		+		+		+		
Stroke, MI						+		+		+		+		+		+		+		
SAEs			+	+		+		+		+		+		+		+		+		

† Clinical scan for index stroke; ‡ In participating centres and patients

ABPM: Ambulatory Blood Pressure Monitoring; BP: blood pressure

3.6 SELECTION AND WITHDRAWAL OF PARTICIPANTS

3.6.1 Recruitment

Participants will be recruited from hospital-based stroke services. The initial approach will be from a member of the participant's usual care team (which may include the investigator and/or research nurses).The investigator or their nominee, e.g. from the usual care team (including research team), will inform the participant about the trial and a participant information sheet will be provided. Initial consent will be taken from participants at this point of contact for telephone assessment of cognition (telephone-mini mental status examination) and function (modified Rankin scale) at 8-26 weeks post-stroke. On the basis of these assessments of cognition and function, the trial aims and outline will be discussed with the participant who can then consider joining the trial.

If eligible and interested, a patient information sheet will again be posted to the participant; a blood test request form (for cholesterol measurement) will also be posted for those participants whose index stroke was of ischaemic type. Participants will be contacted a week later to assess their views and questions about the trial.

If they have agreed, participants with ischemic stroke will be asked to have the blood test (for cholesterol) done at their GP surgery (with the posted blood test form). All participants and their informant will be booked to come to the research clinic for further discussion about the trial and, if agreeable, enrolment and randomisation into the study.

3.6.2 Inclusion criteria

1. Age >70 years and telephone-MMSE >16; or age >60 years and telephone-MMSE 17-19
2. Functionally independent (mRS 0-2)
3. Ischaemic stroke (any cortical OCSP/TOAST type) or primary intracerebral haemorrhage (cortical or basal ganglia)
4. 3-7 months post-event (to allow cognitive,[42] neurological, BP and lipid[43] stabilisation, but avoid attrition)
5. Systolic BP 125-170 mm Hg
6. Total cholesterol 3-8 mmol/l
7. Presence of a reporter: partner, sibling, child, friend (for IQCODE/DEMQoL)
8. Capacity and willingness to give consent

3.6.3 Exclusion criteria

1. Participants not meeting inclusion criteria
2. Subarachnoid haemorrhage
3. Secondary intracranial haemorrhage (trauma, AVM, cavernoma)
4. Posterior circulation ischaemic stroke
5. Posterior circulation haemorrhage
6. No CT/MRI during index stroke

7. Inability to give consent or do study measures, e.g. severe dysphasia, weakness of dominant arm
8. Severe hypertension (systolic BP>170 mmHg)
9. Definite need for 'intensive' BP control;
10. Severe hypercholesterolemia (TC>8 mmol/l)
11. Definite need for 'high intensity' statin or ezetimibe
12. Definite need for a cholinesterase inhibitor
13. Familial stroke associated with dementia, e.g. CADASIL
14. Chronic renal failure: GFR<50
15. Liver disease, ALT>60
16. Ongoing participation in trials involving drug and/or devices, or within the last 3 months.

3.6.4 Informed consent

All participants must have capacity and be willing and able to provide written informed consent. Participants will be screened for potential recruitment during their initial presentation to the hospital stroke service, Initial informed consent will be taken from participants at this point of contact for telephone assessment of cognition (telephone-mini mental status examination) and function (modified Rankin scale) and a blood test for cholesterol at 8-26 weeks post-stroke. A patient information sheet will also be provided explaining about the study. On the basis of these assessments of cognition and function, the trial aims and outline will be discussed with the participant who can then consider joining the trial.

If eligible and interested, a patient information sheet will again be posted to the participant. Participants will be contacted a week later to assess their views and questions about the trial. All participants and their informant will be booked to come to the research clinic for further discussion about the trial and, if agreeable, enrolment and randomisation into the study.

In the research clinic the investigator will further explain the details of the trial and answer any questions that the participant has concerning trial participation.

The principal investigators and trial doctors of the research team will decide if participants have the capacity to give consent at baseline. They will be given some training in assessing capacity at the investigator meeting. Participants will be asked the following series of questions to assess their understanding of the trial before taking consent.

1. What is the trial aiming to achieve? (Answer: if intensive treatment of high blood pressure and cholesterol will prevent cognitive decline)

2. What are the two groups of intervention? (Answer: intensive and standard care)

3. How long will treatment be continued? (Answer: 1-8 years)

Potential participants who answer all the 3 questions correctly will be enrolled into the study. A signed and dated informed consent will then be taken before the participant is recruited into the trial.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the trial. Signed consent forms will be kept by the Participant and Investigator, and in the participant's hospital records. The GP will be informed if the participant agrees to join the trial.

As cognitive decline is one of the objectives of the trial, it is expected and perhaps inevitable that some participants will lose the capacity to maintain consent for the trial. All participants will be asked at enrolment, if they would agree to continue in the study, should they lose the capacity to maintain consent during the study period. For such participants, consent to continue in the study will be obtained from the relative, who will be made aware of the participants wishes at enrolment.

If needed, the usual hospital interpreter and translator services may be used to assist with discussion of the trial, the participant information sheets, and consent forms. But consent forms and information sheets will not be available printed in other languages since it will not be possible to do telephone or clinic outcome assessments in other languages. It will be explained to the potential participant that entry into the trial is entirely voluntary and that routine treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that existing data cannot be erased; consent to use this data in the final analyses will be sought, where appropriate.

Should there be any major amendments to the protocol that might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form, which will be signed by the participant.

3.6.5 Informant

Availability of an informant (partner, sibling, child, friend) for the participant is a key inclusion criterion in the trial, as informant questionnaires (IQCODE/DEMQoL) can give vital information about the participant's cognition. Also as explained above, it is likely some participants may develop cognitive decline and lose the ability to give information or maintain consent during the trial. Participants will be asked to identify more than one informant, in case the first informant is unable to perform their role due to any reason.

3.6.6 Expected duration of participant participation

Trial participation will range from 1- 8 years depending on the time of recruitment. Long follow-up is essential in trials of cognition since cognitive impairment may take many years to develop.

3.6.7 Removal of participants from therapy or assessments

Participants may leave the trial for a variety of reasons, as detailed below. It should be noted that abrupt termination of trial treatment could affect the participant's safety (e.g. hypertensive rebound) and administration of alternative treatment should be considered.

3.6.7.1 *Withdrawal of consent*

Participation in the trial is voluntary and participants are free to withdraw from the trial at any stage without giving a reason. However, if a participant wishes to withdraw (or the relative, if the participant has lost capacity to maintain consent), they will be requested to at least permit primary outcome data to be collected, ideally at the end of the follow-up period, ensuring that enough data are recorded to support the planned analysis. Participants won't be accepted as lost to follow-up unless all attempted contacts have been fruitless, including: phone calls, letters, visits to their home, contact with their next of kin, and contact with their GP. Participants will be made aware (via the information sheet and consent form) that should they withdraw, the data collected up to the date of withdrawal cannot be erased and may still be used in the final analysis.

3.6.7.2 *Clinical need*

The participant's primary physician is not blinded to treatment allocation and may remove, change or add to treatment if they feel this is clinically indicated (e.g. for reasons of safety or new information becoming available on the trial medication or condition being treated).

3.6.7.3 *Failure of participant to adhere to protocol requirements*

The Principal Investigator may remove the participant from the trial if they fail to adhere to the protocol through ***protocol violations*** and/or ***protocol deviations***, and will be reported to the Chief Investigator of the trial centre.

3.6.7.3.1 *Protocol Violation*

A **protocol violation** is a deviation from the trial protocol where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria, or where deviations from the protocol could affect the trial delivery or interpretation significantly.

The following baseline measures constitute a 'protocol violation':

- Participant <60 years of age
- telephoneMMSE <17
- No index stroke
- Randomisations <3 months or >7 months from onset of index stroke
- Failure to obtain consent or assent of participant
- Participant with mRS >2
- Failure to identify haemorrhagic stroke
- Participant enrolled with *known* severe concomitant illness
- Participant enrolled with *known* intracranial pathology other than stroke
- Participant involved at time of randomisation in another medicinal and/or devices clinical trial
- No brain imaging during index stroke event
- No reporter/informant
- No capacity to consent for the trial

- Failure to meet the systolic BP inclusion criteria
- Failure to meet the total cholesterol inclusion criteria
- Absence of a informant: partner, sibling, child, friend (for IQCODE/DEMQoL)

The following practice during the trial constitutes a 'protocol violation':

- Participant continues to receive 'guideline' BP lowering therapy when randomised to 'intensive' therapy
- Participant continues to receive 'guideline' lipid lowering therapy when randomised to 'intensive' therapy
- Failure to complete SAEs where appropriate
- Annual clinic/telephone assessments are not performed

3.6.7.3.2 *Protocol Deviation*

A ***protocol deviation*** is a minor deviation from the protocol that affects the conduct of the trial in a minor way. This includes any deviation from the trial protocol that is not listed as a protocol violation.

