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13 October 2009

Mr Robert Johnson
Vice Chairman
Nottingham Research Ethics Committee 1
1 Standard Court
Park Row
Nottingham NG1 6GN

Dear Mr Johnson and colleagues,

Study Title: **Prevention of Decline in Cognition After Stroke Trial (PODCAST): A factorial randomised trial of Intensive versus guideline lowering of blood pressure and lipids.**

REC reference No: **09/H0403/71**

Thank you for reviewing the ethics application for the PODCAST study. Your letter dated 21 September 2009 asked for further clarification and information on some issues. We have addressed these issues one by one. Clarification on the issues raised by the Scottish A Research Ethics Committee review (letter dated 28 September 2009) have also been addressed.

Further information or clarification required

Point 1

The Committee requests the following modifications to the Participant Information Sheet (PIS): -

a. The document should be rewritten and split into two parts: firstly a summary of the study followed by a second part providing a more detailed explanation

Response

1. **The Participant Informant Sheet has been rewritten. The PIS for the main study has been split into two parts as suggested. The 3 Patient, Carer and Public Involvement (PCPI) representatives on the**

Trial Steering Committee have specifically reviewed the revised versions. The Relative Information sheet has been renamed as 'Informant Information Sheet'

Please see the enclosed information sheets:

1. **PODCAST Main Study: Participant Information Sheet Version 1.1 dated 12 October 2009**
2. **PODCAST Main Study: Informant Information Sheet Version 1.1 dated 12 October 2009 (if participant loses capacity to maintain consent)**

b. Information about exactly what will happen to tissue samples should be included e.g. what will happen to tissue samples, where they will be stored, will they be sold to other companies etc.
Response
The genetics sub study has been rewritten to include more information about storing and use of data. However, this unfortunately extended the length of the information sheets, and so after discussion with the patient-carer representatives, all the three sub studies are now explained in a separate information sheet. The same approach has been adapted for the Informant/Relative information sheets.
The revised information sheets are attached:

1. **PODCAST Sub Studies: Participant Information Sheet Version 1.1 dated 12 October 2009**
2. **PODCAST Sub Studies: Informant Information Sheet Version 1.1 dated 12 October 2009 (if participant loses capacity to maintain consent)**

Point 2
A copy of any peer reviews should be submitted to the Committee
Response
The peer-review comments submitted to The Stroke Association and Alzheimer's Society prior to their funding decision have been enclosed.

Point 3
Copies of all questionnaires / surveys to be used should be submitted to the Committee.
Response
All the questionnaires/surveys to be used for assessments have been attached as appendices to the protocol.

<u>Discussion/Clarification of points raised by Nottingham REC:</u>

Point 1
You clarified that the upper limit of blood pressure will be 170 systolic; the lower limit will be 120.
Response
The systolic BP limits for inclusion are 125-170 mmHg, i.e. lower limit is 125, not 120 mmHg (section 3.6.2)

Point 2
You explained that participants will be recruited from both stroke clinics and wards; most of them will be inpatients. You are confident that you will manage to secure 75-80% of patients that have suffered an ischaemic stroke in Nottingham.
Response
The majority of patients recruited into PODCAST are likely to have has an ischaemic stroke reflecting the proportion of ischaemic versus cerebral haemorrhage (ratio 80:20). It is likely that patients from Nottingham will reflect this balance as well.

Point 3
You underlined the fact that the study is driven by its inclusion/exclusion criteria so it is unlikely that participants will overlap and have both high blood pressure and cholesterol levels.
Response
The level of BP and cholesterol are independent of each other so it is possible that participants may have:

- **high BP/high cholesterol**
- **high BP/non-high cholesterol**
- **non-high BP/high cholesterol, or**
- **non-high BP/non-high cholesterol**

Whatever their starting level, all participants will receive active therapy for both BP and cholesterol, this being either guideline or intensive therapy. So all participants will, at minimum, be treated as they are now, i.e. according to NICE guidelines. The only difference in the trial is that they will have an equal but random chance of receiving intensive rather than guideline treatment.

