PODCAST FREQUENTLY ASKED QUESTIONS

Why are the clinic appointments so long?

The 'clinic' appointments are at Baseline, 6 months, 18 months, 30 months etc (i.e. every 12 months after the 6 month visit). The 'monitoring' appointments are for patients who are randomised to the intensive groups and are performed at 1 month, 2 months and 3 months for the intensive BP group and at 3 months for the intensive lipid lowering group. (If randomised to both intensive arms the 3-month visits are combined).
The monitoring appointments last approximately 20 minutes.
The clinic appointments last approximately 2 hours but this is the nature of cognition testing and ensures an excellent picture of the patient's cognitive status is obtained. Please note this is standard in cognition trials.

What are the time windows for the follow-up appointments?

The window for clinic assessments is +/- 30 days. For the intensive BP group, the window for the monitoring visits is a time period of +/- 14 days, but the time period between the visits cannot be less than 2 weeks. For the intensive lipid lowering appointment at 3 months the window is +/- 14 days.
The live website displays all the time periods for each appointment. In spite of the time windows, if a visit cannot be performed as per follow-up, any follow-up, even if late, is better than none so all visits should be performed.

Can patients be co-recruited into other trials?

Co-enrolment between PODCAST and acute stroke trials is acceptable, provided the other trial has finished its treatment and primary follow-up.

SOS, TARDIS, ENOS
The screening consent and screening visit can be done during the SOS, TARDIS and ENOS follow-up. The screening consent can be obtained as long as the patient has finished their treatment in the trial, i.e. 7 days for ENOS, 72 hours for SOS and 30 days for TARDIS. Once the follow-up of the primary outcome for SOS, TARDIS and ENOS has been done, then the patient can be seen for their baseline PODCAST visit. Naturally co-enrolment into long-term trials, e.g. in vascular prevention (such as IRIS), is not permitted.

What happens if a patient has said they wish to be considered for screening but they go home prior to consenting for the face-to-face screen?

If a patient has been approached on the ward or at clinic and verbal consent for screening is obtained or the patient expresses an interest in the trial then the verbal consent/interest can be documented in the medical notes, and then the patient contacted at home. However, to take blood or do any trial interventions the participant must have given written consent to ensure accordance with Research Governance and adhere to GCP. So for

PODCAST, if verbal consent to be contacted is documented in the medical notes then consent for telephone screening must be obtained prior to the telephone screening call. At 8 weeks + the research nurse could see the patient at home, or at a clinic, or bring them in to the research clinic to consent and perform the screening at the same time.

What happens if a patient has another stroke after having been consented for telephone screening?

The clock restarts, i.e. it is the latest event that sets the time course. The patient will have to be re consented for the telephone screening call and then wait another 8 weeks from the new event to be telephone screened.

Can a nurse consent the informant at Baseline?

No, a medic has to consent both the informant and the patient for all parts of the study.

Who can randomise the patients?

If the PI is not available, another medic listed on the trial log may consent and randomise, e.g. another Consultant or SpR so long as they are trained in the trial, have signed the log, and have active GCP.

If a participant due for screening has an index event lipid result less than 3mmol and has a subsequent lipid result between 3-8mmol can I screen the participant and which result can I use?

Lipids levels decrease during acute stroke so index lipid measurements are likely to be lower than normal for that patient. A participant can be screened if there is cholesterol result afterwards, which falls within the 3-8mmol.

If a patient has already had an ambulatory BP taken prior to randomisation can this be used for a patient's baseline readings for the ambulatory sub study?

ABPM should be performed after consent, and using consistent equipment.

What are the timings for the ABPM machine?

The day readings are from 0700 - 2200, every 20 minutes i.e. x3 per hour. The night readings are 22.00 - 0700 once per hour.

What scans and reports need to be sent to the Co-ordinating Centre?
The images from the index event should be sent to the Co-ordinating Centre once the patient has been randomised. Postage should be via secure courier, where a signature is required upon receipt. Postage costs will be reimbursed.
Please collect and fax all scan reports for MRIs, CT's and Carotid Dopplers' performed from the time of the index stroke until the patient completes the trial.
Please also collect and fax all ECG reports performed from the time of the index stroke until the patient completes the trial.

For the MRI/CT sub study then we require the images and reports, and will reimburse you for the scan being taken.

Why are Subarachnoid and Secondary ICH excluded?

Subarachnoid and secondary ICH are excluded as they are not an ischaemic or primary ICH.

Why and when are we performing ECGs?

To save time at the Baseline visit please simply collect the index event ECG if the patient had one taken at the time of their stroke. If not then please perform an ECG. They are to be performed at all clinic visits for identification of MI and AF.

Which version of Java and Javascript are we using?

Java 6 and Java 7 should both work with IE 8; Chrome version 16; Firefox versions 4, 8 and 9; Opera 11; and Safari 5. Java 6 on Chrome/Safari, and Java 7 on Opera were not tested but should work. Some of the other browsers (IE and Firefox) are likely to warn if Java 6 is being used.
If JavaScript is disabled at any time, the browser should give warnings accordingly.
Javascript must be enabled for the Stroop test results to be captured from the Java applet.

Who performs the telephone follow-ups?

These are performed by the Co-ordinating Centre at 12 months and then yearly after that, i.e. 24 months, 36 months etc. Patients and their informants should be advised when seen at the local research clinics to expect the telephone call from the Co-ordinating Centre.

What is a high dose / guideline statin?