The following practice during the trial constitute a 'protocol deviation'

- Participant has no cranial imaging if they have another stroke
- Clinic or telephone assessments done outside the specified time by more than 30 days.
- Participant is not fully compliant with randomised treatment

3.7 TRIAL TREATMENT AND REGIMEN

The trial will assess management strategies ('intensive' vs. 'guideline'), not particular drugs. Algorithms taking account of NICE guidelines relating to Stroke (CG68), Hypertension (CG34), Lipids (CG67) and type 2 diabetes (CG66) will aid investigators in treatment decision-making so that participants are treated as randomised. All participants will receive lifestyle advice. Medications for participants randomised to the standard groups will be prescribed by the GP as per national/international guidelines. Medications for participants in the intensive groups will be initiated by either the local investigator or GP (following advice from the local investigator), and continued by the GP.

The blood pressure and cholesterol levels will be monitored by the research team. For the intensive group this will involve research clinic visits at one and three months after randomisation. It will include BP measurement at both clinic visits and blood test for cholesterol at 3 months (for participants randomised to the intensive cholesterol lowering arm). The research clinic staff will then suggest dose/drug escalation/weaning based on the BP/lipid algorithms to the GP who will prescribe these medications. A member of the PODCAST international coordinating centre staff will monitor achieved BP and lipids over the database in individual participants, unblinded to therapy, and suggest changes to the local investigator/GP to ensure that BP/lipid levels are appropriate for the participant's randomised management group. All participants will have regular central telephone reminders to reinforce treatment assignment.

3.7.1 BP lowering strategy

Antihypertensive drugs will be chosen according to the NICE/BHS 'A (B)/CD' guideline (CG34) where:[44]

- A = angiotensin converting enzyme inhibitor (ACE-inhibitor, e.g. perindopril 2-8 mg od) or angiotensin receptor antagonist (ARA, e.g. losartan 25-100 mg od, candesartan 8-32 mg od)
- B = ß-receptor antagonist (e.g. atenolol 25-100 mg od, propranolol LA)
- C = calcium channel blocker (e.g. amlodipine 5-10 mg od, nifedipine LA 30-60 mg od, diltiazem, verapamil SR)
- D = diuretic (e.g. bendroflumethiazide 2.5 mg od, hydrochlorothiazide 12.5 mg od)

Participants should be started on either (provided there are no contraindications):

- An 'A' drug, with subsequent addition of a 'C' then 'D' drug (as required); or
- A 'C' drug, with subsequent addition of an 'A' then 'D' drug (as required)

Additional drugs may be added from other classes:

- Potassium sparing diuretics (e.g. spironolactone 25-100 mg od,[45] amiloride 5-20 mg od)
- α-receptor antagonists (e.g. doxazosin XL 4-16 mg od)
- Centrally acting drugs (e.g. moxonidine 200-400 µg od-bd)
- 'B' drugs (e.g. atenolol 25-100 mg od)

Investigators may choose to increase the dose of existing drugs (although this can be associated with adverse events and only moderate further reductions in BP) or add drugs from additional classes. 'Long acting' drugs should be chosen in preference to those which need twice/thrice daily dosing. A detailed algorithm as described in Section 3.7.1.3 for managing BP will be provided to investigators. An updated algorithm, if felt necessary based on new information about blood pressure management, may be provided to investigators as a working practice document.

The composition of antihypertensive agents will vary between participants since the drugs are often used for other indications (e.g. 'A'/'B' post MI) and have contraindications (e.g. avoid 'A' in bilateral renal artery stenosis, avoid 'B' in asthma). The aim is to maintain a difference in SBP >10 mmHg between the randomised treatment groups of 'intensive' versus 'guideline' BP management.

3.7.1.1 *'Intensive' BP treatment group*

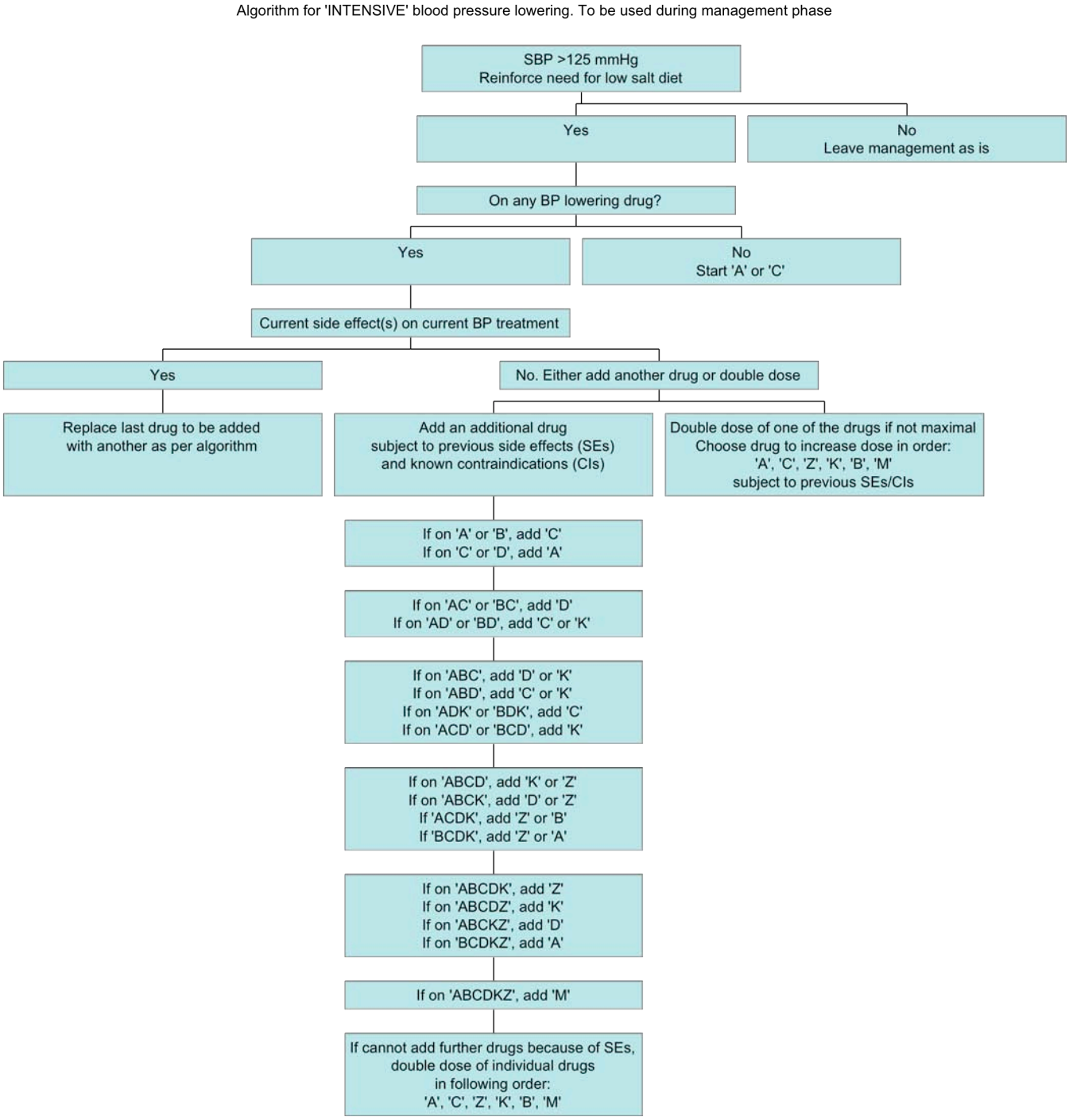
The target is a systolic BP (SBP) of <125 mmHg. Participants will receive specific advice on salt restriction. They will be followed up in the research clinic to monitor BP at one and three months after randomisation. The research clinic staff will then prescribe medications as per the treatment algorithm, or alternatively in some circumstances pass on suggested management plan to the GP, who will be asked to prescribe these medications.Intensive escalation is vital to ensure a difference in BP between the treatment groups is achieved; care will then be handed over to general practice. Drugs will be weaned down if SBP <110 mmHg. A member of the International Coordinating centre staff will monitor recorded BP over the database in individual participants, unblinded to therapy, and suggest changes to the GP/local investigator to ensure that BP levels are appropriate for participant's randomisation.

