PODCAST STUDY
SUBSTANTIAL PROTOCOL AMENDMENT SUMMARY OF CHANGES VERSION, 1.4 to 1.5

Please note all forms requiring approval have been changed to version 1.5.

Listed in the text below are protocol and information sheet changes having implications for research design, conduct or participant safety. 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 1.5: SUMMARY OF CHANGES

The protocol has been version and date controlled from Version 1.4 to Version 1.5.

Please note that pages and sections listed below relate to version 1.4, 26 April 2011 of the protocol. The table of contents has been updated to reflect the changes.

1. Page 2: Trial Personnel and Contact Details, TSC member list and statistician details removed.

2. The intensive target LDL-C target has been changed from <2.0mmol/L to <1.4mmol/L and the intensive target for Total Cholesterol has been changed from <4.0mmol/L to <3.1mmol/L.

a. Page 4, Synopsis, Description of Interventions, lipid lowering strategy:
'Intensive' group – target LDL-cholesterol <2.0 mmol/l (or total cholesterol <4.0 mmol/l if LDL-cholesterol cannot be calculated)
'Guideline' group –target LDL-cholesterol <3.0 mmol/l (or total cholesterol <5.0 mmol/l if LDL-cholesterol cannot be calculated)
Change to
'Intensive' group – target LDL-cholesterol <1.4 mmol/l (or total cholesterol <3.1 mmol/l if LDL-cholesterol cannot be calculated)
'Guideline' group –target LDL-cholesterol <3.0 mmol/l (or total cholesterol <5.0 mmol/l if LDL-cholesterol cannot be calculated)

b. Page 33, Section 3.6.3.1, 1st paragraph, 1st sentence.
The target is a LDL-cholesterol (LDL-c) of <2.0 mmol/l (or total cholesterol <4.0 mmol/l if LDL-cholesterol cannot be calculated, e.g. because of high triglyceride levels).
Change to
The target is a LDL-cholesterol (LDL-c) of <1.4 mmol/l (or total cholesterol <3.1 mmol/l if LDL-cholesterol cannot be calculated, e.g. because of high triglyceride levels).

c. Page 33, Section 3.6.3.1, 2nd paragraph, 1st and 2nd sentences.
At the baseline research clinic, and unless the LDL-cholesterol is <2.0 mmol/l, participants should, ideally, be started on, or switched to, a 'high intensity' statin (e.g. atorvastatin ≥40 mg,[2, 55]). Ezetimibe (10 mg od [56]) may be added at subsequent clinics if the LDL-cholesterol >2.0 (or total cholesterol >4.0 mmol/l if LDL-cholesterol cannot be calculated).
Change to
At the baseline research clinic, and unless the LDL-cholesterol is <1.4 mmol/l, participants should, ideally, be started on, or switched to, a 'high intensity' statin (e.g. atorvastatin ≥40 mg,[2, 55]). Ezetimibe (10 mg od [56]) may be added at subsequent clinics if the LDL-cholesterol >1.4 (or total cholesterol >3.1 mmol/l if LDL-cholesterol cannot be calculated).

d. Changes made to Page 35, Figure 7: Intensive Lipid Treatment Algorithm table, to reflect amended intensive lipid targets. Then moved to a working practice document.

3. Page 5, Abbreviations, updated to reflect addition of HbA1c blood test.

4. Pages 9 - 13, removal of 'Background Information and Rationale' from protocol and placed into a newly created Investigator's Brochure.

5. Page 8, deletion of Appendix J: DEMQOL. Test not used in the conduct of the study.

a. Change made to page 15, 3.2.2. Secondary outcome measures, point three.
3. Quality of life – EuroQoL[37], DEMQOL (by informant) [38]
Change to
3. Quality of life – EuroQoL[37]

b. Change made to page 22, 3.5.2, Inclusion Criteria, point seven.
7. Presence of an informant: partner, sibling, child, friend (for IQCODE/DEMQoL)
Change to
7. Presence of an informant: partner, sibling, child, friend (for IQCODE)

c. Change made to page 24, 3.5.5. Informant (Consultee), 1st paragraph.
Availability of an informant (partner, sibling, child, friend) for the participant is a key inclusion criterion in the trial, as informant questionnaires (IQCODE/DEMQOL) can give vital information about the participant's cognition.
Change to
Availability of an informant (partner, sibling, child, friend) for the participant is a key inclusion criterion in the trial, as informant questionnaires (IQCODE) can give vital information about the participant's cognition.

