Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Prevention of decline in cognition after stroke trial. Version 1.0

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
(●) Other clinical trial or clinical investigation
( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples, other human biological samples and/or data *(specific project only)*
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	(●) Yes	( ) No
b) Will you be taking new human tissue samples (or other human biological samples)?	(●) Yes	( ) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

[x] England
[x] Scotland
[x] Wales
[x] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

(●) England
( ) Scotland

- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which review bodies are you applying to?

- ☑ NHS/HSC Research and Development offices
- ☐ Social Care Research Ethics Committee
- ☑ Research Ethics Committee
- ☐ National Information Governance Board for Health and Social Care (NIGB)
- ☐ Ministry of Justice (MoJ)

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Do you want your application to be processed through the NIHR Coordinated System for gaining NHS Permission?

◉ Yes ○ No

If yes, you must complete and submit the NIHR CSP Application Form immediately after completing this project filter, before proceeding with completing and submitting other applications.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity? *The guidance notes explain how an adult is defined for this purpose.*

◉ Yes ○ No

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service in England or Wales?

○ Yes ◉ No

9. Is the study, or any part of the study, being undertaken as an educational project?

○ Yes ◉ No

10. Is this project financially supported by the United States Department for Health and Human Services?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the clinical care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

NHS
National Patient Safety Agency
National Research Ethics Service

Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Prevention of decline in cognition after stroke trial. Version 1.0

Please complete these details after you have booked the REC application for review.

REC Name:
Scotland A Research Ethics Committee

REC Reference Number:
09/MRE00/65

Submission date:
24/07/2009

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Philip	Bath
Post	The Stroke Association Professor of Stroke Medicine		
Qualifications	BSC MBBS MD FRCPath FRCP FESC		
Employer	University of Nottingham		
Work Address	Division of Stroke Medicine Clinical Sciences Building City Hospital Campus, Nottingham		
Post Code	NG5 1PB		
Work E-mail	Philip.bath@nottingham.ac.uk		
* Personal E-mail			
Work Telephone	01158231768		

* Personal Telephone/Mobile	
Fax	01158231767

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Mrs	Lynn	Stokes
Address	Division of Stroke Medicine		
	Clinical Sciences Building		
	City Hospital Campus, Nottingham		
Post Code	NG5 1PB		
E-mail	lynn.stokes@nottingham.ac.uk		
Telephone	01158230286		
Fax	01158231771		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	09012
Protocol Version:	D 0.4
Protocol Date:	19/06/2009
Funder's reference number:	TSA2008/9

International Standard Randomised Controlled Trial Number (ISRCTN): To be registered

ClinicalTrials.gov Identifier (NCT number):

European Clinical Trials Database (EudraCT) number: NA

Project website: www.podcast-trial.org

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

Stroke and dementia are each common, economically costly to society, and devastating to patients and their family. Hence, their combined effect is catastrophic. Approximately 30% of people with stroke go on to develop problems with memory and thinking (cognition) leading to dementia.

There are no licensed treatments for these people and little investment in research. Lowering blood pressure (BP) and cholesterol both reduce stroke recurrence. Emerging evidence suggests that lowering BP may reduce the risk of dementia in people with high blood pressure; lowering cholesterol might have a similar beneficial effect. However,there have been no studies with cognition or dementia as the main outcome. Critically, the effect of intensive versus moderate treatment on dementia is unknown.

We aim to determine if intensive BP and lipid lowering after stroke, will prevent cognitive decline compared to present moderate lowering treatment. It will be performed in two phases. The first phase (600 people from 30+ UK Stroke Research Network Centres over 3 years) will assess feasibility and assuming success,the trial will seamlessly run into the main phase to recruit a further 2800 participants from 100 international centres.

Participants with strokes will be randomly assigned (computerised toss of coin) to intensive or standard BP lowering treatment; participants with a stroke due to a blocked blood vessel will also be randomised to intensive or standard cholesterol lowering.

Participants in the intensive group will attend research clinics in the first few months to ensure target BP and cholesterol levels are achieved. Participants in the standard group will receive standard care from their GP. Cognition and other assessments will be done regularly.

An interim analysis will be carried out at the end of 3 years, and a full analysis at the end of the main phase. The results will be published in peer-reviewed medical journals.

A6-2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

Purpose:
Approximately 30% of people who have a stroke go on to develop impaired memory and thinking (cognition), and then dementia. Both stroke and dementia are devastating causing people to lose their independence, so that they need care from family or in an institution.

There are no licensed treatments for these people and little investment in research. This study will assess if intensive treatment of high blood pressure and cholesterol, will help in preventing decline in cognition and dementia, compared to present moderate blood pressure and lipid lowering treatment.

If the trial shows benefit, the treatments are readily available and can be introduced into the NHS rapidly and inexpensively, so that the risk of cognitive impairment and dementia can be reduced by 20% or more in stroke survivors.

Design:
The trial, research group and the application arise from a joint UKSRN (UK Stroke Research Network), DeNDRoN (Dementia and Neurodegenerative Diseases Research Network), and Alzheimer's Society workshop on 16 May 2007: 'Prevention, prophylaxis and treatment of cognitive impairment after stroke and other cerebrovascular disease'.

The trial is supported by the Alzheimer's Society Quality Research in Dementia Consumer Advisory Network, Stroke Research Network Prevention Clinical Studies Group, and Trent Stroke Consumer Group. Mr Ossie Newell, a previous stroke patient is a member of the Trial Steering Committee.

The study will be performed in two phases. The start-up phase will aim to recruit approximately 600 participants from 30+ UKSRN Centres in 3 years. An interim analysis will be done at the end of start-up phase, assessing feasibility (recruitment of participants, maintenance of difference in blood pressure and cholesterol between the two groups, tolerability and safety of the interventions etc). Based on the interim assessment, the study will then seamlessly run into the main phase of the trial with the same design, and aim to recruit a further 2800 participants from a total of 100 international centres (total period of 8 years).

The study will randomly (computerised toss of coin) assign participants who have had stroke (caused by either a blocked blood vessel or a bleed into the brain) to intensive or moderate blood pressure lowering treatments. Participants with strokes due to a blocked blood vessel will also be randomly assigned to intensive or moderate cholesterol lowering treatment. The target systolic BP is <125 mm Hg for the intensive group and <140 mm Hg for the moderate group. The target total cholesterol level is <4.0 mmol/L for the intensive group and <5.0 for the moderate group.

The drug or dosage in the intensive group will be escalated on review at the hospital research clinic to achieve target levels in the first six months. Assessments about stroke, cognition and other outcome data will be collected by telephone and research clinic review alternating every six months.

All assessments will be outcome blinded (the persons making the final assessments will not know what treatment group the participant was in). This will help prevent potential bias in the results.

Main inclusion criteria:
• Age >70 with telephone-MMSE (telephone-mini mental status examination) >16; or age >60 & telephone-MMSE 17-19: to include participants who are at an increased risk of cognitive decline.
• 3-7 months post-event: to allow cognitive, neurological, BP and lipid stabilisation, but avoid attrition.
• Presence of a reporter: partner, sibling, child, friend :outcome assessment will include informant questionnaires about participant's cognition.
• Capacity and willingness to give consent: outcome assessments will involve memory and thinking tests.

Main Exclusion criteria:
• Participants not fulfilling inclusion criteria.
• Severe hypertension: may have a definite need for intensive control.
• Severe hypercholesterolemia: may have a definite need for intensive control.
• Familial stroke associated with dementia, e.g. CADASIL: no expected benefit from trial treatment.
• Chronic renal failure, GFR (Glomerular Filtration Rate)<50 and liver disease, ALT (Alanine Transaminase) >60: participants may need a combination of medications that may cause increased adverse events in persons with abnormal liver or kidney function.

Consent:
Only participants who have capacity, and are willing and able to provide written informed consent will be enrolled into the trial.

Should there be any major amendments to the protocol, which 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.

As cognitive decline is the primary outcome of the study, it is expected that some participants may develop significant cognitive decline and lose capacity to maintain consent during the study. Hence consent to continue in the study, should participants lose capacity will be taken at enrollment. We will also seek consent at the outset, for participant's informant to provide information about participants, should they lose capacity to maintain consent during the study.

Risks and burden:
1) Participants will have to give up their time to attend research clinic. The study period will range from one to seven years depending on the time of enrollment.
2) Participants may suffer from adverse events secondary to cholesterol and blood pressure lowering medications.
3) We may ask a few personal questions about participant's memory, thinking and problem solving abilities, as part of the cognition tests to their relative. Some people may find this upsetting. We however won't ask any questions that the participants do not want us to.
4) Ambulatory Blood Pressure (ABP) measurement: This will only be done if participants agree and in centres having access to these recorders. When attached to the recorder for 24 hours, participants will be asked to avoid bathing, showering or any other activity that may get the recorder wet. Participants may find the device uncomfortable, and it may disturb sleep at night on that day.
5) The neuroimaging sub-study will involve one additional scan which may be MRI or CT scan depending on the study centre. The CT scan of the brain will carry additional risk of ionizing radiations (please note medical physics expert section). Some participants may find the MRI scan claustrophobic.