3.7.1.2 *'Guideline' (standard-of-care) group*

The aim is a target SBP <140 mmHg (NICE CG 34). Drug therapy will typically include an 'A' and/or 'D' agent.[3] Drug does/numbers will be increased to achieve the target, particularly if SBP >160 mmHg, with monitoring/treatment in general practice to reflect current community-based practice based on national/international guidelines.

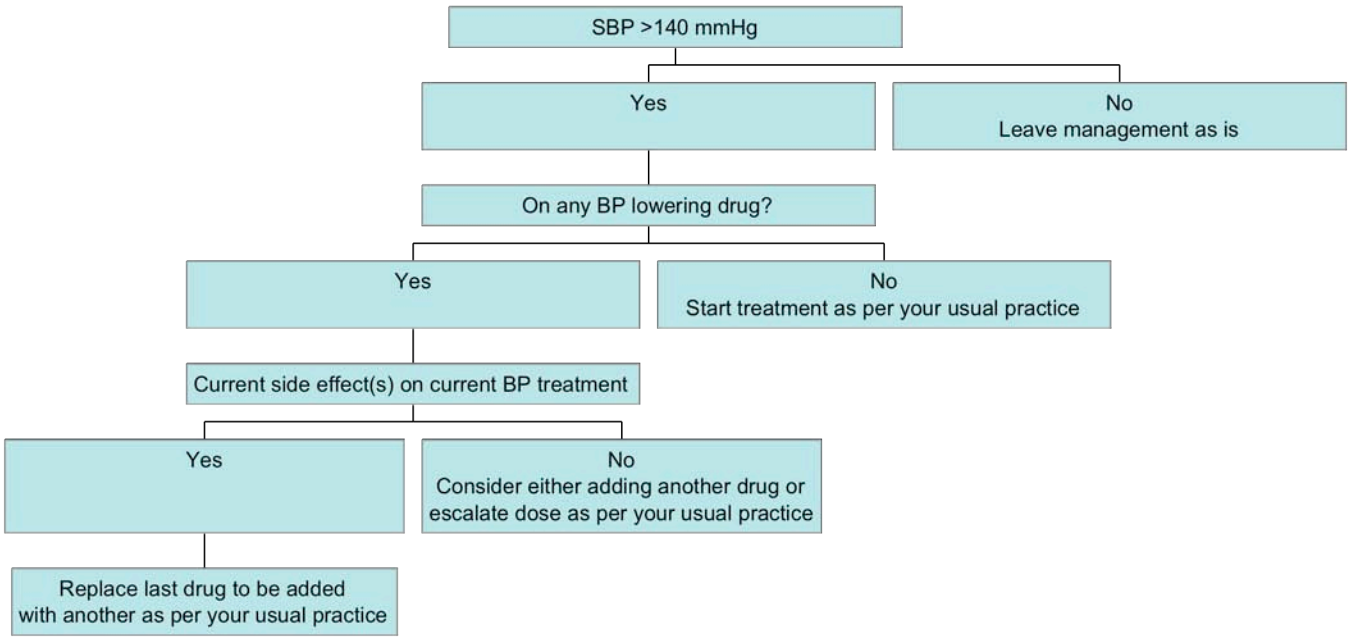
3.7.1.3 BP Treatment Algorithms

3.7.1.3.1 Intensive BP treatment algorithm



3.7.1.3.2 *Guideline BP Treatment Algorithm*

Algorithm for 'GUIDELINE' blood pressure lowering. To be used during management phase



3.7.1.3.3 Legend for blood pressure lowering algorithms

A: angiotensin converting enzyme inhibitor (ACE-I), e.g.
perindopril 2 mg od (range 2, 4, 8 mg od)
ramipril 2.5 mg od (range 1.25, 2.5, 5, 10 mg od)

A: angiotensin receptor antagonist (ARA/ARB), e.g.
losartan 50 mg od (range 25, 50, 100 mg od)

B: ß-receptor antagonist (ß-RA), e.g.
atenolol 50 mg od (range 25, 50, 100 mg od)
bisoprolol 10 mg od (range 5, 10, 20 mg od)

C: calcium channel blocker (CCB), e.g.
amlodipine 5 mg od (range 5, 10 mg od)
nifedipine MR/LA 20 or 30 mg od (range 20, 30, 40, 60 mg od)

D: diuretic, e.g.
bendroflumethiazide 2.5 mg od (max 2.5 mg od)
frusemide 40 mg od (range 20, 40, 80 mg od)

M: centrally active drug, e.g.
moxonidine 200 µg od (max 400 µg od)

K: potassium-sparing diuretic, e.g.
spironolactone 25 mg od (range 25, 50 mg od)
amiloride 10 mg od (range 5, 10, 20 mg od)

Z: alpha-receptor antagonist, e.g.
doxazosin MR/XL 4 mg od (then 8 mg od, max 16 mg od)

3.7.1.3.4 Notes for blood pressure lowering for use in PODCAST trial

- Start drugs at the dose given above. The dose may be increased 2-4 weeks later for additional BP effect although side effects become more prominent as doses tend to the maximum.
- Start with the lowest dose in very elderly patients or those with heart failure.
- Alternatives to the suggested drugs listed above may be used according to local practice and formulary availability.
- Consider escalating drug doses in between trial visits so as to accelerate control of blood pressure, i.e. write prescriptions with 2-4 weeks of one dose then with the next dose up.
- Always treat clinical dehydration/hypovolaemia before adding drugs or increasing doses so as to avoid significant hypotension.
- If 'A' or 'K' are added, check renal function (U&E) after 1 week.
- Specific drug classes may be indicated according to the presence of co-morbidities:
    - Post myocardial infarction – consider 'A' and/or 'B'
    - Diabetes mellitus – consider 'A'
- Specific drug classes are contra-indicated in the presence of known co-morbidities:
    - Asthma – avoid 'B'
    - Renal artery stenosis (bilateral if 2 kidneys, unilateral if 1 kidney) – avoid 'A'
- Consider referring compliant patients with uncontrolled/partially controlled high BP (i.e. SBP>160 on 3 or more BP lowering agents) to a specialist Hypertension clinic for specific investigation of secondary causes.
- If cough or angioedema develops on ACE-I, switch to angiotensin receptor antagonist (ARA), e.g. losartan.
- If bronchospasm develops on 'B', switch to another drug class as per management algorithm.
- If eGFR <60 after addition of 'A', stop 'A' and use alternative algorithm strategy.
- If potassium >5.0 mmol/l after addition of 'A', stop 'A' and use alternative algorithm strategy.
- If potassium >5.5 mmol/l after addition of 'K', stop 'K' and use alternative algorithm strategy.
- If sodium <130 mmol/l after addition of 'D', stop 'D' and use alternative algorithm strategy.
- Significant postural hypotension may occur if adding 'A' to 'D'. .
- Do not use rate limiting 'C' (verapamil) with 'B' (ß-RA).
- If uncertain, always check in the hospital/community/national drugs formulary regarding doses, indications and contra-indications.

3.7.1.4 *Blood pressure measurement*

As a central aim of this trial is to ascertain the effect of lowering blood pressure immediately post stroke, it is vital that BP is measured in an accurate, reproducible, unbiased, and validated manner. Measurements made using routine ward/clinic mercury or aneroid sphygmomanometers, or most semi-automatic devices, are not sufficient in these respects.

All BP measurements should be performed using an Omron 705CP or 705CP II automated blood pressure monitor. This device has been validated by the British

Hypertension Society,[46] in contrast to some other automated devices which have not been found to be accurate or reliable, and is the monitor used in the recent positive ASCOT hypertension trial involving 20,000 patients.[47] Baseline systolic and diastolic blood pressure and heart rate data are taken in triplicate (3 measurements taken in rapid succession) in the non-paretic arm and readings entered on the baseline form. Subsequent blood pressures should be measured in duplicate (2 readings taken in rapid succession) in the non-paretic arm with the participant sitting. BP and heart rate readings should be printed out using the Omron printer and attached to the Omron 'print-out' sheet. The times of last antihypertensive drug ingestion and BP measurement will be recorded on the clinic forms. Two Omron monitors will be supplied to each centre and should only be used for participants in the PODCAST trial. BP monitors will be checked by staff from the PODCAST International Coordinating Centre during site visits; if broken or inaccurate, the monitor will be recalibrated or replaced.