6. **Addition made to page 15, 3.2.1 primary outcome measure, 1st paragraph, and new working practice document created.**
For each of BP-lowering and lipid-lowering arms, comparison between 'intensive' and 'guideline' groups, of cognition, assessed using the Addenbrooke's Cognitive Examination- Revised (ACE-R)[29], (a superset of the Mini-Mental State Examination, MMSE[30]).
Change to
For each of BP-lowering and lipid-lowering arms, comparison between 'intensive' and 'guideline' groups, of cognition, assessed using the Addenbrooke's Cognitive Examination- Revised (ACE-R)[29], (a superset of the Mini-Mental State Examination, MMSE[30]). Certain memorable items in the ACE-R will be cycled at each time point - see working practice document.

7. Addition and changes made to page 16, Section 3.3.1, to minimisation variables.

8. Changes made to page 16, Section 3.4, Duration of the Trial and Participant Involvement, 1st paragraph, and Table 1.
The start up phase will run for 3 years with participant recruitment in the first 2 years (300 participants per annum from 30 UKSRN sites = 1 participant/site/month) with average follow-up 2 years (minimum 1 year). The main phase will then run for a further 5 years (total 8 years).
Change to
The start up phase will run for 3-4 years with participant recruitment from 30 UKSRN sites = 1 participant/site/month) with average follow-up 2 years (minimum 1 year). The main phase will then run for a further 4-5 years (total 8 years).

9. Addition and changes made to page 18, Table 3: Participant measures: Start-up and main phase. Table has been updated to reflect the additional test for HbA1c. The table has also been updated with corrections and omissions ie the informant telephone interviews have now been listed, the times for ABPMs to be conducted have been correctly listed, the times for ECGs to be conducted have been correctly listed, the yearly telephone follow-ups have been listed, the BP will now be obtained at a face-to-face appointment.

10. The telephone screening is to change to a face-to-face appointment at the research clinic. This is to allow for standardisation of the collection of the BP readings used for the eligibility check.

a. Change in page 20, Section 3.5.1, 1st paragraph.
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.
Change to
Informed consent will be taken from participants at this point of contact to perform a face-to-face assessment of cognition ("telephone-mini mental status examination") and function (modified Rankin scale) at 8-26 weeks after the stroke.

b. Change to page 20, Section 3.5.1, 2nd 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 fasting lipids, glucose and urea and electrolytes will also be sent.
Change to
On the basis of the assessments, if the participant is eligible and interested, a participant information sheet, substudy information sheet (if taking part), and informant information sheet, will be given to the participant; a blood test request form for fasting lipids, glucose, urea and electrolytes, and HbA1c will also be provided.

c. Change to page 23, Section 3.5.4, 1st paragraph listing the assessments.
Informed consent for screening will be taken at this point of contact for conducting the following assessments, 8 to 26 weeks after their stroke:

(i) telephone assessment of cognition (telephone-mini mental status examination)
(ii) telephone assessment of function (modified Rankin scale)
(iii) blood test for fasting lipids, glucose, and urea and electrolytes.

Change to
Informed consent for screening will be taken at this point of contact for conducting the following assessments, 8 to 26 weeks after their stroke:

(i) assessment of cognition ("telephone-mini mental status examination")
(ii) assessment of function (modified Rankin scale)
(iii) blood test for fasting lipids, glucose, urea and electrolytes, and HbA1c.

d. Change to page 23, Section 3.5.4, 2nd paragraph.
If participants are eligible and interested, a participant information sheet along with a blood test form for fasting lipids, glucose, urea and electrolytes, and HbA1c will be posted to them.
Change to
If participants are eligible and interested, a participant information sheet, a substudy information sheet (if taking part), and informant information sheet, along with a blood test form for fasting lipids, glucose, urea and electrolytes, and HbA1c will be given to them.