Benefits:
Although, no promises will be made, the study may help improve the understanding of cognitive impairment after stroke and may help reduce the risk of developing dementia in patients with stroke.

Potential issues with the design of the study:
1.Adequate BP/cholesterol lowering effects: The only trial (HOT) aiming to study optimal BP targets, did not achieve target BP differences. The start-up phase will check that differences in BP/lipids are maintained. Participants will receive repeated telephone reminders about treatment.

2.Guideline drift: The present national guidelines for BP and lipid treatment (which presently recommends moderate lowering) could become more intensive with time; but cost and patient resistance to taking multiple treatments are likely to reduce this. The trial will monitor for such drift.

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).

Confidentiality:
All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent.

Publication of Research:
The results of the study will be published and presented at scientific meetings when the study has ended. Published records will not include participant identifiable information. Participants interested in seeing a copy of published material will be asked to see their study doctor at the end of the study.

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

Our principal research questions are:
i) Does intensive blood pressure(BP) lowering as compared with current standard-of-care moderate BP lowering, prevent cognitive (memory and thinking) decline in patients with recent stroke?
ii) Does intensive lipid(cholesterol) lowering, as compared with current standard-of-care moderate lipid lowering, prevent cognitive decline in patients with recent ischaemic stroke ?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

The study will also assess the outcome of intensive blood pressure and cholesterol lowering on quality of life, depression, stroke recurrence, heart attacks and death compared to standard care.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Approximately 30% of people who have a stroke go on to develop impaired memory and thinking (cognition), and then dementia. As a result, there are approximately 250,000 people in the UK with dementia due to stroke or other diseases involving blood vessels in the brain. Both stroke and dementia are devastating causing people to lose their independence, so that they need care from family or in an institution. Both conditions are very expensive to society through lost work, healthcare and family-care costs, and being in an institution.

There are no licensed treatments for these people and little investment in research; in particular, there are no large ongoing clinical trials aiming to prevent cognitive decline and dementia after stroke. Several BP studies have assessed cognition, but not as the main outcome.

1. Older trials (SHEP, MRC Older) were neutral and showed no harm or benefit, but the newer ones (PROGRESS, Syst-Eur, SCOPE) showed reduction in cognitive decline with blood pressure reducing treatment. The likely driver in these trials was the degree of fall in BP.
2. BP lowering was associated with trends to reduced cognitive decline and dementia in the 2008 HYVET trial in the very elderly. Although BP difference was large (15/6 mmHg), follow-up was short (2 years), and so effects on cognition were probably under-estimated.
3. The HOT trial aiming to study optimal BP control in patients with hypertension did not achieve its 5 mmHg differences in target diastolic BP and so the intensity of BP lowering on cognition has not been fully studied. In indirect evidence from the PROGRESS study, patients with previous stroke who took 2 BP reducing agents rather than 1 had bigger reductions in BP, stroke risk and 'all dementia' (secondary outcome), as compared with control participants. However, patients were not assigned randomly to dual/mono therapy, so treatment intensity was not compared directly.

The results of the above BP trials studying cognition are not conclusive as: cognition was only ever a secondary outcome; different cognition tests were used; most studies included patients at comparatively low risk of developing cognitive decline; and trials had comparatively short follow-up (0.5-4.5 years)

Lowering cholesterol could reduce cognitive decline and dementia, in part by preventing stroke, but the evidence to date is limited. Of 3 small trials of lipid lowering treatment in patients with Alzheimer's Disease, 2 suggested efficacy and one found no effect. The results of large randomised controlled trials have not found significant effects of cholesterol lowering treatment on cognition; however, these studies involved individuals with modest high cholesterol and low risk of developing cognitive decline.

A large, well designed study is urgently needed to see whether intensive treatment of high blood pressure and high cholesterol can reduce the number of people developing a decline in cognition, and dementia after stroke. If the trial is positive, the interventions are readily available and can be introduced into the NHS rapidly and inexpensively so that the risk of cognitive impairment and dementia can be reduced by 20% or more in stroke survivors.

A13. Please give a full summary of your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Principal Research Questions:
i) Does intensive blood pressure (BP) lowering as compared with current standard-of-care moderate BP lowering, prevent decline in cognition (memory and thinking) and development of dementia, in patients with recent stroke?

ii) Does intensive lipid (cholesterol) lowering as compared with current standard-of-care moderate cholesterol lowering, prevent decline in cognition (memory and thinking) and development of dementia, in patients with recent stroke?

Background:
Several studies have assessed the effect of BP and cholesterol on cognition in patients with stroke and there is emerging evidence that lowering BP and cholesterol may help prevent cognitive decline. However, there have been no direct studies specifically addressing this issue as the main outcome. Critically it is unknown whether BP and cholesterol should be lowered intensively or modestly as per current guidelines.

In our study we aim to answer these questions by actively seeking out people with stroke who are at risk of cognitive decline, and test whether intensive lowering of BP and cholesterol will prevent cognitive decline and dementia compared to present moderate (standard-of-care) treatment.

Methodology:

The study will be performed in two phases. The start-up phase will aim to recruit approximately 600 participants from 30+ UKSRN Centres in 3 years. An interim analysis will be done at the end of three years to demonstrate feasibility of the study (recruitment of participants, maintenance of difference in blood pressure and cholesterol between the two groups, tolerability and safety of the interventions etc).Based on start-up feasibility, the study will then seamlessly run into the main phase of the trial and aim to recruit a further 2800 participants from a total of 100 international centres (total period of 8 years).

Participant involvement:
Participants will be screened for potential recruitment during their initial presentation to the hospital stroke service, typically on stroke wards or in stroke/TIA out-patient clinics. 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), and a blood test for cholesterol testing at 8-26 weeks post-stroke. A patient information sheet will be given explaining about the trial. 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 (blocked blood vessel). Participants will be contacted a week later to assess their views and questions about the trial.

If they have agreed, participants with ischaemic 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, enrollment and randomisation into the study.

The study will have two arms: BP lowering and cholesterol lowering. The study will randomly assign (computerised toss of coin) participants who have had stroke (caused by either a blocked blood vessel or a bleed into the brain) to intensive versus moderate (present standard-of-care) blood pressure lowering treatments. Participants with strokes due to a blocked blood vessel will also be randomly assigned to intensive versus moderate (present standard-of-care) cholesterol lowering. As the study is based on management strategies, not individual drugs, placebo (dummy drug) control is not relevant. As emerging evidence suggests that both BP and cholesterol lowering may reduce cognitive decline, our design will allow us to individually assess their effect on cognition and dementia, in addition to their interaction effects, in a single design.

Blood Pressure and Cholesterol Lowering Strategy:
Algorithms taking account of National Institute of Clinical Excellence (NICE) guidelines will aid investigators in

treatment decision-making, so that participants are treated as randomised.

Intensive BP lowering treatment group
The target Systolic Blood Pressure (SBP) for this group is <125 mm Hg. 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 or suggest dose/drug escalation/weaning based on the BP algorithms to the GP who will prescribe the medications. Drugs will be weaned down if SBP< 110 mm Hg.A member of the coordinating centre staff(Nottingham) 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.

Moderate (standard-of-care) BP lowering treatment group
The target SBP for this group is <140 mmHg. Drug dose/numbers will be increased to achieve the target, as per current guidelines. The monitoring/treatment will occur in general practice to reflect current community-based practice.

Intensive Cholesterol lowering treatment group
The target LDL-C (Low Density Lipoprotein-Cholesterol) for this group is < 2 mmol/l (or Total cholesterol (TC) < 4.0 mmol/l if LDL-C cannot be calculated). Participants in this group will be started on a high intensity (e.g. atorvastatin 80 mg) statin (cholesterol lowering agent) and given advice to take a plant stanol/sterol spread on butter. They will be reviewed at the research clinic at 3 months and treatment escalated with ezetimibe (another cholesterol lowering agent, 10 mg once a day) if target levels are not achieved.A member of the coordinating centre staff (research nurse/doctor) will monitor recorded cholesterol over the database in individual participants, unblinded to therapy and suggest changes to the GP/local investigator to ensure that cholesterol levels are appropriate for patient's randomisation.

Moderate (Standard –of care) cholesterol lowering treatment group
The target LDL-C for this group is < 3 mmol/l (or TC < 5.0 mmol/l if LDL-C cannot be calculated). Participants in this group will be started on standard statin (e.g. simvastatin 40 mg once a day) as per current NICE guidelines. Monitoring and treatment of their cholesterol levels will occur in general practice to reflect current community-based practice.

All participants will receive standard life style advice and secondary prevention as per NICE guidance.

Study interventions:
1. Telephone assessment for cognition (telephone-MMSE) and function(modified Rankin scale) as a screening tool to assess participants suitability.

2.History and physical examination: The study doctor will take a detailed medical history taken and conduct a physical examination.