3.7.1.5 *Ambulatory blood pressure monitoring (ABPM)*

In centres with the necessary ambulatory blood pressure monitoring equipment (e.g. SpaceLabs 90207), participants will have 24 hour ABPM [48] performed at recruitment and on treatment at 1 and 2 years. ABPM data will provide detailed information on:

- BP and heart rate (HR) levels on treatment
- BP and HR profile over 24 hours (peak and trough effects)
- BP and HR variation (standard deviation)

ABPM data will be printed out and faxed to the PODCAST International Coordinating Centre. Other haemodynamic variables are also related to stroke and recurrence and these will be derived from BP and HR:[49, 50]

- Pulse pressure (PP) = Systolic BP – diastolic BP
- Mean arterial pressure (MAP) = Diastolic BP + (PP / 3)
- Rate-pressure product (RPP) = Systolic BP x HR

Data will be analysed with adjustment for baseline measurements.

3.7.1.6 *Treatment of sustained severe high BP*

If participants develop severe high BP (systolic BP >160 mmHg), treatment should be increased as per the BP algorithm.

3.7.1.7 *Treatment of sustained low/low normal BP*

If participants develop symptomatic low BP (systolic BP <120 mmHg), treatment should be weaned down as per the BP algorithm. This will normally involve stopping the last added drug (i.e. 'last in/first out').

3.7.2 Cholesterol lowering strategy (ischaemic stroke only)

Cholesterol lowering agents will include statins and ezetimibe, e.g. as per UK NICE guidelines.[51-53] Only participants with an ischaemic stroke will be included in this comparison since statins may be associated with intracerebral haemorrhage [54] due

to mild antiplatelet properties. The aim is to maintain a difference in LDL-cholesterol >1.0 mmol/l between the treatment groups.

3.7.2.1 *'Intensive' lipid treatment group*

Start with a 'high intensity' statin (e.g. atorvastatin 80 mg,[2, 51] rosuvastatin 40mg [51, 53]) and give advice to take a plant stanol/sterol spread on bread. They will be reviewed in the research clinic at 3 months.

Treatment algorithms (see section 3.7.2.3) will guide investigators in achieving target cholesterol levels. An updated algorithm, if felt necessary based on new information about cholesterol management may be provided as a working practice document. The research clinic staff will escalate treatment with ezetimibe (10 mg od [52]) if LDL-cholesterol >2.0 (or total cholesterol >4.0 mmol/l if LDL-cholesterol cannot be calculated), or alternatively in some circumstances pass on suggested management plan to the GP, who will be asked to prescribe these medications. . This intensive escalation is vital to ensure that a difference of >1.0 mmol/l in LDL-cholesterol is achieved between the treatment groups.

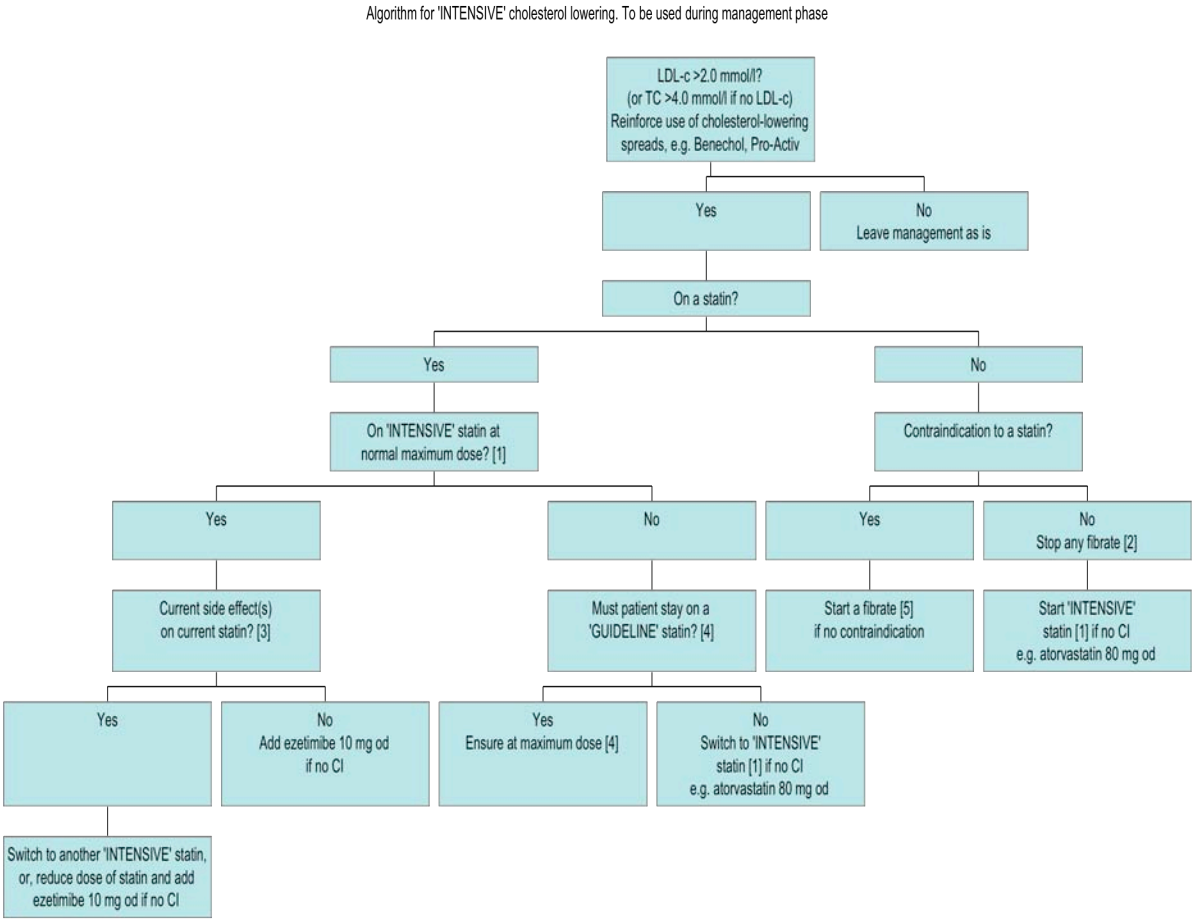
3.7.2.2 *'Guideline' (standard-of-care) group*

Start with a 'guideline' statin (e.g. simvastatin 40 mg on,[12] pravastatin 40 mg on, fluvastatin 40 mg on - see NICE lipid guideline CG 67, 2008 [51]).

This might include doubling the dose (e.g. simvastatin to 80 mg on) if LDL-cholesterol >3.0 mmol/l (or total cholesterol >5.0 mmol/l if LDL-cholesterol cannot be calculated).

