PODCAST STUDY
SUBSTANTIAL PROTOCOL AMENDMENT
SUMMARY OF CHANGES VERSION 1.5 to 1.6

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

PROTOCOL VERSION 1.6: SUMMARY OF CHANGES

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Existing protocol

SYNOPSIS

Sample size estimate- Assuming overall significance α=5%, power 1-β=90%, rate of cognitive decline in 'guideline' BP group = 25% and 'intensive' BP group = 20% (absolute risk reduction 5%, relative risk reduction 20%) at 5 years, we estimate a sample size of 3,400 participants for the whole trial (start-up and main phase). The lipid factor will assume the same relative risk reduction (20 %) but will have a lower statistical power (~86 %), as it will only involve participants with ischaemic stroke (~3,060)

Revised protocol

Originally, the trial was planned as an internal pilot with an overall sample size as follows: Assuming overall significance α=5%, power 1-β=90%, rate of cognitive decline in 'guideline' BP group = 25% and 'intensive' BP group = 20% (absolute risk reduction 5%, relative risk reduction 20%) at 5 years, we estimate a sample size of 3,400 participants for the whole trial (start-up and main phase). The lipid factor will assume the same relative risk reduction (20 %) but will have a lower statistical power (~86 %), as it will only involve participants with ischaemic stroke (~3,060) Low recruitment means the internal pilot no longer justifies the main phase. So, the overall sample size is superseded.

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SYNOPSIS

Number of participants- 3,400 participants (1,700 per BP group, ~1,530 per lipid group), comprising a:
Start-up phase: 600 participants (300 per BP group, ~270 per lipid group)
Main phase: 2,800 participants (1,400 per BP group, ~1,260 per lipid group)

Revised protocol

The aim now is to recruit 120 participants by the end of January 2014.

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Duration of trial- 8 years. The proposed start date is September 2010 Start-up phase: 3 years
Main phase: 5 years

Revised protocol

Duration of trial is 4 years. The proposed start date is September 2010.

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2.4 DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

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). Participant involvement in the whole trial will range from 1-8 years depending on the time of recruitment (**See tables 1,2,3**).

Table 1: Trial timeline: Start-up phase

Time (months)	-6-0	0-2	3-6	7-18	19-24	25-30	31-36
Protocol	<>						
Approvals	<>						
Trial materials	<>						
Site identification	<	=	>				

Funding, TSA/AS		<	=	=	=	=	>
Recruit participants		<	=	=	=	=	>
DMC reviews			<	=	=	=	>
Feasibility reviews				<	=	=	>
Interim analysis (blinded)							<>

Table 2: Trial timeline: Main phase

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

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

Table 3: Participant measures: Start-up and main phase

Time (months)	Pre-screen	Screen	0	1	2	3	6	12	18	24	30	36	42	48
Inclusion	+		+											
Consent	+		+											
Randomise			+											
CT/MR scan	††							<	+	>				
ECG	†††						+		+		+		+	
BP, lipids	†													
Clinic														
BP		+	+	(+)	(+)	(+)	+	+	+	+	+	+	+	+
ABPM ‡			+				+		+		+		+	
Lipids *			+			(+)	+	+	+	+	+	+	+	+
Glucose *			+				+	+	+	+	+	+	+	+
HbA1c *			+				+	+	+	+	+	+	+	+
UE *			+	(+)	(+)	(+)	+	+	+	+	+	+	+	+
Cognition	+	+	+				+		+		+		+	
Stroke, MI							+	+	+	+	+	+	+	+
SAEs			+	(+)	(+)	(+)	+	+	+	+	+	+	+	+
Informant			+				+		+		+		+	
Telephone														

Cognition								+		+		+		+
Stroke, MI								+		+		+		+
SAEs								+		+		+		+
Informant								+		+		+		+

ABPM: Ambulatory Blood Pressure Monitoring; BP: blood pressure; MI: myocardial infarction; SAEs: serious adverse events †: BP, lipids from index event †† Clinical scan for index stroke; ‡ In participating centres; (+) In intensive groups only; ††† Clinical ECG for index stroke; perform ECG at Baseline if ECG from index event not available; Telephone cognition scores will also be used in clinic at Baseline and end of trial to calibrate them against clinic-only measures; T=telephone. * 1 week before

Revised protocol

It was planned to perform the trial in two phases: start-up and main. 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). Participant involvement in the whole trial will range from 1-8 years depending on the time of recruitment (**See tables 1 and 2**).