3.Cognition (memory and thinking) tests: The tests will involve participants going through a short series of tests that will measure language, memory, sight, thinking and the ability to solve problems. The tests will approximately last around 30-45 minutes.

4.Informant questionnaires: Informants will be asked questions about participant's cognition and stroke.

5.Cognition assessments over telephone: Participants will be contacted over the telephone for some memory and thinking tasks. This will take around 10 minutes.

6.Blood Pressure measurement: A BP cuff will be tied around the participant's left arm and BP recorded with an electronic device.

7.Ambulatory Blood Pressure (ABP) measurement: All participants will be invited to take part in a yearly, 24 hour monitoring of blood pressure. Participation will depend on the participant's consent and availability of these services in the trial centre. The test will involve wearing a blood pressure cuff around the arm and a small recorder (approximately 10 x 7 centimetres) with a belt around the waist. Once every hour, the blood pressure cuff will inflate and the recorder will measure the blood pressure. Participants will be able to carry out their daily routine activities. However, they will be asked to avoid bathing, showering or any other activity, which can get the recorder wet. The recorder will be left for 24 hours.

8.Blood sampling: Blood tests for cholesterol will be carried out as specified below. All participants will be invited to take part in the genetic sub-study.If participants agree, an additional blood test will be taken at enrolment, which will look into genetic or inherited differences in how patients respond to therapy.

9. Brain scan: All patients with stroke usually have a brain scan during their stroke. The results of this scan will

be used for the study. However, participants will also be invited to take part in a neuroimaging sub-study. This sub-study may help in developing models that can predict cognitive decline after stroke. Separate funding is being sought for this sub-study. If participants agree they will have an additional scan, 3 years after enrollment. MRI scan of the brain will be the preferred scan of choice(as it is more informative and doesn't involve radiation), but if participants are unable to have an MRI due to medical reasons or the study centre is unable to provide the facility, they will have a CT scan of the brain.

Timelines:

Start-up phase:
i)-6 to 0 months: Preparation of protocol, trial materials and seeking approvals.
ii)0 to 6 months: Site identification.
iii)0 to 24 months: Patient recruitment in the study
iv)6 to 36 months: Data monitoring committee reviews (annually and 6 monthly updates from the statistician to the chairman)
v)7 to 36 months: Feasibility reviews of the study
vi)18 months onwards: Seek main phase funding
vii)31 to 36 months: Interim analysis (blinded assessment: person performing the analysis will not know what treatment groups the participants are randomised to)

Main phase:
i)37 to 66 months: Further site identification
ii)37 to 66 months: Further recruitment of participants
iii)37 to 90 months: Data monitoring committee reviews
iv)79 to 96 months: Final data collection
v)91 to 96 months: Outcome analysis
vi)After 96 months: Presentation at national and international conferences and publication in peer reviewed journals of study findings.

Participant timelines on recruitment:

i)Screening and identification of potential participants from hospital based stroke services (-7 to -3 months).

ii)Telephone assessment of cognition and function and blood test for cholesterol for participants with ischaemic stroke (-26 to -8 weeks)

iii)Baseline visit (Day 0): Informed consent will be taken and participants will be enrolled into the trial. After a baseline medical history and physical examination participants will have cognition tests and informants will be interviewed. Blood tests as described will be taken.

iv)1 month: Participants in the intensive group for blood pressure control will be reviewed in the research clinic for monitoring their BP.

v)3 months: Participants in the intensive group will be reviewed in the research clinic for monitoring of both blood pressure and blood cholesterol levels (blood test).

vi)Six months and then yearly: Stroke data will be collected for all participants. BP, cholesterol and cognition tests will be carried out. Participants in some research centres will also have ABP monitoring. These assessments will be carried out yearly until the end of the trial.

vii)1 year: Cognitive tests will be performed over the telephone in addition to collecting stroke data. This will then be done annually until the end of the trial.

viii)3 years: At the end of start-up phase all participants will have outcome assessments done as specified.

ix)4-8 years: Participants will seamlessly continue into the main phase with assessments continued as above, based on funding and interim analysis after the start-up phase.

The follow-up period for individual participants will range from 1-8 years depending on the time of enrolment.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

☐ Design of the research

- [x] Management of the research
- [x] Undertaking the research
- [ ] Analysis of results
- [ ] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The trial is supported by the Alzheimer's Society Quality Research in Dementia Consumer Advisory Network, Stroke Research Network Prevention Clinical Studies Group, and Trent Stroke Consumer Group.

Mr Ossie Newell, a previous stroke patient is a member of the Trial Steering Committee.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1. Age >70 years and telephone-MMSE >16; or age >60 years and telephone-MMSE 17-22
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, neurological, BP and lipid 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

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

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>160 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.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?

3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed consent	1	0	20 minutes	Research doctor
Telephone reminder about blood tests	5	0	5	Research nurse
Telephone reminder about treatment compliance- intensive group participants	5	0	5	Research nurse

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Screening telephone MMSE/modified rankin scale assessment	1	0	10	Research nurse/doctor
Baseline- history and physical examination	1	0	60 minutes	Research doctor
Blood Pressure measurement intensive group	9	5	5 minutes	Research clinic nurse/doctor
Blood Pressure measurement standard-guideline group	6	5	5 minutes	Research clinic/doctor
Ambulatory Blood Pressure monitoring	5	0	24 hours	Research clinic nurse/doctor
Blood tests-all patients Renal function Liver function	2	1	5 minutes	Initial hospital admission/research screening clinic
Blood samples- cholesterol levels-intensive group	8	5	5 minutes	Research clinic nurse
Blood samples- cholesterol levels-standard-guideline group	7	5	5 minutes	Research clinic nurse
Neuroimaging- CT or MRI- preferably MRI (depending on study centre, MRI contraindications)	2	1	20 minutes	NHS hospital imaging department
Cognitive and mental health assessments Addenbrookes cognitive examination STROOP test Trail making test Zung depression score	5	0	45 minutes	Reserach clinic nurse/doctor
Informant questionnaires cognitive assessment IQCODE	5	0	15 minutes	Research clinic/nurse
Stroke clinical assessment Vascular events	5	1	30 minutes	Research clinic/nurse

Dependency scale				
Telephone Cognitive tests telephone MMSE TICS- M	5	0	10 minutes	Research clinic nurse/doctor

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

The duration of individual participation in the trial will depend on their time of enrollment and range from 1-8 years.

Long follow-up is essential in trials of cognition as, cognitive impairment may take many years to develop.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Potential risks and burden

1. Participants will have to give up their time to attend research clinic with follow-up ranging from one to seven years depending on the time of enrollment.
2. Participants may suffer from adverse events secondary to cholesterol and blood pressure lowering medications.
3.The detailed cognitive tests will take time to adminster.
4.Blood tests: Blood sampling may cause a small amount of bleeding, discomfort or a bruise. Occasionally a person may feel lightheaded or faint when the blood is drawn.
5.BP measurement: Participants may experience an unpleasant sensation when the cuff is inflated. This however lasts only for the time when the blood pressure is taken.
6.We may ask a few personal questions about participants memory, thinking and problem solving abilities, as part of the cognition tests to their relative. Some people may find this upsetting. We however won't ask anything questions that the particpants do not want us to.
7.Ambulatory Blood Pressure (ABP) measurement: This will only be done if participants agree, and in centres having access to these recorders.When attached to the recorder for 24 hours, participants will be asked to avoid bathing, showering or any other activity that may get the recorder wet.Participants may find the device uncomfortable, and it may disturb sleep at night on that day.
8.The neuroimaging sub-study will involve one additional scan (preferred choice MRI but if unable to do MRI then CT will be performed). The CT scan of the brain will carry additional risk of ionizing radiations.The amount of X-ray exposure from one CT scan is about the same as the background exposure from living in Nottingham for 3 years, or Cornwall for 1 year. (please note medical physics expert section). Some participants may find the MRI scan claustrophobic.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◉ Yes ○ No

If Yes, please give details of procedures in place to deal with these issues:

As part of the outcome assessments, participants and their informant will be asked questions on current ability (modified Rankin scale and the Barthel index), quality of life(EuroQOL), cognition (telephone MMSE,TICS,IQCODE for informants), depression (Zung depression scale). If the patient is uanble to answer the questions due to disablility from stroke,their informant will be asked to answer some of the questions as accurately as possible on participant's behalf.

These assessments are standardised and contain questions that have all been validated in previous research studies.We are using similar measurement scales (except cognition) in the ongoing MRC ENOS trial (www.enos.ac.uk). So far around 1200 participants have had these assessments without any significant

problems.

A24. What is the potential for benefit to research participants?