11. All patients will now have fasting lipids, glucose and urea and electrolytes, and HbA1c.
a. Change to page 20, Section 3.5.1, 2nd paragraph, 1st sentence.
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 fasting lipids, glucose and urea and electrolytes will also be sent.
Change to
On the basis of the telephone assessments, if the participant is eligible and interested, a participant information sheet, a substudy information sheet (if taking part), and informant information sheet, will be given to the participant; a blood test request form for fasting lipids, glucose, urea and electrolytes, and HbA1c will also be provided.

b. Addition to page 20, Section 3.5.1, 3rd paragraph, 2nd sentence.
If they have agreed, participants will be asked to have the blood test (for fasting lipids, glucose and urea and electrolytes) done at their GP practice (with the posted blood test form).
Change to
If they have agreed, participants will be asked to have the blood test (for fasting lipids, glucose, urea and electrolytes, and HbA1c) done at their GP practice (with the blood test form provided).

c. Addition to page 23, Section 3.5.4, 1st paragraph, 4th sentence, 3rd point.
(iii) blood test for fasting lipids, glucose and urea and electrolytes
Change to
(iii) blood test for fasting lipids, glucose, urea and electrolytes, and HbA1c

d. Changes to page 23, Section 3.5.4, 2nd paragraph, 1st sentence.
If participants are eligible and interested, a participant information sheet along with a blood test form for fasting lipids, glucose and urea and electrolytes will be posted to them.
Change to
If participants are eligible and interested, a participant information sheet, substudy information sheet (if taking part), and informant information sheet, along with a blood test form for fasting lipids, glucose, urea and electrolytes, and HbA1c will be given to them.

e. Change to page 27, Section 3.6.1, 1st paragraph, 1st sentence.
All participants will be followed up at six months and then annually at the local hospital research centre; a blood form for fasting lipids, glucose and urea and electrolytes will be posted to the participants 2-3 weeks prior to each clinic visit.
Change to
All participants will be followed up every six months at the local hospital research centre; a blood form for fasting lipids, glucose, urea and electrolytes, and HbA1c will be posted to the participants 2-3 weeks prior to each clinic visit.

12. The time between the screening assessment and randomization has been reduced to 1 week.

a. Change to page 20, Section 3.5.1, 3rd paragraph, 1st sentence.
Participants will be contacted a week later to assess their views about participation in the trial and to answer any questions.
Change to
Participants will be contacted a few days later to assess their views about participation in the trial and to answer any questions.

b. Change to page 20, Section 3.5.1, 3rd paragraph, 4th sentence.
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.
Change to
There should be a minimum of 1 week between the screening 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.

c. Change to page 23, Section 3.5.4, 3rd paragraph.
Participants will be contacted a week later to assess their views and answer questions about the trial.
Change to
Participants will be contacted a few days later to assess their views and answer questions about the trial.

13. Clarification of point 3, page 22, Inclusion Criteria, Section 3.5.2.
3. Ischaemic stroke (any cortical OCSP/TOAST type) or primary intracerebral haemorrhage (cortical or basal ganglia)
Change to
3. Ischaemic stroke. Strokes may be of any OCSP/TOAST type and in the anterior or posterior circulation.

14. Posterior strokes will no longer be excluded, page 22/23, 3.5.3 Exclusion Criteria. 4. Posterior circulation ischaemic stroke and 5. Posterior circulation haemorrhage, have both been removed from the list of exclusions.

15. Exclusion list to include NYHA classification of 3 or 4.
Addition of exclusion number 19: NYHA classification of 3 or 4

16. **Follow up visits.** All patients will now be seen in clinic every 6 months. Cognitive testing will still only take place as before ie at 6 months, 18 months, 30 months etc but in addition to the telephone assessments at 12 months, 24 months etc, patients will attend their local research clinic for BP and lipid monitoring and will receive lifestyle advice. If patients are failing to reach BP and lipid targets at these newly scheduled appointments they will be asked to revisit the research clinic one month later for monitoring.

a. Addition and changes made to page 27, Section 3.6.1**.**
All participants will be followed up at six months and then annually at the local hospital research centre; a blood form for fasting lipids, glucose, urea and electrolytes, and HbA1c 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 2.2, appendices A-J)**. All participants will also have telephone follow-up calls assessing cognition and dependency (see **section 2.2, appendices C,D,F,G,H,I,J,**) at 12 months and then annually (alternating 6 month clinic and telephone follow-ups. The index event ECG will be collected at the Baseline visit. An ECG will be taken at each clinic visit.
Change to
All participants will be followed up every six months at the local hospital research centre; a blood form for fasting lipids, glucose, urea and electrolytes, and HbA1c 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 the 6 month, 18 month, 30 month etc clinic visits (see **section 2.2, appendices A-J)**. Cognition data will not be collected at the 12 month, 24 month, 36 month clinic visits as all participants will also have telephone follow-up calls assessing cognition and dependency (see **section 2.2, appendices C,D,F,G,H,I,J,**) at 12 months and then annually. The index event ECG will be collected at the Baseline visit and an ECG will be taken at the 6 month, 18 month, 30 month etc clinic visits.

b. Addition made to page 28, Section 3.6.1.
At formal research clinic appointments, if an intensive patient is found to have BP and/or lipid readings above the specified trial targets please bring them back to a 'floating' appointment. This should be at 1month post clinic. The follow-up comprises assessment of the latest BP and/or lipid levels, current medications, any recent adverse events, and any new other medical history. Subject to these, treatment should be escalated.

