PODCAST STUDY
SUBSTANTIAL PROTOCOL AMENDMENT
SUMMARY OF CHANGES VERSION 1.2

In the text below, protocol and information sheet changes, having implications for research design, conduct or participant safety have been listed. Additional, minor changes to text and formatting to bring protocol/information sheets and consent forms up-to-date are not described below but can be viewed in the 'marked' version of the protocol and information sheets.

PROTOCOL VERSION 1.2: SUMMARY OF CHANGES

Background Information and Rationale

1.2.2 Lipid Lowering

Figure 3 (Effect of Statins on Cognition) has been updated to include data from the LEADe study.

Trial Design

Information under 3.1 Trial Configuration and 3.2 Trial Overview has been merged under one heading: 3.1**: Trial Configuration** and repeat information has been deleted.

3.2.1 Trial flow chart has been moved to 3.4.1 'Duration of trial and participant involvement' as Figure 4.

Safety Outcome measures

Existing protocol (Section 3.3.3)

4.Myositis
5.SAEs

Revised protocol (Section 3.2.3)

4. Myositis and Rhabdomyolysis
5. SAEs

Duration of the trial and participant involvement

Repeat text already covered in other sections is deleted. Trial timelines have been renamed as tables (previously subheadings).

Existing protocol (Section 3.5)

'The start-up phase will demonstrate the trial feasibility (protocol, centre/participant recruitment, intervention tolerability, and effects on BP and lipids, clinic and central follow-up, early safety – see section**Error! Reference source not found.**). Main phase funding will be sought at 18 months. Assuming a 'go' decision at 34 months (based on start-up feasibility and funding), the trial will seamlessly run into the main phase with centre expansion and increased recruitment rate. The trial, including both start-up and main phases, will run for 8 years. Participant involvement in the trial will range from 1-8 years depending on the time of recruitment (long follow-up is essential in trials of cognition since cognitive impairment may take many years to develop)

Revised Protocol (Section 3.4)

The above text has been deleted.

Recruitment

This section has been expanded to clarify trial recruitment including the screening process. A copy of the consent form along with a GP practice briefing sheet will now be posted to the GP after screening consent. GPs will also be asked to contact the research centre if they have any concerns about participating the trial. For this reason there will now be a minimum period of at least 2 weeks from screening consent to randomisation. The figure 'Trial flow chart' (previously section 3.2.1) has been moved under this heading as figure 4.

Existing Protocol (Section 3.6.1, first paragraph, last sentence)

Initial consent will be taken from participants at this point of contact for telephone assessment of cognition (telephone-mini mental status examination) and function (modified Rankin scale) at 8-26 weeks post-stroke.

Revised Protocol (Section 3.5.1)

Patient and GP contact details will be collected. Informed consent will be taken from participants at this point of contact to perform a telephone assessment of cognition (telephone-mini mental status examination) and function (modified Rankin scale) at 8-26 weeks after the stroke.

Existing Protocol (Section 3.5.1, second and third paragraph)

On the basis of these assessments of cognition and function, if the participant is eligible and interested, a participant information sheet will again be posted to the participant; a blood test request form (for lipid measurement) will also be posted for those participants whose index stroke was of ischemic type. Participants will be contacted a week later to assess their views about participating in the trial and answer any questions about the trial.

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

Revised protocol (Section 3.5.1, second and third paragraph)

On the basis of the telephone assessments, if the participant is eligible and interested, a participant information sheet will be posted to the participant; a blood test request form (for lipid measurement) will also be sent for those participants whose index stroke was of ischaemic type. The participant's GP will be informed about the study and a 'GP practice briefing sheet' (with details of GP involvement in the trial) posted to them. Should the GP have concerns about their patient participating in the study, they will be asked to contact the local hospital research centre. It is important to note that GPs will not be involved in screening and recruiting patients.