3.7.2.3 *Treatment Algorithms*

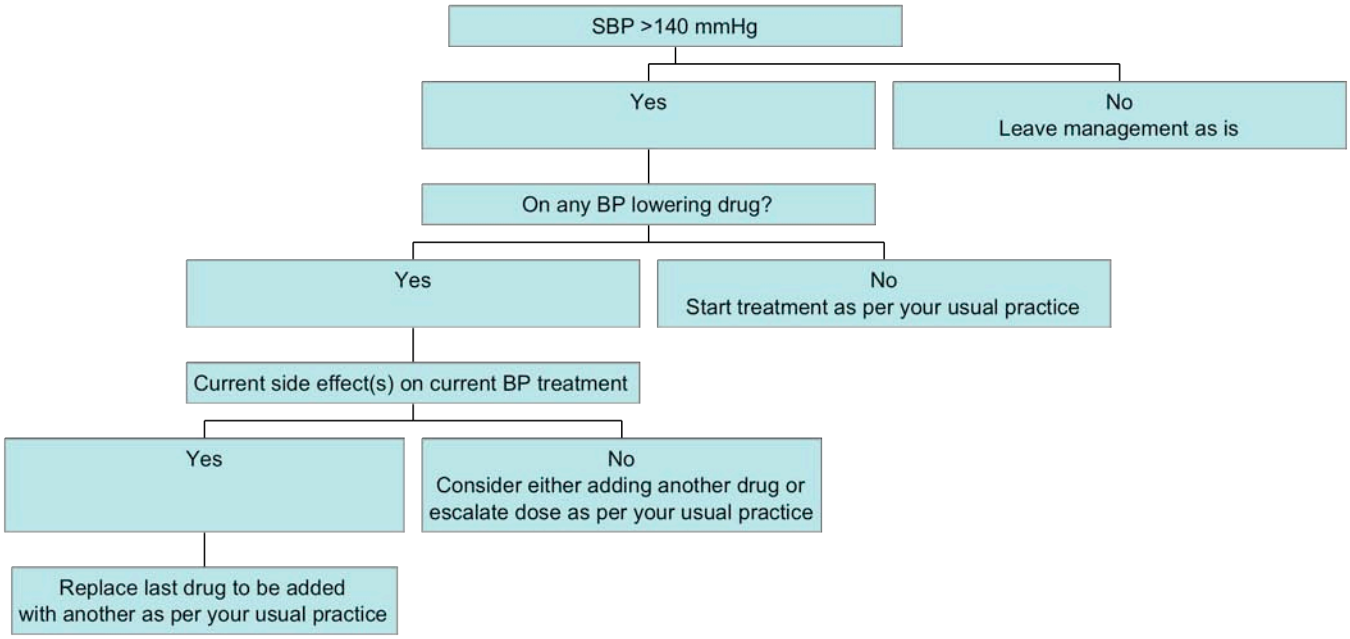
3.7.2.3.1 Intensive Cholesterol Lowering Algorithm



1. 'Intensive' statins: atorvastatin, rosuvastatin.
2. Taking statins and fibrates together can cause rhabdomyolysis.
3. Statin side effects include myositis, headache, liver dysfunction (rarely hepatitis), paraesthesia, gastrointestinal effects (abdominal pain, flatulence, constipation, diarrhoea, nausea and vomiting), rash, and hypersensitivity reactions (including angioedema and anaphylaxis).
4. 'Guideline' statins: simvastatin, pravastatin, fluvastatin
5. Fibrates include bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil.

3.7.2.3.2 Guideline Cholesterol Lowering Algorithm

Algorithm for 'GUIDELINE' blood pressure lowering. To be used during management phase



1. Guideline statins: simvastatin, pravastatin, fluvastatin
2. Simvastatin and fluvastatin may each be taken at 80 mg on; pravastatin should not be used at 80 mg

3.7.2.4 Lipid measurement

Fasting lipids will be measured at an (provisionally) accredited Clinical Biochemistry laboratory proximal to the local centre and GP. Fasting should be performed overnight and at least 1 month after the last change in lipid lowering therapy. Lipid measurement will utilise standard techniques:

- Total cholesterol
- Triglyceride
- HDL cholesterol
- LDL cholesterol (calculated)

3.7.3 Other secondary vascular prophylaxis

All participants with stroke should receive standard life style advice and rehabilitation (as per NICE CG 68, 2008)[55], including:

- Diet – calorie, salt, alcohol
- Exercise
- Smoking cessation
- Rehabilitation (e.g. physiotherapy, occupational therapy, speech & language therapy, as required
- Psychological assessment and therapy

All participants with ischaemic stroke should receive standard secondary prophylaxis (as per NICE CG 68, 2008)[55], including:

- Antiplatelet agents (e.g. combined aspirin 50-81 mg od and dipyridamole MR 200 mg bd)
- Carotid endarterectomy for ipsilateral severe internal carotid artery stenosis

All concomitant treatments will be documented on the CRF and also in the participant's medical record, including any changes to these treatments.

3.7.4 Monitoring interventions

A member of the National Coordinating Centre staff will monitor recorded BP and lipids in individual participants, unblinded to therapy, and suggest dose/drug escalation/weaning based on the BP/lipid algorithms to the local investigator/GP. Their aim will be to ensure that BP/lipid levels are appropriate for the participant's randomisation.

The Trial Management Committee will monitor BP and lipid levels, and treatment crossovers, by treatment assignment, unblinded to therapy. The TMC will report to the Trial Steering Committee at least 4 monthly on the magnitude of separation in BP and lipid levels between the treatment groups. The DMC will also report to TSC on their observations of separation in BP and lipid levels between the treatment groups. [Note: It is acceptable for trialists to un-blind themselves to surrogate outcomes such as BP to ensure that trial protocols are working, as done in HOT [56, 57] and MRC ENOS.[22]]

3.7.5 Blood Biomarkers and Pharmacogenetics Sub-study

Tertiary questions in PODCAST include assessing the effects of the interventions on blood biomarkers, and by participant's genotype. These blood measures are optional. Centres who wish to participate in the blood biomarker study should have appropriate storage facilities including access to a centrifuge and freezer.

Blood samples will be taken at baseline (4 ml into EDTA, 8 ml clotted). If it is not possible to take a blood sample at enrolment, both clotted (8 ml) and EDTA (4 ml) samples will be taken during a follow-up clinic visit. Clotted (serum) samples should be centrifuged prior to freezing; the EDTA samples should be frozen without centrifugation. Blood samples should be anonymised (identifiable by the centre number, participant trial number, participant initials, and date of sample) and stored locally in a freezer at -20^{o}C (or lower if possible at -60^{o}C to -80^{o}C) and accounted for using the Blood Sample Freezer Log. The PODCAST International Coordinating Centre at Nottingham will arrange transfer of blood samples to Nottingham UK, for analysis. Blood samples will be destroyed once analysis is completed, this being dependent on the trial's completion date.

3.7.5.1 Soluble markers of outcome and efficacy

The exact identity of blood biomarkers will depend on developing knowledge on what may most usefully be measured. Examples include markers of vasomotor activity, lipid metabolism, thrombosis and inflammation.

3.7.5.2 Genetic studies

The exact identity of genetic markers also will depend on developing knowledge o what may most usefully be measured. Examples include genes related to Apo-E, mechanism of action of drugs, lipid metabolism, thrombosis and inflammation.

The consent forms will allow the participant to opt-in to the genetic sub-study. Participants may continue in the trial, even if they elect not to consent to the genetics sub-study. The participant may request destruction of the genetic samples at any time after consent and prior to creation of an anonymised database.

3.7.6 Neuroimaging Sub-Study

Cerebral white matter lesions (WML) have been associated with cognitive impairment in demented and non demented elderly subjects. Whether lesion progression parallels this decline over time and whether treatment can modify this is less clear.

Separate funding is being sought to perform systematic neuro-imaging in a subset of participants. All participants will be invited to take part in the imaging sub study. All participants will have a base line scan (done as part of routine clinical care at or soon after the index stroke), and is an inclusion criteria for the study. Participants will have an additional scan, as part of the imaging sub-study at the end of 3 years. An MRI scan of the brain will be the preferred imaging method for the additional scan, as it is more informative of cognitive change. However, where MRI cannot be performed, a CT scan of the brain will be done. A typical x-ray dose for a CT brain scan is 1.5 msv, but due to variation in protocols, machines and patient sizes, this could be as much as 5mSv per scan.

The consent forms will allow the participant to opt-in to the neuro-imaging sub-study. Participants may continue in the trial, even if they elect not to consent to the neuro-imaging sub-study.

3.8 STATISTICS

A medical statistician will support the TSC with analyses. A blinded interim analysis will be done during the start-up phase to demonstrate feasibility of the trial, recruitment of centres and participants, whether sufficient on-treatment differences in BP and lipids are obtained and maintained, and whether cognition is being assessed satisfactorily.