Point 4
You confirmed that the guideline group will be driven by standard practice; the participants' GP will decide whether they receive treatment or not.
Response
Participants randomised to guideline therapy will be treated as they are now by their GP, i.e. most are likely to receive some BP-lowering and/or cholesterol lowering therapy. Of course, if their BP or cholesterol is already relatively low then their GP may elect not to give drug treatment for this.

Point 5
The Committee asked whether you felt that three years would be long enough to obtain the necessary data from 600 patients; you responded that these first three years simply amount to the start up / feasibility phase of the study. Your team are attempting to establish whether the study is even achievable as opposed to finding out if it is possible to reduce cognitive decline. The questions under scrutiny in this feasibility phase are: can the study actually been done; can participants be recruited; can cognition be measured? The main phase of the study would begin after these initial three years therefore participants could be enrolled for up to seven to eight years.
Response
The start-up phase with 600 patients will provide the foundation for the whole trial by demonstrating its feasibility:

- **Recruitment of sites and participants**
- **Measurement of cognition**
- **Maintenance of differences in BP and cholesterol between the treatment groups**

However, we do not believe that 600 patients, nor 3 years, will be sufficient to allow differences in cognition to be found. As a result, a larger and longer lasting trial will be required. Naturally, the 600 patients recruited in the start-up phase will contribute to the main phase, so they could be in the trial for up to 8 years.

Point 6
You confirmed that the method of assessing participants' cognition is evidence based; you will be utilising questionnaires followed by telephone assessments.
Response
Yes, the clinic and telephone-based cognitive measures are standard, standardised and validated. Research staff will be trained in their use.

Point 7
The Committee enquired as to what would happen about the telephone assessment if the participant was hard of hearing; you stressed that it is important to include the telephone assessment so that there is a central,

blinded component to the assessments. A relative / friend of the participant will be involved at the clinic and on the telephone so that an attempt can be made to address any complications / anxiety participants might experience with their assessment.

Response

Subsequent to our discussion with the committee, the Trial Steering Committee met and discussed this issue. We believe it would be best to exclude patients who are severely hard of hearing. The screening telephone call will provide, as a side benefit, a test that hearing is sufficient to participate in the trial. The protocol has now been updated to exclude participants with profound hearing loss. (Section 3.6.3)

Point 8

You confirmed that a minority of participants may find some of the questions asked (both at the clinic and over the telephone) distressing but underlined that the interviewer will be trained in how to deal with the situation as and when necessary.

Response

Yes, trial research staff will be trained in the administration of the cognition and other questions, and how to deal with anxiety or distress in the participant.

Point 9

The Committee indicated that they will require copies of the questionnaires mentioned in the documentation; you agreed that these will be submitted and pointed out that these have been validated for use with deaf participants.

Response

All the questionnaires/surveys to be used for assessment have been attached as appendices to the protocol. As above, the specific assessments are all validated. However, we now believe that their delivery is not practical in profoundly deaf people who, will, therefore be excluded form the trial (Section 3.6.3).

Point 10

You clarified that the genetic sub study will only be carried out at a sub-set of hospitals.

Response

Yes. Hospitals may elect to take part in this, a decision that will, in part, be dependent on whether they have sufficient local sample freezing capability.

Point 11

You confirmed that if participants do not have the capacity to consent at the beginning of the study then they will not be eligible to take part.

Response

Yes, participants who do not have capacity for consent at baseline will be excluded.

Point 12

The Committee enquired whether or not the funding has been found for the participants' additional brain scans; you confirmed that this has not yet been secured but will only be necessary in two to three years time.

Response

Yes, funding for the imaging sub study will be sought separately from the trial itself (which has already secured funding).

Point 13

The Committee informed you that procedure should be expanded on in the PIS, e.g. what will happen to tissue samples, where they will be stored, will they be sold to other companies etc.

Response

Yes. This information is now included in a separate sub studies information sheet explained as above.