17. Removal of Figure 6: Intensive BP Treatment Algorithm (page 31) from the protocol and working practice document created.
Addition at the end of section 3.6.2.3, page 30 to clarify:
Further information on intensive blood pressure management is given in a working practice document.

18. Page 33, change in Section 3.6.2.3, 2nd paragraph.
Clarification regarding number of blood pressures to be obtained
Baseline and follow-up systolic and diastolic blood pressure and heart rate data are taken in triplicate (3 measurements taken in rapid succession) in the non-paretic arm with the participant sitting and readings entered on the baseline form.
Change to
Baseline and follow-up systolic and diastolic blood pressure and heart rate data are taken (4 measurements taken in rapid succession) in the non-paretic arm with the participant sitting (3 readings) and standing (1 reading) entered on the baseline form.

19. Clarification regarding intensive and guideline lipid medications.

a. Change in page 33, Section 3.6.3.2, 3rd sentence.
Drug therapy will typically comprise a 'guideline' statin, e.g. simvastatin 40 mg on, pravastatin 40 mg on, fluvastatin 40 mg on - see NICE lipid guideline CG 67, 2008.
Change to
Drug therapy will typically comprise a 'guideline' statin, e.g. simvastatin range 10-40 mg on, pravastatin 10-40 mg on, fluvastatin 10-80mg on - see NICE lipid guideline CG 67, 2008.

b. Change in Appendix L, page 81: Definitions of Statin Classification ('guideline' statins and 'intensive' statins)
'Guideline' statins: Simvastatin ≤ 40 mg, any dose of Pravastatin or Fluvastatin, Atorvastatin 10 mg, ***'Intensive' statins:*** Atorvastatin ≥ 40 mg,
Change to
Statin Classification ('guideline' statins and 'intensive' statins)
'Guideline' statins: Simvastatin ≤ 40 mg, any dose of Pravastatin or Fluvastatin, Atorvastatin ≤20 mg, ***'Intensive' statins:*** Atorvastatin > 20 mg, Rosuvastatin

20. Addition at the end of Section 4.2.2, page 39
The final analysis will be described in detail in a statistical analysis plan, available on the trial website.

21. Removal of SAE categories from the protocol and working practice document created. Addition and changes in Section 5.3.3, page 43.

So the following expected SAE'S will be recorded in the trial database but not reported to regulatory authorities. This list is a guide, and will be updated through a working practice document on the trial website (so that protocol amendments are not required).

Change to

SAE'S that can be expected after stroke will be recorded in the trial database but not reported to regulatory authorities. A list is provided in a working practice document on the trial website. This list is a guide, and will be updated through the working practice document on the trial website.

PARTICIPATION INFORMATION SHEET, PARTICIPANT CONSENT FORMS, GP LETTERS

All the documents below have been version and date controlled. The information sheet has been revised to reflect the changes made to the updated version of the protocol. The changes have been highlighted with track changes.

1**. Participant Information Sheet: Main study, Version 1.4, 26 April 2011**

a. Section 'what will happen?' Page 1, 1st paragraph

A member of the research team will contact you 2-6 months after your stroke and ask you some simple questions about your memory and thinking and activities of daily living over the telephone, to assess your eligibility for the study.

Change to

A member of the research team will contact you 2-6 months after your stroke and will arrange a 'screening' appointment at your local hospital. At the appointment you will be asked some simple questions about your memory and thinking and activities of daily living, and have your blood pressure measured to assess your eligibility for the study.

b. Section 'what will happen?' Page 1, 2nd paragraph

If eligible, an appointment will be booked for you to come to the research clinic along with a relative or a friend, as we need them to answer some questions about you, mainly about your memory and thinking.

Change to

If eligible, another appointment ('baseline') will be booked for you to come back to the research clinic along with a relative or a friend, as we need them to answer some questions about you, mainly about your memory and thinking.

c. Section 'what will happen?' Paqe 1, 3rd paragraph

In the research clinic, a study doctor will ask you questions about your stroke, perform an examination and assess your memory, thinking, mood, quality of life and activities of daily living with questionnaires and simple pen and paper tests.