3.8.1 Minimisation of bias

As the trial is based on management strategies, placebo-control is not relevant. Sources of bias will be minimised with:

- Central randomisation/concealment of allocation/data registration with real-time validation using an internet-based database
- Blinded telephone/clinic assessment of cognitive/vascular outcomes
- Blinded central adjudication of cognition/dementia and vascular events
- Assessment of participant recall of treatment groups ('intensive', 'standard') at end of trial
- Exclusion of participants enrolled in other drug trials
- Analysis by intention-to-treat with adjustment for stratification/minimisation factors, number of BP-lowering treatments and use of ezetimibe

3.8.2 Methods of analysis

3.8.2.1 Primary outcome

Comparison of cognition (ACE extended to include death) between 'intensive' and 'guideline' BP/lipid lowering groups. The proportion of participants with cognitive decline or who have died will be compared between the treatment groups, as done previously for MMSE (a subset of ACE).[4, 12]

Analyses will be adjusted for baseline stratification variables:

- Stroke type (ischaemic stroke, PICH)
- Country

And minimisation variables:

- Age (<70/≥70 yrs)
- Sex (female/male)
- Stroke side (left/right)
- Dysphasia (no/yes)
- MMSE (>28/≤28)
- SBP (<140/≥140 mmHg)
- Total cholesterol (<5.0/≥5.0 mm)
- Diabetes (diet-tablets/insulin)
- Function/dependency (mRS<1/≥1)
- Imaging method (CT/MR)
- Brain region on imaging (subcortex/cortex)
- Leukoaraiosis on imaging (no/yes)
- Time since index stroke (<4/≥4 months)
- Number of antihypertensive drugs (<2/≥2)
- Already on a statin (no/yes)

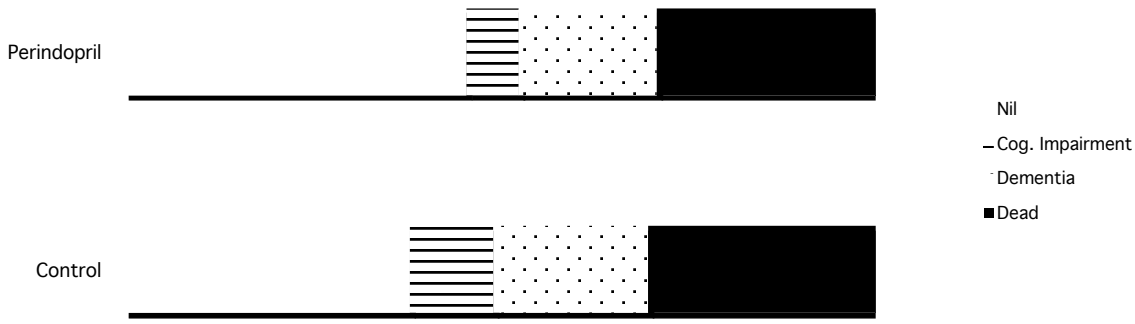
3.8.2.2 Analysis of cognition data

Analyses based on binary outcomes are likely to be sub-optimal since dichotomisation of ordered categorical or continuous data is statistically inefficient, as seen in the 'Optimising Analysis of Stroke Trials' collaboration for functional outcome after stroke.[58]

As a result, we are comparing, in the 'Optimising Analysis of Stroke Trials-Cog' collaboration (OAST-Cog), ordinal and binary approaches using individual patient data from existing vascular trials where cognition was recorded; if this shows that ordinal approaches are statistically more efficient, we will change the analysis of cognition to

use such an approach. Figure 4 illustrates how an ordered categorical scale may be created from cognition data.

Figure 4: Ordinal cognition scale using data from PROGRESS[16, 59]. 2000 patients without cognitive impairment (of the total ~3,300 patients) have been removed from each treatment group to make the illustration of cognition more clear. Perindopril-based BP lowering shifted patients from dementia/dead to no or some cognitive dysfunction (Mann-Whitney U, p=0.021, Bath P, unpublished).



Methods of analysing cognition vary considerably. We have set up an international collaboration using existing BP/cholesterol-cognition trial data to optimise statistical approaches (as we did with stroke [58, 60]) with comparison of:

- Gradient [59]
- Mean cognition [15, 16, 61]
- Median cognition
- Mean change in cognition [17, 61-64]
- Ordinal cognitive score (figure 4)

Analysis of the primary outcome will use the optimum approach once this has been identified. Additionally, techniques will be compared for dealing with participants who die:

- Assign MMSE=-1
- Use last cognition score carried forward
- Calculate gradient of cognition scores,[59] assuming both linear and curvilinear models
- Create and ordered categorical scale from data on cognition, dementia and death (figure 4)

Dementia will be analysed as:

- Proportions [4]
- As part or an ordered categorical scale (figure 4)

Differential dropouts will also be assessed.[65]

3.8.2.3 *Other outcomes*

Secondary and safety outcomes will be analysed using multiple regression, ordinal logistic regression or binary logistic regression, depending on the type of data. Where possible, dichotomous outcomes will be converted into ordinal outcomes (as in figure

4). Analyses will be adjusted for the covariates as listed in section 3.8.2.1since this approach increases statistical power [66] and is recommended by EMEA ('Points to consider').

3.8.3 Sample size and justification

3.8.3.1 *Start-up phase*

Recruitment of 600 participants (300/BP group, ~270/statin group) will be sufficient to demonstrate adequacy in recruitment of centres and participants, whether sufficient on-treatment differences in BP and lipids can be obtained and maintained, and whether cognition can be assessed satisfactorily. No formal sample size calculation is relevant to this part of the trial.

3.8.3.2 *Main phase*

Currently, ACE will be analysed as cognitive decline using binary approaches (although this will, hopefully, be changed to an ordinal analysis as discussed in section 3.8.2.2). The whole trial (start-up + main phases) will need a sample size of 3,400 (1,700 per group) post-stroke participants, assuming:

- Significance, α = 5%
- Power (1-ß) = 90%
- Rate of cognitive decline in guideline' BP group = 25% at 5 years (main trial, average length of follow-up 4 years) [34]
- Rate of cognitive decline in 'intensive' BP group = 20%, i.e. absolute risk reduction (ARR) = 5% (number-needed-to-treat = 25), relative risk reduction (RRR) = 20%
- Losses to follow-up = 3%

Hence, 765 participants (0.225 x 3,400) will need to develop cognitive decline. The sample size allows a smaller but clinically worthwhile decline in cognitive decline to be identified with 80% power, i.e. ARR = 4.5% (RRR 18%). Since there are less existing data on the effect of cholesterol lowering on cognition, the statin factor will assume the same RRR (20%) but have less power (~86%) since it will only involve participants with ischaemic stroke (~3,060).

Changing from a binary to ordinal analysis of the primary outcome will allow a reduction in sample size of almost 30%, as seen in the 'Optimising Analysis of Stroke Trials' collaboration for functional outcome after stroke.[60] Providing ordinal analysis appears to be more efficient than binary analysis for cognition data, the trial will be re-sized according to the method of Whitehead.[67] Any such change will be performed blinded to treatment.

3.8.4 Definition of populations analysed

3.8.4.1 Safety Set

All randomised participants.

3.8.4.2 *Full Analysis Set (FAS)*

All participants in the Safety Set, and who took at least one treatment dose, and for whom at least one post-baseline assessment of the primary endpoint (MMSE) is available.

3.8.4.3 *Per Protocol Set (PPS)*

All participants in the Full Analysis Set, and who are deemed to have no ***protocol violations*** (i.e. no severe deviations that might have interfered with the objectives of the trial).

3.8.4.4 *Analyses*

Efficacy will be assessed using the ***Full Analysis Set***; secondary analyses will also assess efficacy in the ***Per Protocol Set***. Safety summaries will be performed on the ***Safety Set***. Major protocol deviations will lead to exclusion of a participant from the ***Per Protocol Set***.

3.8.5 Health economic analysis

The impact of 'intensive' BP and lipid lowering on quality of life will be assessed using the EuroQoL. A full health-economic analysis will be performed as part of the main trial and will include costs of dementia/cognitive impairment, costs of excess treatment, cost/event (cognitive decline) prevented and cost/QALY.

3.8.6 Potential analysis issues

3.8.6.1 Falling event rates

As seen in vascular prevention trials (often requiring more participants) - the main issue in cognition/dementia studies is to ensure long follow-up, i.e. 5 years, so that cognition has time to decline.

3.8.6.2 Adequate BP/lipid effects

The only large intensity BP trial (HOT [56, 57]) did not achieve its target BP differences. The start-up phase will check that differences in BP/lipids can be maintained; participants will receive reminders about treatment during each clinic and telephone follow-up. Secondary observational analyses will assess the relationship between individual changes in BP/lipids and cognition.

3.8.6.3 Guideline drift

Guidelines may change over the life of the trial such that guideline BP and lipid targets could be reduced with time. In contrast, cost and participant resistance to taking multiple interventions may oppose this trend. The trial will monitor and adapt to such drift if detected.

3.8.6.4 Analysis of cognition

Methods for analysing cognition vary considerably and those using binary approaches may be sub-optimal. We have set up an international collaboration using existing BP/cholesterol-cognition trial data to optimise statistical approaches, as discussed in section 3.8.2.2, which will improve statistical efficiency thereby allowing a reduction in sample size.