Potential benefits:

1. The study may show benefits of intensive management of blood pressure and cholesterol versus standard care in preventing dementia.
2. Participants in the intensive group will be followed up more often in the first six months and they will have an opportunity to report adverse events at the research clinic.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

All participants will go back to standard care ant the end of the study period. This will be explained to all participants at the start of the trial.This will be explained to all participants at the beginning of the trial

A26. What are the potential risks for the researchers themselves? *(if any)*

1. Needle stick injuries from blood samples

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Participants will be identified by members of their usual care team (which may include the investigator and research nurse) on presentation to NHS based hospital services including both inpatient and outpatient services. This will involve a review of their NHS medical notes.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
Identification of potential participants will involve review of their NHS medical records by a member of the patient's direct health care team (this may include the investigator and/or research nurse).

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

( ) Yes (●) No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

( ) Yes (●) No

A29. How and by whom will potential participants first be approached?

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 of all aspects pertaining to participation in the trial.

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 their 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 their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

A30-1. Will you obtain informed consent from or on behalf of research participants?

(●) Yes ( ) No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

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, typically on stroke wards or in stroke/TIA out-patient clinics. 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, and blood testing for cholesterol at 8-26 weeks post-stroke. They will also be provided with a patient information sheet explaining about the trial.

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 and an appointment booked to come to the research clinic for enrolling into the study.

In the research clinic, the Investigator will explain the details of the trial and answer any questions that the participant has concerning trial participation.An informed consent will then be taken, signed and dated by the participant before they enter the trial.Signed consent forms will be kept by the Participant and Investigator, and in the participant's hospital records.

Should there be any major amendments to the protocol which 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.

As cognitive decline is the primary outcome of the study, it is expected that some participants may develop significant cognitive decline and lose capacity to maintain consent during the study. Hence consent to continue in the study, should participants lose capacity will be taken at enrollment. We will also seek consent at the outset for participant's informant to provide information about participants, should they lose capacity during the study.

If you are not obtaining consent, please explain why not.

Consent will be taken for all participants at enrollment. However,as cognitive decline is the primary outcome of the study, it is expected that some participants may develop significant cognitive decline and lose capacity during the study. Hence consent to continue in the study, should participants lose capacity to maintain consent will be taken initially at enrollment. We will also seek consent at the outset for participant's informant to provide information about participants should they lose capacity during the study.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

Participants will be screened for potential recruitment during their initial presentation to the hospital stroke service. 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) and a blood test for cholesterol at 8-26 weeks post-stroke. A participant information sheet will be given to the patient explaining about 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.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

( ) Yes
(●) No
( ) Not Known

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters)*

If needed, the usual hospital interpreter and translator services will be available 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.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

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

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
( ) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
(●) The participant would continue to be included in the study.
( ) Not applicable – informed consent will not be sought from any participants in this research.

Further details:

As cognitive decline is the primary outcome of the study, it is inevitable that some participants will develop significant cognitive decline and even dementia, and therefore lose capacity to maintain consent during the study. Hence, consent to continue in the study, should participants lose capacity, will be taken at enrollment. We will also seek consent at the outset for the participant's informant to provide information about participants should they lose capacity during the study.

Please complete Part B, Section 6, giving further information about arrangements for including adults unable to consent for themselves.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [x] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [x] Manual files including X−rays
  - [x] NHS computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
Access to medical records by those outside the direct healthcare team

The Case Report Forms(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, Sponsor’s designee and inspection by relevant regulatory authorities.

Electronic Transfer by magnetic or optical media, email or computer networks.

Baseline and subsequent clinical or research CT and/or MR brain scans will be sent electronically over the web (ideally), on a CD or DVD. Ideally, investigators should use the secure internet upload facility that will be provided on the PODCAST website (www.podcast-trial.org/) which includes automatic checking, and then anonymisation of images.All digital brain image data will be stored on computer servers for adjudication, analysis and archiving. 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.

Sharing of data with other organisations

PODCAST will be a large trial assessing cognition post stroke, and there are other trials assessing cognition after stroke although not as a primary outcome. Therefore, data may potentially be shared with larger academic collaborators such as the Cochrane Collaboration who combine data sets of all trials assessing similar questions in order to provide scientifically robust answers.Data sharing usually involves summary/group data where individuals cannot be identified. However, individual patient data may also be shared, but this will be anonymised with identifiers removed thereby preventing identification of individuals.

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.

The investigator will keep a separate confidential record in the Trial Recruitment Log of the participant's name, date of birth, local hospital number or NHS number, and a Participant Trial Number, to permit identification of all participants enrolled in the trial, so that follow-up may be performed.

CRFs will be treated as confidential documents and held securely in accordance with regulations. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log'.

Personal data on manual files (CT/MRI images)
If CT/MRI images are sent on film (mailed to the PODCAST International Coordinating Centre in Nottingham), they will be digitised and the resulting data anonymised.

The investigator will keep a separate confidential record in the Trial Recruitment Log of the participant's name, date of birth, local hospital number or NHS number, and a Participant Trial Number. This data will be stored on secure university or NHS computers that will be password prtoected and accessed only by personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log'.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

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 Case Report Forms (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 and password to the PODCAST staff (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.

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.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Access to case report forms and participants personal data at individual sites may be accessed by the participant's direct health care team. They can also be accessed by personnel from the research team approved by the Chief or local Principal Investigator and recorded on the Trial Delegation Log.

The CRF'S, other source documents and trial documentation which may include participants' personal data will be accessible to the trial co-ordinator or where required, a nominated designee of the Sponsor for carrying out monitoring of trial data as an ongoing activity.

The CRF'S, other source documents, progress notes and copies of laboratory and medical test results, and trial documentation which may include participants' personal data shall be made available at all times for review by the Chief Investigator, PODCAST staff, Sponsors designee and inspection by relevant regulatory authorities.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

- (●) Less than 3 months
- ( ) 3 – 6 months
- ( ) 6 – 12 months
- ( ) 12 months – 3 years
- ( ) Over 3 years

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

(●) Yes ( ) No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
Patients will be reimbursed for travel to and from the research clinic.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

( ) Yes (●) No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may

give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

◉ Yes ○ No

Please give details, or justify if not registering the research.
The study will be registered on the ISRCTN website.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A53. Will you inform participants of the results?

○ Yes ◉ No

Please give details of how you will inform participants or justify if not doing so.
Participants will be informed at enrollment, that at the end of the trial they will be able to receive a summary of the trial results by contacting the research team. They could also view the results and conclusions from the trial website www.podcast-trial.org.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The research has been peer-reviewed during the funding process independently from The Stroke Association UK and the Alzheimer Society UK.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Mr	Michael	Tracy
Department			
Institution	University of Nottingham		
Work Address	Division of Stroke Medicine		
	Clinical Sciences Building		
	City Hospital Campus, Nottingham		
Post Code	NG5 1PB		
Telephone	01158231772		
Fax	01158231771		
Mobile			
E-mail	michael.tracy@nottingham.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The trial will compare cognition assessed using the Addenbrooke's Cognitive Examination between the intensive and moderate standard-of-care groups for each of the blood pressure and lipid lowering arms.

A58. What are the secondary outcome measures? *(if any)*

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

1. Dementia
a. Using AD (Alzheimer's Disease) - NINCDS/ADRDA and VaD(Vascular Dementia)- NINDS-AIREN criteria
b. With/without recurrent stroke
2. Cognition outcomes
a. Global – MMSE (Mini mental status examination), tMMSE (telephonic MMSE, TICS (telephone instrument for cognition scale)
b. Association – trail making A/B
c. STROOP test
d. Cognitive decline with/without recurrent stroke
e. Ordinal cognition (MMSE>28/23-28/10-22/<10/dementia/dead)
f. IQCODE (Informant Questionnaire on Cognitive Decline for the Elderly)
3. Quality of life – EuroQoL, informant (DEMQoL)
4. Depression (Zung)
5. Dependency (modified Rankin Scale, mRS)
6. Disability (Barthel Index, BI)
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
11. Myocardial infarction: fatal/non-fatal/angina/none
12. Vascular: fatal/non-fatal/none
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 (Total Cholesterol, Triglycerides, HDL, calculated LDL)
18. Neuroimaging (in a subset of participants)

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	600
Total international sample size (including UK):	3400
Total in European Economic Area:	2500

Further details:
The sample size for both the start-up and main phase is approximately 3400 patients. All participants will be randomised to the BP lowering arm and around 3060 patients to the cholesterol lowering arm (ischemic strokes-approximately 90 %). Of these we aim to recruit 600 patients in the start-up phase across UK and 2,800 participants in the main phase internationally.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

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 moderate standard-of-care BP group = 25% at 5 years (main trial, average length of follow-up 4 years)
• 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).

Currently, Addenbrooke's Cognitive Examination will be analysed as cognitive decline using binary approaches (although this will, hopefully, be changed to an ordinal analysis as discussed in the protocol). 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. 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. Any such change will be performed blinded to treatment.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

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

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.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The proportion of participants with cognitive decline or who have died
(Addenbrooke's Cognitive Examination extended to include death) will be compared between the treatment groups, as done previously for MMSE (a subset of ACE).

Analyses will be adjusted for baseline stratification variables and minimisation variables as described above.