Participants will be contacted a week later to assess their views about participation in the trial and to answer any questions. If they have agreed, participants with ischaemic stroke will be asked to have the blood test (for lipids) done at their GP practice (with the posted blood test form). All participants and their informant (see **Section 3.5.5**) will be booked to come to the local hospital research centre for further discussion, and if agreeable, enrolment and randomisation into the study.There should be a minimum of 2 weeks between the screening telephone assessment and randomisation, so as to give time for the GPs to report any concerns they may have regarding their patient participating in the study. It is assumed that most GPs will want to support their patients if they elect to take part in clinical research; however, if GPs refuse, such patients will be withdrawn from the trial.

Inclusion Criteria

To allow wider cognitive scores for participants aged 60-69, the inclusion criteria has been revised

Existing Protocol (Section 3.6.2)

1. Age>70 years and telephone-MMSE >16; or age >60 years and telephone-MMSE 17-19

Revised Protocol (Section 3.5.2)

1. Age>70 years and telephone-MMSE >16; or age >60 years and telephone-MMSE 17-20/22

3.6.3 Exclusion Criteria

To allow PODCAST screening of participants randomised into acute studies, the exclusion criteria has been revised

Existing Protocol

17. Ongoing participation in trials involving drug (including CTIMP trials) and/or devices.

Revised Protocol
17. Ongoing participation in trials involving drug (including CTIMP trials) and/or devices. Particpants may be screened if already in another trial, provided the participation in that trial is complete prior to PODCAST randomisation.

3.6.4 Informed Consent

Following feedback from the Scottish REC and interested sites, it was felt that al all participants have consented to participate in the study, re-consenting by informants should participants lose capacity, was not necessary. However, as per the Mental Capacity Act 2005, England, if participants lose capacity during the trial, and the informant felt it was not in the participant's best interests to continue participation, they may choose to withdraw participants from the study. The informant sheets/consent forms related to participants losing capacity have been withdrawn and this section of the protocol has been revised.

Existing Protocol (Section 3.6.4 Paragraph 3, 2nd sentence)
Principal investigators and trial doctors taking consent will have had training in the requirements of the Mental Capacity Act. Other research staff/nurses involved will also have some training in assessing capacity.

Revised protocol (Section 3.5.4)
The above 2 sentences have been deleted.

Existing protocol (Section 3.6.4 Paragraph 4, 2nd sentence)
These questions will be asked at every clinic visit and telephone follow-up to assess participant's capacity to maintain consent during the trial.

Revised protocol (Section 3.5.4)
The above sentence has been deleted.

Existing protocol (Sec 3.6.4 paragraph 7)
As assessment of cognitive impairment is one of the objectives of the trial, it is inevitable that some participants will lose the capacity to maintain consent for the trial. All participants will be asked at enrolment, if they would agree to continue in the study, should they lose the capacity to maintain consent during the study period. For such participants, proxy consent to continue in the study will be obtained from the informant (relative/friend), who will be made aware of the participant's wishes at enrolment as in Figure 4.

Revised Protocol (Section 3.5.4)
The above sentences have been deleted and revised as follows.

As assessment of cognitive impairment is one of the objectives of the trial, it is inevitable that some participants will lose the capacity to maintain consent for the duration of their participation. This will be explained to potential participants. Consent will be taken at enrolment, to continue in the trial, should participants lose the capacity to maintain consent during the trial. However, if a participant

has lost capacity and the participant's informant feels that continuing in the trial is not in the participant's best interests, the informant can withdraw the participant from the trial.

Trial Treatment And Regimen

This section has been revised and rearranged following feedback from the participating centres. Repeat information has been deleted. A new subsection 3.6.1 ***Follow up visits*** has been added. Algorithms for guideline BP and lipid lowering have been withdrawn due to varying local practice; investigators/GPs will be advised to follow local policy and current national/international guidelines.

Algorithms for intensive BP and lipid lowering have been updated to reflect current evidence and practice. The protocol emphasises that these algorithms are only a guide and where possible, local policy/patient indications should be adhered, as the trial is testing management strategies, not individual drugs.

Existing protocol (Section 3.6 First paragraph)

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

Revised Protocol (section 3.6 3rd pargraph)

The trial will assess management strategies ('intensive' vs. 'guideline'), not particular drugs. All participants will receive lifestyle advice. Participants randomised to the guideline groups will be managed by their GP as per the current national/international guidelines and local practice. Participants in the intensive group will be managed by the local hospital research centre and medications initiated by either the local investigator or GP (following advice from the local investigator), and continued by the GP. The trial does not stipulate specific drugs but gives examples of these and relevant doses. The local hospital research centres and clinicians can use locally supported interventions as long as they fit with the overall design of the trial, i.e. intensive versus guideline BP and lipid lowering.