3.9 ADVERSE EVENTS

3.9.1 Definitions

3.9.1.1 Adverse Event

An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.

3.9.1.2 Adverse reaction

An adverse reaction (AR) is any untoward and unintended response in a participant to drug which is related to any dose administered to that participant.

3.9.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or reaction occurring following trial-mandated procedures, having received BP and/or lipid lowering therapy that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalisation or prolongation of existing hospitalisation
- A disability / incapacity
- A congenital anomaly in the offspring of a participant
- Important medical events – these are events which are not fatal, life-threatening, or require hospitalisation, but nevertheless may jeopardise the participant and may require medical or surgical intervention to prevent one of the other outcomes listed above

3.9.1.4 Suspected Unexpected Serious Adverse Reactions (SUSAR)

SUSARs are serious adverse reactions, which are serious (as defined for SAEs), and unexpected (i.e. they are not recognised reactions for the trial medications).

3.9.1.5 *Serious versus severe adverse events*

A distinction is drawn between serious and ***severe adverse events***. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe adverse event need not necessarily be serious (e.g. most severe headaches are not serious). Adverse events will not be recorded since the management interventions are based on lifestyle changes, and licensed drugs with considerable trial and post-marketing data.

3.9.2 Causality

3.9.2.1 *Not related or improbable*

Clinical event, including laboratory test abnormality, with a temporal relationship to trial treatments which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation. This will be counted as 'unrelated' for notification purposes.

3.9.2.2 *Improbable*

Clinical events, including laboratory test abnormalities, with a temporal relationship to trial treatments which makes a causal relationship unlikely, or for which other treatments, chemicals or disease provide a plausible explanation. This will be counted as 'unrelated' for notification purposes.

3.9.2.3 *Possible*

Clinical events, including laboratory test abnormalities, with a temporal relationship to trial treatments which makes a causal relationship a reasonable possibility, but which could also be explained by other treatments, chemicals or concurrent disease. This will be counted as 'unrelated' for notification purposes.

3.9.2.4 *Probable*

Clinical events, including laboratory test abnormalities, with a temporal relationship to trial treatments, which makes a causal relationship a reasonable possibility, and is unlikely to be due to other treatments, chemicals or concurrent disease. This will be counted as 'related' for notification purposes.

3.9.2.5 *Definite*

Clinical events, including laboratory test abnormalities, with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as 'related' for notification purposes.

3.9.3 Recording and Safety Reporting

3.9.3.1 Adverse events

AEs will not be recorded or reported due to their high incidence in stroke patients.

3.9.3.2 Adverse Reactions

All ARs listed in the British National Formulary for individual drugs (antihypertensive and cholesterol lowering drugs) used by participants will be recorded in the trial database, but not reported to regulatory authorities. It is important to record ARs, since they will influence blood pressure and/or cholesterol management strategies as

per the guiding algorithms. A list of recognized ARs associated with blood pressure and cholesterol lowering drugs will be given in a working practice document; this will be updated as necessary

3.9.3.3 SAEs related to Stroke

Stroke is a disease with high morbidity and mortality, and several adverse events may occur during a patient's participation in the trial. So the following expected SAE'S will be recorded in the trial database but not reported to regulatory authorities. This list is a guide, and will be updated through a working practice document on the trial website (so that protocol amendments are not required)

3.9.3.3.1 Cardiovascular

Acute coronary syndrome
Atrial fibrillation
Cardiac failure
Cardiac arrhythmias
Collapse
Deep vein thrombosis (DVT)
Hypotension
Myocardial infarction
Pulmonary embolism

3.9.3.3.2 Central Nervous System

Depression
Haemorrhagic transformation of infarct
Intracerebral bleed
Recurrent stroke
Seizures - fit, epilepsy, blackout
Transient ischaemic attack (TIA)

3.9.3.3.3 Gastro-intestinal

Gastrointestinal bleed
Genito-urinary
Incontinence, urinary
Urinary retention – urinary disturbance
Urinary tract infection (UTI) - haematuria

3.9.3.3.4 Respiratory

Chest infection
Pneumonia
Pulmonary embolism (PE)
Bronchospasm
Exacerbation of COPD (emphysema and chronic bronchitis)

3.9.3.3.5 Miscellaneous

Bacteraemia - septicaemia
Extracranial bleeding (not GI haemorrhage)
Fall
Infection (not otherwise specified, non chest, non UTI)

3.9.3.4 SARs

As the trial is testing management strategies, not individual drugs, adverse reactions that are serious will be recorded on the trial database, but not reported to the regulatory authorities.

3.9.3.5 Suspected Unexpected Serious Adverse Reactions (SUSAR)

As the trial is testing management strategies, not individual drugs, and due to the long established nature of these drugs, SUSARs are not collected and recorded specifically, except as part of the recording of serious adverse reactions. However investigators are free to report adverse reactions/serious adverse reactions to national agencies as they wish, e.g. through the Commission of Human Medicines Yellow Card pathway (www.yellowcard.gov.uk) in the UK.

3.9.4 SAE adjudication

All SAEs will be recorded and monitored until resolution, stabilisation, or until it has been shown that the trial treatment is not the cause. Such SAE' should be completed within one week of investigators being aware of the event. Likely causality will be entered.

For SAEs, the Chief Investigator and SAE adjudicator(s) shall:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- Make any amendments as required to the trial protocol and inform the REC as required

3.9.5 Participant removal from the trial due to adverse events

Any participant who experiences an AE or SAE may be withdrawn from treatment at the discretion of the Principal Investigator, or at the request of the participant. However there are usually alternative treatments for reducing blood pressure and cholesterol, which may be used instead of a particular drug causing an AE/SAE. Hence it should usually be possible to avoid withdrawing a participant from treatment. If patients do withdraw from treatment, ideally they should stay in the trial for the purposes of follow up.

3.10 TRIAL MANAGEMENT

3.10.1 Sponsor

The University of Nottingham is the trial sponsor in the UK and will delegate responsibility for design and conduct of the trial to the Chief Investigator via our Sponsor/Chief Investigator agreement. The sponsor contact details are

Mr Paul Cartledge
Head of Research Grants and Contracts
Research Innovation Services
King's Meadow Campus, Lenton Lane

Nottingham, NG7 2NR UK

3.10.2 Coordinating Centre

The Stroke Trials Unit (STU), part of the University of Nottingham's Clinical Trials Unit (which has provisional registration), will co-ordinate the trial. STU will have overall responsibility for the conduct of the trial and will be responsible for provision of trial materials, collation and analysis of data and reporting of the final results. They will act as the International Coordinating Centre, UK National Coordinating Centre, and the primary point of contact for UK centres.

Stroke Trials Unit
Division of Stroke Medicine
University of Nottingham
Clinical Science Building
City Hospital campus
Nottingham, NG5 1PB UK

Tel: +44 115 823 1769
Fax: +44 115 823 1771

3.10.3 Trial Steering Committee (TSC)

The TSC will provide overall supervision, as per their charter, and ensure that the trial is conducted in accordance with the principles of the ICH GCP and the relevant regulations. Any amendments to the trial will be agreed by the TSC. The TSC will provide advice to the investigators on all aspects of the trial.

3.10.4 Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) will monitor efficacy and safety as per their charter. As well as outcome measures, the DMC will also review recruitment, baseline data, balance in baseline factors between the treatment group, completeness of data, compliance to treatment, co-administered treatments, and outcome by sub groups. They will also review all serious adverse events (both adjudicated and unadjudicated) and protocol violations. The DMC will usually meet at least yearly by teleconference; the chairman will receive 6 monthly updates from the statistician.

We will use a similar Data Monitoring Committee charter for electively stopping the trial that is agreed for the MRC ENOS trial. (Please see section 3.11.6)

3.10.5 Event adjudication committees

There will be 2 committees, one adjudicating cognitive decline and dementia, and the other stroke/vascular events. The committees will follow their respective charters.

3.10.6 Serious Adverse Event adjudication

SAEs will be assessed blinded to treatment group(s) by members of the SAE adjudication committee.

3.11 ETHICAL AND REGULATORY ASPECTS

3.11.1 Ethics Committee and regulatory approvals

The trial will not be initiated before the protocol, informed consent forms, and participant and GP information sheets have received approval / favourable opinion from the UK Multi Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets have been reviewed and received approval/favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice (GCP), and the UK Department of Health Research Governance Framework for Health and Social care, 2005.