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) with comparison of:
• Gradient
• Mean cognition
• Median cognition
• Mean change in cognition
• Ordinal cognitive score

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,62 assuming both linear and curvilinear models
• Create and ordered categorical scale from data on cognition, dementia and death

Dementia will be analysed as:
• Proportions
• As part or an ordered categorical scale

Differential dropouts will also be assessed.

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 . Analyses will be adjusted for the covariates as described in the protocol since this approach increases statistical power and is recommended by EMEA(European Medicine Agency).

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Professor	Gary	Ford
Post	Professor of Pharmacology of Old Age		
Qualifications	BA MB BChir MA MRCP(UK) FRCP FESC		
Employer	Newcastle University		
Work Address	Clinical Research Centre 4th floor Leazes wing Royal Victoria Infirmary,Newcastle		
Post Code	NE1 4LP		
Telephone	01912227744		
Fax			
Mobile			
Work Email	g.a.ford@ncl.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Peter	Passmore
Post	Professor of Geriatric medicine		
Qualifications	BSc MD FRCP FRCPI		
Employer	Queen's University Belfast		
Work Address	Dept of Geriatric Medicine Whitla Medical Building, 97 Lisburn Road, Belfast		
Post Code	BT9 7BL		
Telephone	02890972158		
Fax			
Mobile			
Work Email	p.passmore@qub.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Alistair	Burns
Post	Professor of Old Age Psychiatry		
Qualifications	MBChB FRCP FRCPsyh MD MPhil DHMSA		

Employer	University of Manchester
Work Address	Room 3,304,3/F,UniversityPlace East
	University of Manchester
	Oxford Road, Manchester
Post Code	M13 9PL
Telephone	01613067947
Fax	
Mobile	
Work Email	alistair.burns@manchester.ac.uk

Title	Forename/Initials	Surname
Professor	Clive	Ballard

Post	Professor of Old-Age Diseases
Qualifications	MBChb MRCPsych M.med.Sci MD
Employer	King's College London
Work Address	Wolfson Centre, Wolfson wing
	Hodgkin Building, Kings College Lon
	Guy's Campus London
Post Code	SE1 1UL
Telephone	02078486568
Fax	
Mobile	
Work Email	Clive.ballard@kcl.ac.uk

Title	Forename/Initials	Surname
Dr	Robert	Steward

Post	Clinical Reader and Head of Section of Epidemiology, Institute of Psychiatry
Qualifications	MBChb MRCPscyh MSc Epidemiology MD
Employer	King's College London
Work Address	Box 60, Institute of Psychiatry
	De Crespigny Park
	London
Post Code	SE5 8AF
Telephone	02078480136
Fax	
Mobile	
Work Email	r.stewart@iop.kcl.uk

Title	Forename/Initials	Surname
Professor	Joanna Marguerite	Wardlaw

Post	Professor and Honorary Consultant Neuroradiologist
Qualifications	BSc MBChB MRCP(UK) DMRD FRCR MD FRCP FMedSci
Employer	University of Edinburgh
Work Address	Division of Clinical Neuroscience
	Western General Hospital
	Crewe Road Edinburgh
Post Code	EH4 2XU
Telephone	01315372943
Fax	01313325150
Mobile	

Work Email	jwardlaw@staffmail.ed.ac.uk

Title	Forename/Initials	Surname
Professor	Jonathan	Mant

Post	Professor of Primary Care Research, University of Cambridge
Qualifications	MA Msc MBBS MD FFPH
Employer	University of Cambridge
Work Address	GP and Primary Care Reserach Unit Forvie Site, Addenbrookes Hospital Cambridge
Post Code	CB2 0SR
Telephone	01223763830
Fax	
Mobile	
Work Email	Jm677@medschl.cam.ac.uk

Title	Forename/Initials	Surname
Dr	John Philip David	Reckless

Post	Consultant Endocrinologist and Honorary Reader in Medicine
Qualifications	DSc MD FRCP
Employer	Royal United Hospital Bath
Work Address	Dept of Endocrinology Royal United Hospital Combe Park, Bath
Post Code	BA1 3NG
Telephone	01225824527
Fax	
Mobile	
Work Email	mpsjpdr@bath.ac.uk

Title	Forename/Initials	Surname
Dr	Sandeep	Ankolekar

Post	Clinical Research Fellow
Qualifications	MBBS MD MRCP(UK)
Employer	University of Nottingham
Work Address	Division of Stroke Medicine Clinical Sciences Building City Hospital Campus, Nottingham
Post Code	NG5 1PB
Telephone	01158231769
Fax	
Mobile	
Work Email	sandeep.ankolekar@nottingham.ac.uk

Title	Forename/Initials	Surname
Mr	Michael	Tracy

Post	Statistician
Qualifications	BSc(Hons)(statistics) MSc(medical statistics)
Employer	University of Nottingham

Work Address	Division of Stroke Medicine Clinical Sciences Building City Hospital Campus, Nottingham
Post Code	NG5 1PB
Telephone	01158231772
Fax	
Mobile	
Work Email	michael.tracy@nottingham.ac.uk

Title	Forename/Initials	Surname
Mrs	Lynn	Stokes

Post	Joint Nurse Co-ordinator
Qualifications	BA(Hons)Dip.Mid
Employer	University of Nottingham
Work Address	Division of Stroke Medicine Clinical Sciences Building City Hospital Campus, Nottingham
Post Code	NG5 1PB
Telephone	01158230286
Fax	
Mobile	
Work Email	lynn.stokes@nottingham.ac.uk

Title	Forename/Initials	Surname
Mrs	Fiona	Hammonds

Post	Joint Nurse Co-ordinator
Qualifications	RGN
Employer	University of Nottingham
Work Address	Division of Stroke Medicine Clinical Sciences Building City Hospital Campus, Nottingham
Post Code	NG5 1PB
Telephone	01138231773
Fax	
Mobile	
Work Email	fiona.hammonds@nottingham.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)

Commercial status:

○ Other

If Other, please specify:

Contact person

Name of organisation	University of Nottingham
Given name	Paul
Family name	Cartledge
Address	University Park
Town/city	Nottingham
Post code	NG7 2RD
Country	UNITED KINGDOM
Telephone	01159515151
Fax	01159513666
E-mail	

Is the sponsor based outside the UK?

○ Yes ◉ No

Where the lead sponsor is not established within the UK, a legal representative in the UK may need to be appointed. Please consult the guidance notes.

Co-Sponsor

Status:
- ○ NHS or HSC care organisation
- ○ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status:

If Other, please specify:

Contact person

Name of organisation	
Given name	
Family name	
Address	
Town/city	
Post code	
Country	
Telephone	
Fax	
E-mail	

Is the sponsor based outside the UK?

○ Yes ○ No

Where the lead sponsor is not established within the UK, a legal representative in the UK may need to be appointed. Please consult the guidance notes.

A64-2. Please explain how the responsibilities of sponsorship will be assigned between the co-sponsors listed in A64-1

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Dr	Maria	Koufali
Organisation	Nottingham University Hospital NHS Trust		
Address	E11 Curie Court		
	Queen's Medical Centre		
	Derby Road, Nottingham		
Post Code	NG7 2UH		
Work Email	maria.koufali@nottingham.ac.uk		
Telephone	01159709049		
Fax	01158493295		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/01/2010
Planned end date: 31/12/2017
Total duration:
Years: 8 Months: 0 Days:

A71-1. Is this study?

○ Single centre
◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

☑ England
☑ Scotland
☑ Wales
☑ Northern Ireland

☑ Other countries in European Economic Area

Total UK sites in study 30

Number of sites anticipated in the Community 0

Does this trial involve countries outside the EU?
◉ Yes ○ No

☑ USA
☑ Other international (please specify)
Trial will be international in main phase.

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

☑ NHS organisations in England	18
☑ NHS organisations in Wales	4
☑ NHS organisations in Scotland	5
☑ HSC organisations in Northern Ireland	3
☑ GP practices in England	
☑ GP practices in Wales	
☑ GP practices in Scotland	
☑ GP practices in Northern Ireland	
☐ Social care organisations	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent hospitals	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	

Total UK sites in study:

A75-1. Will a data monitoring committee (DMC) be convened?

◉ Yes ○ No

If Yes, please forward details of the membership of the DMC, its standard operating procedures and summary reports of interim analyses to the Research Ethics Committee which gives a favourable opinion of the study (or to GTAC if applicable).

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

We will use the same Data Monitoring Committee charter that is agreed for the MRC funded ENOS (Efficacy of Nitric Oxide in Stroke)trial which states:

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 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 study (or to seek extra data).

* 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. This criterion has the practical advantage that the exact number of interim analyses is of little importance statistically, and so
no fixed schedule is necessary.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

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.

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

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

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.

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

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of

investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- [x] NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- [ ] Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

- ○ Yes
- ◉ No

Please enclose a copy of relevant documents.