Revised protocol (Section 3.6)-added text

Study participants will be randomised to:

- Intensive or guideline BP lowering (all participants)
- Intensive or guideline lipid lowering (ischaemic stroke only)

As a result, patients can be randomised to one of 6 groups:

- Intensive BP lowering and intensive lipid lowering (ischaemic stroke only)
- Intensive BP lowering and guideline lipid lowering (ischaemic stroke only)
- Guideline BP lowering and intensive lipid lowering (ischaemic stroke only)
- Guideline BP lowering and guideline lipid lowering (ischaemic stroke only)
- Intensive BP lowering only (intracerebral haemorrhage only)
- Guideline BP lowering only (intracerebral haemorrhage only)

Revised protocol (Section 3.6.1 Follow up visits)-added text
All participants will be followed up at six months and then annually at the local hospital research centre; a blood form for U&E and lipids (ischaemic stroke patients only) will be posted to the participants 2-3 weeks prior to each clinic visit. They will be advised to have the test done, at their GP practice, 1-2 weeks prior to the visit, to aid treatment decisions during the clinic visit. Cognition and other outcome data will be collected at each clinic visit (see **section 3.2, appendices A-K)**.All participants will also have telephone follow-up calls assessing cognition and dependency (see **section 3.2, appendices C,D,F,G,H,I,J,K**) at 12 months and then annually (alternating 6 month clinic and telephone follow-ups).

Participants in the intensive blood pressure group will have additional follow-up at one, two and three months after randomisation to monitor and modify treatment if necessary. These participants will be provided with a blood test form for U&E (urea and electrolytes) at: baseline, one month and two month visits, and advised to have the test at their local GP practice, 1-2 weeks prior to the next clinic visit. Rapid escalation and continuing intensive maintenance treatment is vital to ensure that a long-term difference in SBP of at least 10 mmHg is present between the treatment groups.

Participants in the intensive lipid lowering group will have an additional follow-up at three months after randomisation to monitor and modify treatment if necessary. These participants will be provided with a blood test form for lipids at the baseline visit and advised to have the test done at their local GP practice, 1-2 weeks priot to their 3 month visit.

The following data collected during clinic follow-up visits will be fed back to the GPs by the PODCAST ICC annually, as they also qualify as 'Quality and Outcomes Framework (QOF)' indicators: type of stroke, presence of myocardial infarction, angina, heart, failure, atrial fibrillation, dementia, depression, asthma or COPD (chronic obstructive pulmonary disease); BP, BMI (Body Mass Index), cholesterol levels, eGFR (estimated glomerular filtration rate); list of participant's medications such as antihypertensive medications, lipid lowering agents, antiplatelets and anticoagulants; smoking status, advice on smoking cessation and dietary changes. Prior consent will be taken from all participants to share this information with their GPs.

Statistics

Analysis of cognition data (Existing protocol Section 3.8.2.2, Revised protocol 4.2.2)
Figure 8 has now been updated with a scale for the 'X' axis

Existing protocol Section 3.8.3.2, Revised Protocol 4.3.2 Main Phase
Correction has been made to the Number needed to treat from 25 to 20

Adverse Events

Text relating to recording adverse events/reactions from 'Definitions' (existing protocol 3.9.1, revised protocol 5.1) is deleted as this information is already covered in Recording and Safety reporting(existing protocol 3.9.3, revised protocol 5.3)

Existing Protocol (Section 3.9.1.2)
An adverse reaction (AR) is any untoward and unintended response in a participant to a drug, which is related to any dose administered to that participant. PODCAST will collect and record ARs; although these will be presented to the Data & Monitoring Committee, they will not be reported to National Competent Authorities.