Point 14
The Committee queried the fact that participants will be referred back to standard care after three years; what if they had experienced cognitive decline? You reassured the Committee that you will not be testing for cognitive decline at three years; the first feasibility phase is simply to see if the data can be collected.
Response
Cognitive assessments will be performed thought the trial, both start-up and main phases. Patients enrolled in the 3-year start-up phase will continue into the main phase. We have amended the PIS (and GP letter) to explain that GPs will be informed if dementia or other serious conditions develop (as is standard in trials).

Point 15
The Committee queried whether the PIS had been trialled with a service user group; you confirmed that it had not but has been reviewed by the Alzheimer's Society group. The Committee mentioned that they were concerned about the length of the PIS and suggested that you rewrite it, splitting it into two parts, one of which giving a summary of the information and the other providing further explanation of this.
Response
The PIS has been adapted as requested. It has also been reviewed by the Patient, Carer and Public Involvement representatives.

Point 16
You agreed that participants may not be aware that up to 30% of stroke patients go on to develop dementia and it may come as a shock to them. You will attempt to attenuate the shock through a two part assessment: firstly, consent will be sought in hospital during the initial three to seven month period after stroke and provide further explanation of the study. Secondly participants will have a simple phone screening to test cognition; only upon passing this will they be invited to follow up at the clinic and formally entered into the study. You agreed to re-look at the tone of the language used and where possible make this less frightening.
Response
Yes, the hospital 'pre-screen' and screening telephone will be used to introduce the issue of post stroke dementia. We have adjusted the PIS to tone the language down as you suggest.

Point 17
The Committee drew attention to the fact that no peer reviews had been submitted; you agreed to submit these.
Response
Yes, see enclosed

Point 18
You agreed to submit an in date insurance certificate; this was simply an administrative oversight.
Response
Yes, see enclosed.

<u>Discussion / Clarification of points raised by Scottish REC:</u>

Point 1
There was concern over the study entry criteria, which allow blood pressure of 170 mmHg, despite evidence from trials such as PROGRESS that lowering of BP even within the normal range confers lower recurrent stroke risk i.e. at least the entry BP should lie within the recommended limits e.g. systolic below 140 mm Hg as per NICE guidance.

Response
The target for both BP management groups is systolic BP<140 mmHg so we would expect any patient in the trial whose baseline systolic BP was 140-170 mmHg to have this lowered. The target BP in the two groups are given in 3.7.1.1 and 3.7.1.2.

Point 2
The inclusion and exclusion blood pressure criteria conflict with each other.
Response
We cannot see any conflict and have left the criteria as is.

Point 3
Concern over the implication that atorvastatin would be restricted to the aggressive treatment group, since atorvastatin 80 mg was one of the standard treatments that was used by many stroke physicians; was supported by a large RCT; and was specifically recommended fro consideration under SIGN guidelines (more prominently than simvastatin 40 mg). If specific drug therapy was required for one or more groups, then this becomes a CTIMP.
Response
Either atorvastatin or rosuvastatin may be used as 'intensive' statins. If investigators wish to explicitly use atorvastatin, then their patients would not be eligible for the trial (exclusion criteria 3.6.3 bullet 12.).

Point 4
If the above concerns were allowed to stand by Nottingham 1 REC, then potential participants should be informed of recommended treatment and permitted to take an informed choice.
Response
This point is addressed as immediately above.

Point 5
Most secondary prevention trials have found reduction in recurrent stroke risk before effects on myocardial infarction or cognitive function have occurred; it would not be reasonable to continue the trial if significant differences in stroke recurrence ($p<0.05$) favour the aggressive treatment group(s) within either arm of the study even though the primary endpoint may not have been reached.
Response
This is an issue for the Data Monitoring Committee who would need to balance any statistically significant difference in vascular events with trends (or otherwise) in effects on cognition/dementia. Accounting for the balance between primary and secondary/safety outcomes is standard in DMC discussions in trials. By example and of direct relevance to PODCAST is the discussion in the large ASCOT trial of BP and lipid lowering where a balance between reduced mortality (significant, a safety outcome) and a trend to reduce vascular events (primary outcome) led to the trial continuing until the primary outcome also became positive.