Due to low recruitment, the trial will not proceed to the main phase. Participant involvement in the trial will be 4.5 years.

Table 1: Trial timeline

Time (months)	-6-0	0-2	3-6	7-18	19-24	25-30	31-36	43-48
Protocol	<>							
Approvals	<>							
Trial materials	<>							
Site identification	<	=	>					
Funding, TSA/AS		<	=	=	=	=	>	
Recruit participants		<	=	=	=	=	>	
DMC reviews			<	=	=	=	>	
Final visit for participants								<>
Final data cleaning							<	>
Analysis								<>

Table 2: Participant measures: Timeline

Time (months)	Pre-screen	Screen	0	1	2	3	6	12	18	24	30	36	42	48
Inclusion	+		+											
Consent	+		+											
Randomise			+											
CT/MR scan	††							<	+					>
ECG	†††						+		+		+		+	
BP, lipids	†													

Clinic														
BP		+	+	(+)	(+)	(+)	+	+	+	+	+	+	+	+
ABPM ‡			+				+		+		+		+	
Lipids *			+			(+)	+	+	+	+	+	+	+	+
Glucose *			+				+	+	+	+	+	+	+	+
HbA1c *			+				+	+	+	+	+	+	+	+
UE *			+	(+)	(+)	(+)	+	+	+	+	+	+	+	+
Cognition	+	+	+				+		+		+		+	
Stroke, MI							+	+	+	+	+	+	+	+
SAEs			+	(+)	(+)	(+)	+	+	+	+	+	+	+	+
Informant			+				+		+		+		+	
Telephone														
Cognition								+		+		+		+
Stroke, MI								+		+		+		+
SAEs								+		+		+		+
Informant								+		+		+		+

ABPM: Ambulatory Blood Pressure Monitoring; BP: blood pressure; MI: myocardial infarction; SAEs: serious adverse events †: BP, lipids from index event †† Clinical scan for index stroke; ‡ In participating centres; (+) In intensive groups only; ††† Clinical ECG for index stroke; perform ECG at Baseline if ECG from index event not available; Telephone cognition scores will also be used in clinic at Baseline and end of trial to calibrate them against clinic-only measures; T=telephone. * 1 week before

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Existing protocol

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

Revised protocol

3. How long will treatment be continued? (Answer: 4 years)

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Existing protocol

2.5.6. Expected duration of participant participation

Trial participation will range from 1- 8? 4 years depending on the time of recruitment.

Revised protocol

2.5.6. Expected duration of participant participation

Trial participation will range up to 4 years depending on the time of recruitment.

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2.6.7 Neuroimaging Substudy

Cerebral white matter lesions (WML) have been associated with cognitive impairment in demented and non-demented elderly subjects. Whether lesion progression parallels this decline over time and whether treatment can modify this is less clear.
Separate funding is being sought to perform systematic neuro-imaging in a subset of participants. Is funding now available? All participants will be invited to take part in the imaging sub study. All participants will have a base line scan (done as part of routine clinical care at or soon after the index stroke), and is an inclusion criteria for the study. Participants will have an additional scan, as part of the imaging substudy at the end of 4 years or the end of follow up period, whichever is later. An MRI scan of the brain will be the preferred imaging method for the additional scan, as it is more informative of cognitive change. However, where MRI cannot be performed, a CT scan of the brain will be done. A typical x-ray dose for a CT brain scan is 1.5 mSv, but due to variation in protocols, machines and patient size, this may reach 5mSv per scan.
The consent form will allow the participant to opt-in to the neuro-imaging substudy. Participants may continue in the overall trial, even if they elect not to consent to the neuro-imaging substudy.