PART B: Section 3 – Exposure to ionising radiation

Complete sub-sections A and/or B as applicable with input from relevant experts. It is advisable to discuss the proposed research at an early stage with (a) a Medical Physics Expert and (b) a Clinical Radiation Expert, who will carry out the required assessments for sub-sections C and D. The lead MPE can also facilitate the completion of sub-sections A and/or B if necessary.

1. Does the study involve exposure to radioactive materials?

- ○ Yes
- ◉ No

2. Does the study involve other diagnostic or therapeutic ionising radiation?

- ◉ Yes
- ○ No

A. Radioactive materials

Details of radioactive materials

B. Other ionising radiation

B1. Details of other ionising radiation

Give details by completing the table below:

Procedure	No of procedures	Estimated procedure dose *(use national Diagnostic Reference Levels where available)*
CT scan brain (only patients unable to have an MRI scan brain)	1	5mSV

C. Dose and risk assessment

C1. What is the total research protocol dose from the exposures in A1 and/or B1, and what component of this is the additional dose over and above standard practice? What are the risks associated with these two doses (total and additional)?

The dose and risk assessment should be set out below. This should be prepared by a Medical Physics Expert (MPE) who is a registered health care professional and has expertise relevant to the planned exposures. Where the study involves different types of exposure (for example, both radioactive materials and other ionising radiation, or more than one imaging method), advice may need to be sought from other MPEs with relevant expertise. The lead MPE should produce a combined assessment for the ethics committee, giving the names of any other MPEs who have contributed to the assessment. Further guidance is available by clicking on the information button or in the document "Approval of research involving ionising radiation", available here: http://www.nres.npsa.nhs.uk/applicants/guidance/

There is a preference for scanning this patient group with MRI if possible. CT will be performed where MRI is unavailable.

Participation in the standard trial will involve a CT scan at the time of presentation with stroke. Participants who agree will be recruited to the imaging 'sub-study'. These patients will receive an additional CT at the end of the three years. The CT scan at the time of stroke would have been given whether or not the patient went on to participate in the trial and is considered the baseline.

CT scan for stroke will involve a single non-contrast run through the head. From NRPB – W 67 Doses from Computed Tomography (CT) Examinations in the UK – 2003 review. A typical dose for a head scan is 1.5mSv but due to variation in protocols, machines and patient sizes, this could be as much as 5mSv per scan.

Based on a risk coefficient for developing fatal radiation induced cancer (all ages) of 5%/Sv (ICRP), two CT brain scans would lead to a risk of 1.5/10,000 for a typical dose to 5/10,000 for a maximum radiation exposure incurred as part of the trial. This is comparable with the annual risk of dying in a road traffic accident.

Only the scan at the time of stroke would be routine, the scan at the end of the study would be additional.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

C2. Declaration by lead Medical Physics Expert

I am satisfied that the information in sub-sections A and/or B and the assessment in sub-section C provide a reasonable estimate of the ionising radiation exposure planned in this research and the associated risks.

Signature:…….. Date: 23/07/2009

C3. Details of person acting as lead Medical Physics Expert

	Title	Forename/Initials	Surname
	Mr	Andy	Rogers
Post	Radiation Protection Advisor		
Details of professional registration			
Organisation	Nottingham University Hospitals NHS Trust		
Address	Department of Medical Physics		
	City Hospital, Hucknall Road		
	Nottingham		
Post Code	NG51PB		
Telephone	0115 9691169		
Fax			
Mobile	0115 9691169		
Email	Andy.Rogers@nuh.nhs.uk		

D. Clinical assessment

This sub-section should be completed by a Clinical Radiation Expert (CRE) who is a registered health professional with clinical expertise relevant to the planned exposures. The assessment should cover potential exposure at all research sites, taking account of possible variation in normal clinical practice. Where the study involves different types of exposure (for example, both radiotherapy and other ionising radiation), advice may need to be sought from other CREs with relevant expertise. The lead CRE should produce a combined assessment for the ethics committee, giving the names of any other CREs who have contributed to the assessment. The guidance notes give advice to Chief Investigators on who can act as lead Clinical Radiation Expert (CRE) and advice for the CRE on the assessment of exposures having regard to IRMER.

Special attention must be paid to pregnant/potentially pregnant women or those who are breast feeding, or other potentially vulnerable groups.

D1. Will the exposure exceed the exposure that might be received as part of normal care at any proposed research site?

(●) Yes ( ) No

D2. Assessment of additional exposure

Explain how the planned exposure compares with normal practice and assess whether it is appropriate, using language comprehensible to a lay person. Consideration should be given to the specific objectives of the exposure, the characteristics of participants, the potential diagnostic or therapeutic benefits to the participant, the potential benefits to society, the risk to the participant and the availability of alternative techniques involving less, or no, ionising radiation.

If pregnant or breast-feeding mothers are to be studied give reasons and details of special radiation protection measures to be taken.

Participants who agree to the imaging sub study will have an additional scan of the brain at 3 years. MRI brain scan is the preferred imaging modality of choice as it gives more information about changes in the brain that are associated with changes in cognition (memory and thinking). Participants will have a CT scan if an MRI is contraindicated, or the study centre is unable to do an MRI.

Objectives of the exposure:
The study will aim to find features on the scans that may predict cognitive decline in stroke, and whether intensive treatment with blood pressure and lipid lowering may modify those features.

Characteristics of participants:
All participants that agree to the main study will be asked to take part in the imaging sub study.

Potential diagnostic benefits to patients:
The tests may not offer any additional benefits to patients but may help in predicting cognitive decline after stroke.

Potential benefits to society:
The study will add to the knowledge about cognition after stroke. The study may help in developing models to predict cognitive decline after stroke based on the initial scan of patients. If the main study is positive and shows that intensive blood pressure and lipid lowering after stroke is better than present standard/moderate lowering, the substudy will give additional information about imaging changes associated with drug treatment.

Risk to the participant:
The amount of X-ray exposure form one CT-scan is about the same as the background exposure from living in Nottingham for 3 years or Cornwall for 1 year.
Availability of alternative techniques involving less /no radiation:

MRI scan is the preferred imaging modality as it gives more information about brain structural features associated with cognitive change. Participants will have a CT scan if an MRI is contraindicated or the study centre is unable to do an MRI."

D3. Declaration by lead Clinical Radiation Expert

I am satisfied that the exposure to ionising radiation planned in this research study (as defined in A1 and/or B1) is reasonable and that the risks are adequately described in the participant information sheet for the study.

Signature:…….. Date: 23/07/2009

D4. Details of lead Clinical Radiation Expert

	Title	Forename/Initials	Surname
	Professor	Joanna Marguerite	Wardlaw
Post	Professor and Honorary Consultant Neuroradiologist		
Details of professional registration	BSc MBChB MRCP(UK) DMRD FRCR MD FRCP FMedSci		
Organisation	University of Edinburgh		
Address	Division of Clinical Neuroscience		
	Western General Hospital		
	Crewe Road Edinburgh		
Post Code	EH4 2XU		
Telephone	01315372943		
Fax	01313325150		
Mobile			
Email	jwardlaw@staffmail.ed.ac.uk		

Employers responsible for radiation facilities at research sites must have written procedures to meet the requirements of the Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER). R & D offices for NHS sites will seek confirmation from local radiation experts that local IRMER authorisation procedures have been followed. Where the local Medical Physics Expert or IRMER Practitioner disagrees with the assessments made in this Section and/or the care organisation is unable to adhere to the protocol, this should be discussed with the Chief Investigator and the lead experts for the study. Any necessary variation in the protocol or participant information sheet at particular sites should be notified to the main REC as a substantial amendment and an ethical opinion sought.

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Blood samples (whole blood and clotted serum). Routine blood tests include testing for cholesterol which will be processed in the NHS laboratories. Blood tests will also be taken for the pharmacogenetics and blood biomarkers sub-study if participants agree and consent to the substudy.

2. Who will collect the samples?

Blood samples will be collected by members of the participant's direct health care team (this may involve the investigator or research nurses) and the stroke network research nurses.

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?

(•) Yes ( ) No

In future research?

( ) Yes ( ) No (•) Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (•) No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

( ) Yes ( ) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

( ) Yes ( ) No

In a form in which the donor could be identifiable to researchers?

( ) Yes ( ) No

9. What types of test or analysis will be carried out on the samples?

Tertiary questions in PODCAST in the genetics substudy include assessing the effects of the interventions on blood biomarkers, and by participants 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.

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.

The exact identity of genetic markers also will depend on developing knowledge of what may most usefully be

measured. Examples include genes related to Apo-E, mechanism of action of drugs, lipid metabolism, thrombosis and inflammation.

10. Will the research involve the analysis or use of human DNA in the samples?

(●) Yes ( ) No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

( ) Yes (●) No

12. If so, will arrangements be made to notify the individuals concerned?

( ) Yes (●) No ( ) Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

Genotyping is exploratory and therefore results will be non-definitive.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

The samples will be stored in locked freezers, Division of Stroke Medicine, Clinical Sciences building, University of Nottingham. The samples will carry patient initials, trial number and sample date but no identifiable personal information. Only the project research staff will have access to the freezer samples.
Chief Investigator Professor Philip Bath will have responsibility as custodian of the samples.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☑ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

The laboratories used for storage at the University of Nottingham already hold a license with the HTA.