3.11.2 Informed consent and participant information

The process for obtaining participant informed consent will be in accordance with REC guidance, GCP, and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the trial.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the hospital notes that informed consent was obtained for the trial.

The decision regarding participation in the trial is entirely voluntary. The investigator or their nominee shall emphasise to them that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

As cognitive decline is one of the objectives of the trial, it is expected and perhaps inevitable that some participants will lose the capacity to maintain consent for the trial. All participants will be asked at enrolment, if they would agree to continue in the study, should they lose the capacity to maintain consent during the study period. For

such participants, consent to continue in the study will be obtained from the relative, who will be made aware of the participants wishes at enrolment.
.
The investigator will inform the participant or the relative, of any relevant information that becomes available during the course of the trial, and will discuss with them whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

3.11.3 Records

3.11.3.1 Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRFs, other trial documents, and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or middle name initial when available) and age.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record, in a separate participant database, of the: participant's name, date of birth, local hospital number or NHS number, address, telephone number, relative/friend's contact details, and Participant Trial Number, to permit identification of all participants enrolled in the trial, so that follow-up may be performed. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log'.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out, but not obliterated with correction fluid, and the correction inserted, initialled and dated. The Chief or Principal Investigator, or designate, shall sign a declaration ensuring accuracy of data recorded in the electronic-CRF through signing off database forms by the use of their Postal Index Number (PIN) code.

3.11.3.2 *Source documents*

Source documents shall be filed at the investigator's site and may include, but are not limited to, consent forms, current medical records, laboratory results, and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

3.11.3.3 *Scan Transfer and Storage*

Baseline and subsequent clinical or research CT and/or MR brain scans should be sent electronically over the web (ideally), or on a CD or DVD, or by film (the latter two mailed to the PODCAST International Coordinating Centre in Nottingham). Ideally,

investigators should use the secure Internet upload facility provided on the PODCAST website (www.podcast-trial.org/) which includes automatic checking then anonymisation of images. If films are posted, these will be digitised and the resulting data anonymised. All digital brain image data will be stored on computer servers for adjudication, analysis and archiving. Anonymised imaging data shall be adjudicated by trained neuroradiologists who may be based at the Coordinating Centre or elsewhere. The systems have been designed to ensure the highest levels of data security and participant confidentiality, and will be further enhanced if future technological advances permit it. The enhancements to the current system may include the use of e-Science and Grid technologies (e.g. NeuroGrid, www.neurogrid.ac.uk/) if they prove to be superior to current systems.

3.11.3.4 *Direct access to source data and documents*

The CRF and all source documents, including progress notes and copies of laboratory and medical test results, shall made be available at all times for review by the Chief Investigator, PODCAST staff, Sponsor's designee and inspection by relevant regulatory authorities.

3.11.4 Data protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the UK Data Protection Act (1998). The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers, passwords and PINs (encrypted using a one way encryption method).

Personal information (e.g. name and address of participants and secondary contacts) about trial participants will be held at local centres and will be passed onto the National Coordinating Centre and International Coordinating Centre (Nottingham UK). Participant information will be held on a database at the ICC but will be separated from all clinical information; the latter remain anonymous (identifiable only by initials, trial number and age). Computer data will be backed up regularly to an off site secure repository (to enable disaster recovery). Personal participant information will be used only for the purposes of the PODCAST trial and will not be passed on to third parties. The personal participant information will be deleted at the end of the trial.

Where permissible, the PODCAST International Coordinating Centres may use central databases to obtain additional follow-up information on participants enrolled into the trial. In the UK, this will involve use of the NHS Medical Research Information Service, Office of National Statistics (ONS) database. When information will be gathered on participants in this way, it will be clearly stated in the country specific patient/relative information sheets.

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

3.11.5 Quality assurance and audit

3.11.5.1 *Insurance and indemnity*

Insurance and indemnity for trial participants and local trial staff is covered within the UK NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48.[68] There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

3.11.5.2 *Trial conduct*

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents:

- Permissions to conduct the trial
- Trial Delegation Log
- CVs of trial staff and training received
- Local document control procedures
- Consent procedures and recruitment logs
- Adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits)
- Serious Adverse Event recording and reporting; accountability of trial materials and equipment calibration logs

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit, at least yearly, and an audit report shall be made to the Chief Investigator.

3.11.5.3 *Trial data*

Monitoring of trial data shall include:

- Confirmation of informed consent – for all participants
- Source data verification – for ROUNDUP SQR (number of participants at centre since last monitoring)
- Data storage and data transfer procedures
- Local quality control checks and procedures
- Back-up and disaster recovery of any local databases and validation of data manipulation

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs [ROUNDUP SQR (number of participants at centre since last monitoring)] will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

3.11.5.4 *Record retention and archiving*

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham's Research Code Of Conduct, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years after the end of the trial, or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

3.11.6 Discontinuation of the trial by the sponsor

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee, Data Monitoring Committee, and funder(s) as appropriate in making this decision.

We will use a similar Data Monitoring Committee charter for electively stopping the trial that is agreed for the MRC ENOS trial. This states that:

"During the period of recruitment into the study, the trial statistician will perform interim analyses on major outcome events and supply these, in strict confidence, to the members of the Data Monitoring Committee, along with any other analyses that the committee may request. In the light of these analyses, the Data Monitoring Committee will advise the Chairman of the Steering Committee and Principal Investigator if, in their view, the randomised comparisons in the trial have provided both:

(i) "Proof beyond reasonable doubt"† that for all, or for some, specific types of patient, treatment is clearly indicated or clearly contraindicated in terms of the primary outcome measure, and

(ii) Evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of any other relevant trials.

The Steering Committee can then decide whether to modify intake to the trial (or to seek extra data). Unless this happens, however, the Steering Committee, the collaborators, and the central administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results.

Collaborators, and all others associated with the trial, may write through the PODCAST office, Nottingham to the Chairman of the Data Monitoring Committee, drawing attention to any worries they may have about particular categories of patient requiring special consideration, or about any other matters that may be relevant.

†Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a common view is that a difference of at least 3 standard deviations in an interim analysis of a major outcome event may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.

If a trial is discontinued for any of the above reasons, participants will go back to receiving standard care from their GP's.

3.11.7 Statement of confidentiality

Individual participant medical information obtained as a result of this trial are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

3.11.8 Publication and dissemination policy

Data and results will be shared as follows:

3.11.8.1 *Presentation*

The main trial results will be presented to the investigators, and to funding bodies, and at major international and national scientific meetings, in the name of the trial and Investigators.

3.11.8.2 *Publication*

The main results from the trial will be written by a 'Writing Committee' and published in quality peer-reviewed journal(s) in the name of the investigators, i.e. PODCAST Investigators.

Secondary publications will be published as 'Person(s), for the PODCAST Investigators', where the person(s) are those who conceived, designed, or wrote the paper, or analysed and/or interpreted the data for the publication.

Abstracts will be presented as 'PODCAST Investigators, person(s)', where the person(s) act as a contact point for the trial.

Local investigators may present or publish data relating to their centre once the main trial findings have been published and following agreement by the Trial Steering Committee.

3.11.8.3 *Sharing of data*

Anonymised subsets of data may be shared with other research groups and projects (e.g. Cochrane Collaboration, OAST-Cog) once the main trial findings have been published, and following agreement by the Trial Steering Committee.

3.11.9 User and public involvement

The trial has been reviewed, and is supported, by:

- Alzheimer's Society Quality Research in Dementia Consumer Advisory Network
- UK Stroke Research Network Prevention Clinical Studies Group
- Trent Stroke Consumer Group

Several participants and carers will constitute a 'Patient & Carer Advisory Committee'.

3.12 TRIAL FINANCES

3.12.1 Funding sources

The start-up phase is jointly funded by The Stroke Association and Alzheimer Society UK. Funding for the main funding phase will be sought mid-way through the start-up phase subject to the trial being considered feasible by the Trial Steering Committee and Data Monitoring Committee.

3.12.2 Participant stipends and payments

Participants will not be paid to participate in the trial. Travel or mileage/parking expenses will be offered for hospital visits.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Professor Philip Bath

Signature: _____

Date: _____

Lead Investigator (BP arm): Professor Gary Ford

Signature: _____

Date: _____

Trial Statistician: Mr Michael Tracy

Signature: _____

Date: _____

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