Revised Protocol (5.1.2)
An adverse reaction (AR) is any untoward and unintended response in a participant to a drug, which is related to any dose administered to that participant. Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Existing Protocol (Section 3.9.1.4)
PODCAST will collect and record SAEs/SARs; although these will be presented to the Data & Monitoring Committee, they will not be reported to National Competent Authorities

Revised Protocol (Section 5.1.4)
The above sentence has been deleted

Recording and Safety Reporting (Adverse reactions)

Existing Protocol (3.9.3.2)
All ARs listed in the British National Formulary for antihypertensive and lipid lowering drugs and occurring in participants will be recorded in the trial database, but not reported to regulatory authorities. It is important to record these ARs, since they will influence blood pressure and/or lipid management strategies as per the guiding algorithms. A list of recognised ARs associated with blood pressure and lipid lowering drugs will be given in a working practice document; this will be updated as necessary.

Revised Protocol (5.3.2)
Medically important ARs listed in the British National Formulary for antihypertensive and lipid lowering drugs will be recorded in the trial database, but not reported to regulatory authorities. It is important to record these ARs, since they will influence blood pressure and/or lipid management strategies as per the guiding algorithms.

Ethical and regulatory aspects

Existing protocol (Section 7.2, Paragraph)

Revised protocol
Text relating to re-consent if participants lose capacity has been deleted

Scan Transfer and Storage

This section has been revised to be compliant with the Data Protection Act and NHS guidelines regarding transfer of electronic data. In summary, postage of unanonymised CD/DVDs is not allowed and centres will be asked to use the secure web upload facility that automatically checks and anonymised the data or send encrypted CD/DVDs with password communicated separately.

Existing protocol (Section 3.11.3.3)
Baseline and subsequent clinical or research CT and/or MR brain scans should be sent electronically over the web (ideally), or on a CD or DVD, or by film (the latter two mailed to the PODCAST International Coordinating Centre in Nottingham). Ideally, investigators should use the secure Internet upload facility provided on the PODCAST website (www.podcast-trial.org/) which includes automatic checking then anonymisation of images. If films are posted, these will be digitised and the resulting data anonymised. All digital brain image data will be stored on computer servers for adjudication, analysis and archiving.

Revised protocol (Section 7.3.3)
- Baseline and subsequent clinical or research CT and/or MR brain scans should be sent electronically (ideally) using the secure internet webload facility provided on the PODCAST website (www.podcast-trial.org/). Scans should not be anonymised prior to upload as certain fields such as study date, birth date and sex are essential to ensure that the scan is matched to the patient. The upload facility will transfer data using RC4-MD5 (128 bit) cipher encryption and anonymise the DICOM header of the images automatically. The DICOM header attributes that are anonymised are a subset of those specified in the 'Basic Application Level Confidentiality Profile' of the DICOM standard 3.15; namely the institution name, institution address, referring physician, referring physician's address, patient name, patient identifier, date of birth,other patient id, other patient names and patient's address attributes.
- If centres are unable to use the web upload facility, non anonymised scans can be copied on a CD/DVD with the data encrypted. The encrypted CD/DVD

should be sent via recorded delivery to the PODCAST ICC. The password should be communicated separately via email. The data will be unencrypted at the PODCAST ICC and uploaded to the database as described previously (see above)

- If centres are unable to send the scans by the above methods, they will be advised to contact the PODCAST ICC, who will help them with the process.
- Under exceptional circumstances, for centres where the only method of transferring images is by films/hardcopies, centres will be advised to send non anonysmised films (this is essential as the co-ordinating centre can ensure that the scans can be checked against patient details) via recorded delivery.These will be digitised and the resulting data anonymised.
- All digital brain image data will be stored on secure computer servers owned and maintained by the Information Services, University of Nottingham, with access restricted both physically (locked server rooms) and by password. Access for adjudication, analysis and archiving will be by password.
- Anonymised imaging data shall be adjudicated by trained neuroradiologists who may be based at the Coordinating Centre or elsewhere.

Definitions: Appendix L

Definition for statins has been added

Statin Classification ('guideline' statins and 'intensive' statins)

'Guideline' statins: Simvastatin ≤ 40 mg, Any dose of Pravastatin, Fluvastatin, Atorvastatin 10 mg.