Blood tests taken for cholesterol will not be stored and destroyed as per the protocol and regulations of the NHS laboratories.

B. All research other than CTIMPs

In this sub-section, an adult means a person aged 16 or over.

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

Only participants who have capacity and are willing to take part will be enrolled into the study. However, as cognitive decline is the primary outcome of the study, it is inevitable that some participants will develop significant cognitive decline and even dementia, and therefore lose capacity to maintain consent during the study.

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

The study is actively seeking out participants who are at an increased risk of developing cognitive decline and dementia, and develop treatment strategies to reduce its occurrence. All participants will have capacity to give consent at enrolment but
it is inevitable that some participants will develop significant cognitive decline and even dementia, and therefore lose capacity to maintain consent during the study.

B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

The principal investigators and trial doctors of the research team will decide if participants will have the capacity to give consent. 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? (if intensive treatment of high blood pressure and cholesterol will prevent cognitive decline)
2. What are the two groups of intervention? (intensive and standard care)
3.How long will treatment be continued? (Answer: 1-8 years)

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

(●) Yes ( ) No

If Yes, please indicate the nature of this benefit. You may refer back to your answer to Question A24.

Although no promises will be made the study may show benefits of intensive management of blood pressure and cholesterol versus standard care in preventing or reducing the decline in cognition after stroke.

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

(●) Yes ( ) No

If Yes, please explain how the research will achieve this:

We hypothesize that intensive lowering of blood pressure and cholesterol to near normal levels will help in preventing cognitive decline and dementia compared to present moderate standard-of-care lowering of BP and cholesterol.

The research will certainly contribute to the knowledge about cognition and stroke and if positive, it may provide treatment strategies to prevent cognitive decline after stroke.

B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

( ) Yes (●) No

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

All participants will have capacity to give consent at enrollment. The presence of a reporter (partner,sibling,child,friend) is one of our inclusion criteria. We will ask all participants if they would want to continue in the study, should they lose the capacity during the course of the research study. We will also ask them, if they would be happy for their informant to provide continuing consent and provide information about themselves, should they lose the capacity to give consent during the course of the study. 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.

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant might need to be treated urgently as part of the research before it is possible to identify and consult a person under B7?

○ Yes ◉ No

B7-1. What arrangements will be made to identify and seek consent from a guardian or welfare attorney or, if there is no such person, from the participant's nearest relative?

Attempts will be made to identify more than one informant at enrolment (partner,sibling,child,friend),in case the first informant is unable to perform their role due to any reason.

Please enclose a copy of the written information to be provided and the consent form to be used. The information sheet should provide information about the research similar to that which might be given to participants able to consent for themselves.

B7-2. What arrangements will be made to consult, and seek assent from, a close relative or other person able to advise on the inclusion of the participant and on their presumed wishes and feelings?

As only participants with an informant will be enrolled into the study, they will be contacted to seek assent about continuing in the study. This will be explained to the participants at enrollment.

Please enclose a copy of the written information to be provided and the consent form to be used. The information sheet should provide information about the research similar to that which might be given to participants able to consent for themselves.

B8-2. Is it possible that a participant might need to be treated urgently as part of the research before it is possible to seek assent from a close relative or other person?

○ Yes ◉ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants.

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

Participant informants will be contacted as part of the follow-up for the study. Their opinion about continuation of participant in the study will be taken.

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

Only those participants who have capacity, are willing, and able to provide informed consent will be enrolled into the study. Their wishes and feeling, and informed consent will also be taken about whether they will be happy

to continue in the study should they lose capacity to give consent during the study.

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

In susceptible individuals, one would expect cognition to gradually decline and it is less likely to fluctuate significantly. However, it is possible in the short term and attempts will be made to note the participants wishes, and respect their feelings,at times when their cognition is better.

B12. What will be the criteria for withdrawal of participants?

Participants may be withdrawn from the trial for a variety of reasons

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, 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, 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.

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).

Failure of participant to adhere to protocol requirements
The Principle Investigator may remove the participant from the trial if they fail to adhere to the protocol through protocol violations and/or protocol deviations.

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

The study will be an outpatient based trial and trial interventions will mainly include BP measurement, blood tests for cholesterol, ambulatory blood pressure monitoring in addition to taking randomised treatment. Outcome assessments include cognition tests and other questionnaires about dependency, vascular events etc. If the participants appear to object, these would not be carried out, although all effort will be made to have atleast the basic information like blood pressure and blood cholesterol testing in addition to getting randomised treatment.

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?

If participants are not happy to continue in the study, or for their informant to provide information about them, should they lose capacity to maintain consent during the study, they will not be enrolled in the study.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Research site		Investigator/ Collaborator/ Contact	
Institution name	University of Nottingham	Title	Professor
Department name	Division of Stroke Medicine, Clinical Sciences Building	First name/ Initials	Philip
Street address	City Hospital Campus, Hucknall Road	Surname	Bath
Town/city	Nottingham		
Post Code	NG5 1PB		
Institution name	Countess of Chester NHS Foundation Trust	Title	Ms
Department name	Ward 52	First name/ Initials	Christine
Street address	Liverpool Road	Surname	Kelly
Town/city	Chester		
Post Code	CH2 1UL		
Institution name	East Sussex Hospitals NHS Trust	Title	Dr
Department name	Eastbourne District General Hospital	First name/ Initials	Conrad
Street address	Kings Drive	Surname	Athulathmudali
Town/city	Eastbourne, East Sussex		
Post Code	BN212UO		
Institution name	The Rotherham NHS Foundation Trust	Title	Ms
Department name	Rotherham General Hospital	First name/ Initials	Cheryl
Street address	Moorgate Road	Surname	Draper
Town/city	Rotherham		
Post Code	S602UD		
Institution name	Blackpool, Fylde and Wyre Hospitals NHS Foundation Trust	Title	Dr
Department name	Blackpool Victoria Hospital	First name/ Initials	James
Street address	Whinney Heys Road	Surname	McIlmoyle
Town/city	Blackpool		
Post Code	FY38NR		
Institution name	Lancashire Teaching Hospitals NHS Foundation Trust	Title	Mr
Department name	Royal Preston Hospital	First name/ Initials	Stephen
Street address	Sharoe Green Lane	Surname	Duberley
Town/city	Preston		
Post Code	PR2 9HT		

Institution name	Ashford and St Peter's Hospital NHS Trust	Title	Dr
Department name	Ashford and St Peter's Hospitals	First name/ Initials	Bhaskar
Street address	Guildford Road	Surname	Mandal
Town/city	Chertsey, Surry		
Post Code	KT16 0PZ		

Institution name	Abertawe Bro Morgannwg University NHS Trust	Title	DR
Department name	Morriston Hospital	First name/ Initials	Mushtaq
Street address	Heol Maes Eglwys	Surname	Wani
Town/city	Morriston		
Post Code	SA6 6NL		

Institution name	Mid Yorkshire Hospitals NHS Trust	Title	Dr
Department name	Dewsbury District Hospital	First name/ Initials	Prabal
Street address	Halifax Road	Surname	Datta
Town/city	Dewsbury		
Post Code	WF13 4HS		

Institution name	Mid Staffordshire NHS Foundation Trust	Title	Dr
Department name	Stafford Hospital	First name/ Initials	Anthony
Street address	Weston Road	Surname	Oke
Town/city	Stafford		
Post Code	ST163SA		

Institution name	Bronllys Hospital	Title	Dr
Department name	Stroke Medicine	First name/ Initials	Ailsa
Street address		Surname	Dunn
Town/city	Powys		
Post Code	LD30LU		

Institution name	University Hospitals Coventry and Warwickshire NHS Trust	Title	Ms
Department name	Clinical Sciences Research Institute	First name/ Initials	Martine
Street address	Clifford Bridge Road	Surname	Pritchard
Town/city	Coventry		
Post Code	CV22DX		

Institution name	Kettering General Hospitals NHS Foundation Trust	Title	Dr
Department name	Kettering General Hospital	First name/ Initials	Khalid
Street address	Rothwell Road	Surname	Ayes
Town/city	Kettering		
Post Code			

Institution name	Dartford and Gravesham NHS Trust	Title	Ms
Department name	Stroke Ward	First name/ Initials	Tracey
Street address	Darenth Wood Road	Surname	Daniel
Town/city	Dartford, Kent		