Change to

In the research clinic, a study doctor will ask you questions about your stroke, perform an examination including a 'heart tracing', and assess your memory, thinking, mood, quality of life and activities of daily living with questionnaires and simple pen and paper tests.

d. Section 'what will happen?' Page 2, 'both groups'

The assessments will alternate between research clinic visits and telephone assessments such that participants will be seen in the research clinic once a year, starting at six months from enrolment. Your relative or friend will also be asked questions about your health and memory, each time you are seen.

Change to
You will have 6 monthly research clinic visits and yearly telephone assessments, such that participants will be seen in the research clinic every 6 months, starting at six months from enrolment. Your relative or friend will also be asked questions about your health and memory every 6 months.

e. Page 3, Section 'What will happen to me if I take part?', 3rd paragraph, 3rd sentence
An ECG will be taken at each visit.
Change to
An ECG ('heart tracing') will be taken once each year.

f. Page 4, Section 'What will happen to me if I take part?', 4th paragraph.
The assessments will alternate between research clinic visits and telephone questionnaires such that participants will be seen in the research clinic once a year starting at six months from the study. Your relative or friend will also be asked questions about your health and memory, every time when you are seen.
Change to
The assessments will involve 6 monthly research clinic visits and yearly telephone questionnaires such that participants will be seen in the research clinic every 6 months, starting at six months from enrolment. Your relative or friend will also be asked questions about your health and memory, every 6 months.

2. **Participant Consent Form: Screening, Version 1.4, 26 April 2011**
a. **Point one**
I confirm that I have read and understand the information sheet dated 26 April 2011 (Version 1.4) for the above study, and have had the opportunity to ask questions.
Change to
I confirm that I have read and understand the information sheet dated 28 February 2012 (Version 1.5) for the above study, and have had the opportunity to ask questions.

b. **Point three**
I agree to be contacted at home for a telephone assessment of my memory, thinking and activities of daily living.
Change to
I agree to be contacted at home to arrange an appointment, at my local hospital, to assess my memory, thinking and activities of daily living.

3**. Participant Consent Form: Main study, Version 1.4, 26 April 2011**

a. Point one

I confirm that I have read and understand the information sheet dated 26 April 2011 (Version 1.4) for the above study, and have had the opportunity to ask questions.

Change to

I confirm that I have read and understand the information sheet dated 28 February 2012 (Version 1.5) for the above study, and have had the opportunity to ask questions.

4**. GP Letter: Briefing, Version 1.5, 12 July 2011**

a. **Overview of the trial, paragraph 3**

The 'intensive' lipid-lowering group will aim for a target LDL cholesterol <2.0 mmol/l, and the 'guideline' group a target LDL-cholesterol of <3.0 mmol/l.

Change to

The 'intensive' lipid-lowering group will aim for a target LDL cholesterol <1.4 mmol/l, and the 'guideline' group a target LDL-cholesterol of <3.0 mmol/l.

b. **Outline of consumer involvement in the research project**

Three members of the Patient, Carer and Public Involvement Group have specifically reviewed and advised on the content of the information sheets. [The names of the members have been removed from the letter].

c. **What is expected of the GP practices: Blood Tests**

GP practices will be asked to perform blood tests for fasting lipids, U&E (urea and electrolytes) and glucose prior to baseline and yearly clinic visits.

Change to

GP practices will be asked to perform blood tests for fasting lipids, U&E (urea and electrolytes), glucose and HbA1c, prior to baseline and 6 monthly clinic visits.

5. **GP Letter: Screening, Version 1.1, 22 July 2010**

Patients are initially screened when they present to the hospital services and have a further telephone assessment of cognition and dependency, 2-6 months after their stroke. Your patient was found to be eligible based on the telephone screening assessment done on …… (dd/mm/yyyy) and is keen to participate in the study.

Change to

Patients are initially screened when they present to the hospital services and have a further assessment of cognition and dependency, 2-6 months after their stroke. Your patient was found to be eligible based on the screening assessment done on …… (dd/mm/yyyy) and is keen to participate in the study.

6**. GP Letter: Participation, Version 1.4, 26 April 2011**

Blood tests

All patients will be given a blood request form for urea and electrolytes, glucose and lipids prior to their local hospital research centre follow-up and will be asked to have the test done at their GP practice.

Change to

All patients will be given a blood request form for urea and electrolytes, glucose, lipids and HbA1c prior to their local hospital research centre follow-up and will be asked to have the test done at their GP practice.