'Intensive' statins: Atorvastatin ≥ 40 mg,

Moderate bleeds

Existing protocol

Bleeding causing fall in haemoglobin of less than 2 g/l (1.24 mmol/l), and leading to no transfusion, or transfusion of only 1 unit of whole blood or red cells.

Revised protocol

Bleeding causing fall in haemoglobin of 1-2 g/l, and leading to no transfusion, or transfusion of only 1 unit of whole blood or red cells.

INFORMATION SHEET AND CONSENT FORMS

The information sheets and consent forms have been version and date controlled. The information sheets have been renamed to achieve naming consistency. The revised names are highlighted in bold text.

1. PODCAST MAIN STUDY: PARTICIPANT INFORMATION SHEET:
   PARTICIPANT INFORMATION SHEET: MAIN STUDY
2. PODCAST SUB STUDIES: PARTICIPATION INFORMATION SHEET
   PARTICIPANT INFORMATION SHEET: SUB STUDY
3. PODCAST MAIN STUDY: PARTICIPANT SCREENING CONSENT FORM
   PARTICIPANT CONSENT FORM: SCREENING
4. PODCAST MAIN STUDY:PARTICIPANT CONSENT FORM
   PARTICIPANT CONSENT FORM: MAIN STUDY
5. PODCAST SUBSTUDIES: PARTICIPANT CONSENT FORM
   PARTICIPANT CONSENT FORM: SUB-STUDIES
6. INFORMATION FOR THE GENERAL PRACTITIONER:REGARDING PATIENT SCREENING FOR PODCAST STUDY
   GP LETTER: SCREENING
7. PODCAST STUDY ENROLMENT: INFORMATION FOR THE GENERAL PRACTITIONER:
   GP LETTER: ENROLMENT
8. GP LETTER: RE: PATIENT DEVELOPING PROBABLE DEMENTIA
   GP LETTER: DIAGNOSIS OF PROBABLE DEMENTIA
9. PODCAST MAIN STUDY: INFORMANT INFORMATION SHEET
   INFORMANT INFORMATION SHEET
10. INFORMANT CONSENT FORM; AS INFORMANT FOR THE STUDY
    INFORMANT CONSENT FORM

The following information sheets/consent forms will be withdrawn from the study, as re-consent from informants will not be taken, should participants lose capacity to maintain consent.

1. INFORMANT INFORMATION SHEET: PODCAST Main Study (If participant loses capacity to maintain consent)
2. INFORMATN INFORMATION SHEET: PODCAST Sub Studies (If participant loses capacity to maintain consent)
3. INFORMANT CONSENT FORM:PODCAST Main Study (If participant loses capacity to maintain consent)
4. INFORMANT CONSENT FORM:PODCAST Sub studies (If participant loses capacity to maintain consent)

PARTICIPANT INFORMATION SHEET: SUMMARY OF CHANGES

PART 2A: PURPOSE AND WHAT WILL HAPPEN IF YOU TAKE PART? What is the purpose of the study? Sentence one:

The first sentence in 'Purpose of the study' has been updated with facts to highlight the problem.

Existing Information sheet

Many patients who have had a stroke develop problems with memory and thinking that may lead to dementia.

Revised information sheet

Upto 30 % of patients who have had a stroke develop problems with memory and thinking that may lead to dementia in the following 5 years.

PART 2A: PURPOSE AND WHAT WILL HAPPEN IF YOU TAKE PART: What are the possible disadvantages and risks of taking part? Point 1

This section has been expanded to include the common generic side effects of BP and cholesterol lowering drugs. It is however, not possible to include all the side effects as several drugs will be used in the trial

Existing information sheet

Participants may have side effects as drug and doses are escalated to achieve blood pressure and cholesterol target levels. Participants however, will be able to inform the study staff should they develop any side effects to allow adjustments of treatment.

Revised information sheet

Drug and/or doses may need to be increased to achieve target levels for BP and cholesterol. This may increase the chance of side effects from drugs, more so for the intensive groups. However, you can inform the study staff should you develop any side effects, to allow adjustments of treatment. Your doctor will be able to tell you more about these side effects, as they will depend on the medications you are on.