Post Code	DA282A		
Institution name	Stepping Hill Hospital	Title	Mr
Department name	The Blood Pressure and Heart Research Centre	First name/ Initials	Andrew
Street address		Surname	Brown
Town/city	Poplar Grove, Stockport		
Post Code	SK27JE		
Institution name	Aintree University Hospitals NHS Trust	Title	Dr
Department name	University Hospital Aintreee	First name/ Initials	Helen
Street address	Lower Lane	Surname	Martin
Town/city	Liverpool		
Post Code	L97AL		
Institution name	South Tees Hospitals NHS Trust	Title	Mr
Department name	James Cook University Hospital	First name/ Initials	David
Street address	Marton Road	Surname	Broughton
Town/city	Middlesbrough		
Post Code	TS4 3BW		
Institution name	North Devon Healthcare NHS Trust	Title	Ms
Department name	North Devon District Hospital	First name/ Initials	Jane
Street address	Raleigh Park	Surname	Hunt
Town/city	Barnstaple		
Post Code	EX314JB		
Institution name	South Devon Health Care NHS Trust	Title	Dr
Department name	Torbay Hospital	First name/ Initials	Debs
Street address	Lawes Bridge	Surname	Kelly
Town/city	Torquay		
Post Code	TQ27AA		
Institution name	Yeovil District Hospital NHS Foundation Trust	Title	Dr
Department name	Yeovil District Hospital	First name/ Initials	Khalid
Street address	Higher Kingston	Surname	Rashed
Town/city	Yeovil, Somerset		
Post Code	BA214AT		
Institution name	Royal Bournemouth Hospital and Christchurch Hospitals NHS Trust	Title	Ms
Department name	Royal Bournemouth Hospital	First name/ Initials	Anna
Street address	Castle Lane East	Surname	Orpen
Town/city	Bournemouth		
Post Code	BH77DW		
Institution name	NHS Lothian	Title	Professor

Department name	Western General Hospital	First name/ Initials	Martin
Street address	Crewe Road	Surname	Dennis
Town/city	Edinburgh		
Post Code	EH42XU		

Institution name	Birmingham Heartlands & Solihull NHS Trust	Title	Dr
Department name	Heartland Hospitals	First name/ Initials	David
Street address	Bordesley Green East	Surname	Sandler
Town/city	Birmingham		
Post Code	B95SS		

Institution name	James Paget University Hospitals NHS Trust	Title	Dr
Department name	James Paget Hospital	First name/ Initials	Peter
Street address	Lowestoft Road	Surname	Harrison
Town/city	Gorleston		
Post Code	NK340AW		

Institution name	Chesterfield Royal Hospitals NHS Foundation Trust	Title	Dr
Department name	Chesterfield Royal Hospital	First name/ Initials	Sunil
Street address	Calow	Surname	Punnoose
Town/city	Chesterfield		
Post Code	S445BL		

Institution name	Doncaster and Bassetlaw Hospitals NHS Trust	Title	Dr
Department name	Doncaster Royal Infirmary	First name/ Initials	Dinesh
Street address	Armthorpe Road	Surname	Chadha
Town/city	Doncaster		
Post Code	DN25LT		

Institution name	NHS Lanarkshire	Title	Mr
Department name	Monklands Hospital	First name/ Initials	Derek
Street address	Monkscourt Avenue	Surname	Esson
Town/city	Airdrie		
Post Code	ML6OJS		

Institution name	Royal Liverpool and Broadgreen University Hospitals NHS Trust	Title	Dr
Department name	Royal Liverpool Hospital	First name/ Initials	Aravind
Street address	Prescot Street	Surname	Manoj
Town/city	Liverpool		
Post Code	L78XP		

Institution name	East Kent Hospitals University NHS Trust	Title	Dr
Department name	Queen Elizabeth the Queen Mother Hospital	First name/ Initials	Gunaratnam
Street address	St Peters Road	Surname	Gunathilingam
Town/city	Margate Kent		
Post Code	CT94N		

Institution name	Northampton General Hospitals NHS Trust	Title	Dr
Department name	Northampton General Hospital	First name/ Initials	Angela
Street address	Cliftonville	Surname	Kannan
Town/city	Northampton		
Post Code	NN15BD		

Institution name	South Eastern Trust and Social Care Trust	Title	Dr
Department name	Ulster Hospital	First name/ Initials	Michael
Street address	Dundonald	Surname	Power
Town/city	Belfast		
Post Code	BT161RH		

Institution name	Kings College Hospital NHS Trust	Title	Professor
Department name	Kings College Hospital	First name/ Initials	Lalit
Street address	Denmark Hill	Surname	Kalra
Town/city	London		
Post Code	SE58AF		

Institution name	Royal Devon and Exeter NHS Foundation Trust	Title	Ms
Department name	Royal Devon and Exeter Hospital	First name/ Initials	Nicola
Street address	Barrack Road	Surname	Wedge
Town/city	Exeter		
Post Code	EX25DW		

Institution name	Harrogate and District NHS Trust	Title	Ms
Department name	Harrogate District Hospital	First name/ Initials	Jackie
Street address	Lancaster Park Road	Surname	Strover
Town/city	Harrogate		
Post Code	HG27SX		

Institution name	Northern Health and Social Care Trust	Title	Ms
Department name	Antrim Hospital	First name/ Initials	Sharon
Street address	Bush Road	Surname	Hope
Town/city	Antrim		
Post Code	BT43 6DA		

Institution name	Royal Cornwall Hospitals NHS Trust	Title	Ms
Department name	Royal Cornwall Hospital	First name/ Initials	Frances
Street address		Surname	Harrington
Town/city	Truro, Cornwall		
Post Code	TR1 3LJ		

Institution name	North West London Hospitals NHS Trust	Title	Dr

Department name	Northwick Park Hospital	First name/ Initials	David
Street address	Watford Road		
Town/city	Harrow, London	Surname	Cohen
Post Code	HA13UJ		

Institution name	Calderdale and Huddersfield NHS Trust	Title	Mr
Department name	Calderdale Royal Hospital	First name/ Initials	John
Street address	Salterhebble		
Town/city	Halifax	Surname	Hodgson
Post Code	HX3OPW		

Institution name	University Hospitals of North Staffordshire NHS Trust	Title	Professor
Department name	The Royal Infirmary	First name/ Initials	Christine
Street address	Princes Road		
Town/city	Hartshill, Stoke-on-Trent	Surname	Roffe
Post Code	S747LN		

Institution name	Salford Royal NHS Foundation Trust	Title	Dr
Department name	North West Stroke Research Network	First name/ Initials	Pippa
Street address	Stott Lane		
Town/city	Salford	Surname	Tyrell
Post Code	M68HD		

Institution name	Northern Lincolnshire and Goole NHS Hospitals NHS Trust	Title	Dr
Department name	Diana Princess of Wales Hospital	First name/ Initials	Joseph
Street address	Scartho Road		
Town/city	Grimsby	Surname	Adiotomre
Post Code	DN332BA		

Institution name	Brighton and Sussex University Hospitals NHS Trust	Title	Professor
Department name	Royal Sussex County Hospital	First name/ Initials	C
Street address	Eastern Road		
Town/city	Brighton	Surname	Rajkumar
Post Code	BN2 5BE		

Institution name	Taunton and Somerset NHS Foundation Trust	Title	Ms
Department name	Musgrove Park Hospital	First name/ Initials	Libby
Street address			
Town/city	Taunton	Surname	Caudwell
Post Code	TA15DA		

Institution name	Devon NHS Primary Care Trust	Title	Mr
Department name	Newton Abbot Community Hospital	First name/ Initials	Alex
Street address	West Golds Road		
Town/city	Newton Abbot	Surname	Beck
Post Code	TQ122SL		

Institution name	Royal United Hospital Bath NHS Trust	Title	Ms
Department name	Royal United Hospital	First name/ Initials	Denise
Street address	Combe Park	Surname	Button
Town/city	Bath		
Post Code	BA13NG		

Institution name	Mayday Health Care NHS Trust	Title	Dr
Department name	Mayday University Hospital	First name/ Initials	Enas
Street address	530 London Road	Surname	Lawrence
Town/city	Croydon, London		
Post Code	CR77YE		

Institution name	Plymouth Hospitals NHS Trust	Title	Mr
Department name	Derriford Hospital	First name/ Initials	Benjamin
Street address	Crownhill Road	Surname	Hyams
Town/city	Plymouth		
Post Code	PL68DH		

Institution name	Leeds Teaching Hospitals NHS Trust	Title	Dr
Department name	Leeds General Infirmary	First name/ Initials	Ahamad
Street address	Great George Street	Surname	Hassan
Town/city	Leeds		
Post Code	LS13EX		

Institution name	North Cumbria University Hospitals NHS Trust	Title	Ms
Department name	West Cumberland Hospital	First name/ Initials	Rachel
Street address	Whitehaven	Surname	Jolly
Town/city	Cumbria		
Post Code	CA288JG		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the main REC or the GTAC (as applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the main REC, in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs.
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- [x] Chief Investigator
- [ ] Sponsor
- [ ] Study co-ordinator
- [ ] Student
- [ ] Other – please give details
- [ ] None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

- [ ] I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name: Professor Philip Bath

Date: 24/07/2009 *(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

4. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

5. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

6. I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Signature: .....

Print Name:

Post:

Organisation:

Date: *(dd/mm/yyyy)*