Revised protocol

2.6.7. Neuroimaging Substudy

Cerebral white matter lesions (WML) have been associated with cognitive impairment in demented and non-demented elderly subjects. Whether lesion progression parallels this decline over time and whether treatment can modify this is less clear.
Separate funding is allocated to perform systematic neuro-imaging in a subset of participants. All participants will be invited to take part in the imaging sub study. All participants will have a base line scan (done as part of routine clinical care at or soon after the index stroke), and is an inclusion criteria for the study. Participants will have an additional CT scan

of the brain, as part of the imaging substudy from the end of 1 year up to the final follow up visit. A typical x-ray dose for a CT brain scan is 1.5 mSv, but due to variation in protocols, machines and patient size, this may reach 5mSv per scan.
The consent form will allow the participant to opt-in to the neuro-imaging substudy. Participants may continue in the overall trial, even if they elect not to consent to the neuro-imaging substudy. However, information will be collected from any CT or MRI scan performed for clinical reasons after recruitment until the end of the follow up period.

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Existing protocol

3.3 Sample size and justification

3.3.1 Main phase

Currently, ACE-R will be analysed as combined cognitive impairment or death using logistic regression; however the intention is to change this to an approach which optimises statistical power, depending on the results of the OA-Cog study (as discussed in section **3.2.2**). The whole trial (start-up + main phases) will need a sample size of 3,400 (1,700 per group) post-stroke participants, assuming:

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

Hence, 765 participants (0.225 x 3,400) will need to develop cognitive impairment or die. The sample size allows a smaller but clinically worthwhile decline in cognitive decline to be identified with 80% power, i.e. ARR = 4.5% (RRR 18%). Since there are less existing data on the effect of cholesterol lowering on cognition, the statin factor will assume the same RRR (20%) but have less power (~86%) since it will only involve participants with ischaemic stroke (~3,060).
Changing from a binary to ordinal analysis of the primary outcome may allow for a reduction in sample size of up to 30%, as seen in the 'Optimising Analysis of Stroke Trials' collaboration for functional outcome after stroke.(38-40) 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.(51) Any such change will be performed prior to database lock, blinded to treatment, and defined explicitly in the Statistical Analysis Plan.

Revised protocol

3.3 Sample size and justification

3.3.1 Main phase

Currently, ACE-R will be analysed as combined cognitive impairment or death using logistic regression; however the intention is to change this to an approach which optimises statistical power, depending on the results of the OA-Cog study (as discussed in section **3.2.2**). The trial was planned as an internal pilot with an overall sample size calculated for the whole trial (start up and main phase) of 3400 as follows:

. Significance, α=5%
  Power (1-ß) = 90%

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

Assuming 3400 participants, 765 participants (0.225 x 3,400) will need to develop cognitive impairment or die. The sample size allows a smaller but clinically worthwhile decline in cognitive decline to be identified with 80% power, i.e. ARR = 4.5% (RRR 18%). Since there are less existing data on the effect of cholesterol lowering on cognition, the statin factor will assume the same RRR (20%) but have less power (~86%) since it will only involve participants with ischaemic stroke (~3,060).
Changing from a binary to ordinal analysis of the primary outcome may allow for a reduction in sample size of up to 30%, as seen in the 'Optimising Analysis of Stroke Trials' collaboration for functional outcome after stroke.(38-40) 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.(51) Any such change will be performed prior to database lock, blinded to treatment, and defined explicitly in the Statistical Analysis Plan. Low recruitment means the internal pilot no longer justifies the main phase. So, the overall sample size is superseded. The aim now is to recruit 100 participants by the end of January 2014.

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Existing protocol

7.1 Funding sources

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

Revised protocol

7.1 Funding sources

The Stroke Association UK, Alzheimer's Society UK and top-up funding by the Division of Stroke, University of Nottingham, jointly fund the trial.