One of the common side effects of BP medications is low blood pressure and falls. Some BP drugs may irritate the kidneys (renal impairment) and alter the salt levels (electrolytes) in your blood. Blood tests will be performed to monitor these side effects initially, as they are more common when medications are started.

Well known but uncommon side effects of cholesterol lowering medications are muscle aches, tenderness and weakness and very rarely muscle inflammation (rhabdomyolysis occurring in 1 in 30,000 patients/year). These medications may rarely also cause damage to the nerves in the limbs (approximately 1 in 8,000 patients/year).

It is however important to note that these drugs are licensed, well established and widely used for the treatment of BP and cholesterol, and are not experimental.

PART 2B: CONDUCT OF THE STUDY: Will my taking part in this study be kept confidential? Paragraph 3.
'Quality and Outcome Framework' indicators information collected DURING follow-up will be shared with the GPs, to help them with monitoring of their patients.

Existing information sheet
Your contact details, and those of a relative or friend that you provide, will be passed to the Trial Coordinating Centre in Nottingham. All patient information is confidential, but as your GP will be involved in you treatment they will be contacted and notified of your participation in the study.

Revised information sheet
Your contact details, and those of a relative or friend that you provide, will be passed to the Trial Coordinating Centre in Nottingham. All patient information is confidential, but as your GP will be involved in you treatment they will be contacted and notified of your participation in the study. We will also feed back to your GP, some of the information that we collect during the follow-up visits like your cholesterol levels, BP etc that will help them, to monitor your health. If you would like to know more about the information shared, please ask a member of the research staff, who will provide your more details.

PODCAST MAIN STUDY: PARTICIPANT SCREENING CONSENT FORM

Point 5 has been added.

I agree to have a blood test done to check my cholesterol levels (ischaemic strokes only*).*

PODCAST MAIN STUDY: PARTICIPANT CONSENT FORM

Point 4
has been revised, as consent from informant will no longer be taken, should the participant lose capacity during the study.

Existing Consent Form
During the period of research (up to 8 years) it is possible that I may be unable to provide continuing consent. I am however, happy for my informant (relative, friend) to provide information about me and make decisions on my behalf to continue participation in the study. I am aware that this is voluntary and my

informant (relative, friend) is free to withdraw me from the study if they feel, I will be unable to continue.

Revised Consent Form
During the period of research (up to 8 years) it is possible that I may be unable to provide continuing consent. I am however, happy for my informant (relative, friend) to provide information about me and make decisions on my behalf.

Points 6 has been changed, Point 7 added

Consent will be taken to provide information about QOF to GPs**.**

Existing Consent Form
6. I agree to take part in the above study

Revised Consent Form
6. I understand that my GP will be informed about my health status annually. I am happy for this information to be shared with my GP.

7. I agree to take part in the above study

PODCAST SUB-STUDIES: PARTICIPANT INFORMATION SHEET

GENETIC SUB STUDY: What will happen to me if I take part? First Paragraph
As the genetics blood test will involve an extra blood test, this part of the protocol has been revised

Existing Information Sheet
This study involves obtaining a single blood sample (less than one tablespoon of blood), which will be used for research purposes only. This blood sample will be obtained at the same time when your blood is taken for the main study

Revised Information Sheet
This study involves obtaining a single blood sample (less than one tablespoon of blood), which will be used for research purposes only. This blood sample will be obtained at the time of your first or second visit to the local hospital research centre.

GENETICS SUB STUDY:What are the advantages and disadvantages of taking part?
As the genetics blood test will involve an extra blood test, this part of the information Sheet has been revised

Existing Information Sheet
The blood sample will be drawn at the same time a routine blood test is obtained and therefore there will not be an additional risk for you. The amount of blood taken for the study will not be harmful to you.

Revised Information Sheet
The amount of blood taken for the study will not be harmful to you.

GP LETTERS PODCAST SCREENING/STUDY ENROLMENT

The GP letters have been extensively revised and rewritten following feedback from participating sites. Dr M Bicknell, GP from Nottingham has been actively involved in the designing of these letters. The rewritten GP letters are enclosed. A new letter called the 'GP practice briefing sheet' will now be posted to the GPs following the screening telephone assessment and at enrolment.