It should be noted that a significance value of $p<0.05$ would not be used by the DMC since this would not take account of multiple comparisons; the charter (based on that used in the MRC ENOS trial) uses a difference of at least 3 standard deviations in interim analyses of the primary outcome (section 3.10.6).

Point 6
Scotland A REC would have been prepared to approve only for a fixed pilot sample of 600 initially, pending evidence of enrolment rates and the achieved difference between groups in blood pressure and cholesterol, since the full study may prove impractical and underpowered.
Response

We are seeking REC approval for the whole trial, as we did previously for the ongoing MRC ENOS and BHF TARDIS trials. We are not aware, following our discussion of this point at the previous Nottingham REC meeting, that this is a concern.

Point 7

There seems to be no barrier to continuation of the allocated treatment at the end of the study followed by a rapid switch to whichever option has proven better as soon as results were announced. It was an open label study, and so there was no issue over supply of medication.

Once the trial has completed, participants and their GP may discuss future management of BP and lipids. Naturally, if the trial is positive, we will share this information rapidly with the medical and scientific community so that all patients anywhere may benefit from this knowledge. We have added this point as a new section 3.10.8.4.

Other protocol/information sheet changes

2. We have made other changes to the protocol with the aim of simplifying the text and addressing discussion at the recent Trial Steering Committee (held on 21 September 2009). We provide a copy of the protocol with Track Changes turned on so that new text is easily seen.
3. An informed consent will now be taken from the informants at enrolment. Please see
    a. **Informant Information Sheet Version 1.0 dated 12 October 2009 (As Informant)**
    b. **Informant Consent Form Version 1.0 dated 12 October 2009 (As informant)**
4. GPs will be informed about the telephone screening for potential participants. Please see
    a. **GP Information letter: Participant Screening for PODCAST Version 1.0 dated 12 October 2009**
5. GPs will be informed should participants develop dementia such that participants can be referred to the appropriate specialist and support services. Please see
    a. **GP letter: Participant developing probable dementia Version 1.0 dated 12 October 2009**

Other issues for the Research Ethics Committee

1. Dr Sandeep Ankolekar will be assisting in the running of this trial as part of his higher research degree. As such, he will be analysing blinded data (i.e. no treatment groups) for his thesis.
2. His CV is attached as suggested.

Enclosures:

1. Protocol Version 1.1 dated 12 October 2009
2. Participant Information Sheet Main Study Version 1.1 dated 12 October 2009
3. Participant Information Sheet Sub Studies Version 1.1 dated 12 October 2009
4. Informant Information Sheet (as informant) Version 1.0 dated 12 October 2009
5. Informant Information Sheet Main Study (if participant loses capacity to maintain consent) version 1.1 dated 12 October 2009
6. Informant Information Sheet Sub Studies (if participant loses capacity to maintain consent) version 1.0 dated 12 October 2009
7. GP Letter- Participant Screening Version 1.0 dated 10 October 2009
8. GP Letter- Participant Enrolment Version 1.1 dated 12 October 2009
9. GP Letter- if participant develops dementia Version 1.0 dated 12 October 2009
10. Participant Consent Form Main Study Version 1.1 dated 12 October 2009
11. Participant Consent Form Sub Studies Version 1.0 dated 12 October 2009
12. Informant Consent Form (as informant) Version 1.0 dated 12 October 2009

13. Informant Consent Form Main Study (if participant loses capacity to maintain consent) version 1.1 dated 12 October 2009
14. Informant Consent Form Sub Studies (if participant loses capacity to maintain consent) version 1.0 dated 12 October 2009
15. Peer Review- Alzheimer Society Uk
16. Peer Review – The Stroke Association UK
17. Evidence of Sponsor Insurance
18. CV- Sandeep Ankolekar

We hope that the above responses are to your satisfaction and that the trial meets with your final approval for favourable opinion.

Yours sincerely

Professor Philip Bath
Professor of Stroke Medicine