Definition of a **guideline** statin is:
Simvastatin 10 - 40mg
Atorvastatin <20mg
Pravastatin 10 - 40mg
Fluvastatin 10 - 80mg

Definition of a **high** dose statin is:
Simvastatin 80mg NB NICE has said that 80mg of simvastatin needs to be used with care in older people as higher AE event (myositis) rates may occur.
Atorvastatin ≥40mg
Ezetimibe – 10mg once daily

Information received from the MHRA recommend the use of statins with certain anti hypertensive medication.

http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199561

Briefly, both amlodipine and diltiazem are substrate inhibitors of CYP3A4, which

metabolises simvastatin. Simvastatin and simvastatic acid levels increase as a result. A number of cases have shown increased rhabdomyolysis, myopathy and/or CK levels. The MHRA now do not recommend that simvastatin is used at 40 mg when amlodipine (either 5mg or 10mg) or diltiazem are co-prescribed; instead simvastatin should be used at 20 mg (which will lead to a small reduction in its LDL-lowering effect).

Implications for PODCAST:
Simvastatin at 40 mg is a mainstay treatment for the lipid guideline (non-intensive) group, so the MHRA advice applies to patients in this group. Conversely, atorvastatin or rosuvastatin are the mainstay treatments in the intensive lipid-lowering group, so the information on simvastatin should not be relevant to them. Calcium channel blockers, especially amlodipine, are commonly used in both intensive and guideline BP lowering groups.

Following discussion by the PODCAST Trial Management Committee (with support by members of the Trial Steering Committee), and bearing in mind that PODCAST is a management rather than treatment trial (i.e. we do not tell Investigators what to use), we suggest the following practice:

Guideline lipid group
If simvastatin is not being used (e.g. pravastatin or fluvastatin are being used), then no change is required.
If simvastatin, but neither amlodipine nor diltiazem, are being used, then no change is required.
If both simvastatin 40 mg and either amlodipine or diltiazem are being used, then either:
Reduce simvastatin dose to 20 mg on, or
Switch simvastatin 40 mg to atorvastatin 20 mg (since simvastatin 40 mg and atorvastatin 20 mg are equivalent). Doses of atorvastatin higher than 20 mg are not appropriate for patients randomised to the PODCAST guideline group since this amounts to giving them intensive lipid lowering therapy.
If simvastatin 80 mg is being used consider reducing this anyway, as per previous MHRA advice regarding its use at this does in older people.

Intensive lipid lowering group
In general, simvastatin (and pravastatin or fluvastatin) are not appropriate treatments for patients in this group.
Simvastatin, pravastatin or fluvastatin are being used in Intensive lipid lowering group
These 'weaker' statins are not recommended for this group since they will not lower LDL-cholesterol levels sufficiently, i.e. we will not achieve the target LDL-c<1.4 mmol/l, and 1 mmol/l difference between Intensive and Guideline groups.

Atorvastatin or Rosuvastatin are being used in Guideline lipid lowering group
Atorvastatin at doses >20 mg od are not recommended for this group since it will lower LDL-cholesterol levels excessively, i.e. we are more likely to reach the Intensive target LDL-c<1.4 mmol/l inappropriately, and we will not achieve the 1 mmol/l difference between Intensive and Guideline groups.

GP communication
You may wish to pass on this advice, and any changes in medications, to GPs in respect of individual patients, where it applies.
Clinical management

Naturally, the above suggestions may need to be over-ridden due to individual patient clinical factors, as decided by the responsible physician and/or site Principal Investigator.

What can be done if no lipids are available from the index event?

A lipid profile must be performed and be within our inclusion criteria (TC-3-8 mmol/l) prior to screening assessment being undertaken. The PI can ask for the lipids to be obtained at the GPs or at the hospital during their clinic follow-up at 6 weeks.

What if there is no evidence of stroke on the CT/MRI?

The CT/MRI (within 10 days of the index stroke) is required to identify ICH and IS and exclude other pathologies. We do not require a repeat CT/MRI if there is no evidence of ischaemic stroke seen on the scan so long as we have confirmation that a stroke has been diagnosed.

How can we maintain blinding when there is only one nurse at a centre?

DeNDRoN nurses can be used to help with the cognitive testing and nurses from centres local to each other can 'swap' patients. Unintentional unblinding may occur by looking at the sequence of patients monitoring appointments and also patients may contact the nurse mentioning their medications but this should be avoided where possible. Patients should not be reminded about which group(s) they are in where possible. Telephone follow-up by the Co-ordinating Centre at 12 months, 24 months etc will be truly blinded.

What happens if a patient is diagnosed as having dementia?

The patient still remains in the trial and is followed up as normal.

What happens when a centre already prescribes to the lower intensive targets?

Currently NICE guidelines recommend lowering of blood pressure to <130/80 mm Hg and total cholesterol to less than 4 mmol/litre, for secondary prevention in patients with stroke. Based on these national guidelines and some local guidelines, we are aware that some trusts are unable to participate in the PODCAST trial as their targets are below those of our guideline treatment groups.

While such guidance should be followed in routine clinical practice, the guidelines acknowledge the lack of evidence and call for research studies to test such target based interventions. Indeed the European Society of Hypertension (ESH) revised their 2007 hypertension guideline recommendation of BP lowering from <130/80 mmHg to <140/85 mmHg in 2009 due to lack of evidence, especially for elderly patients and those with previous stroke. Similarly, while NICE recommends target lowering of total cholesterol to less than 4 mmol/litre, it acknowledges that the cost and clinical effectiveness of such a policy is not known and calls for research studies to study target based interventions- TC <4 mmol vs < 5 mmol/l (section 1.8.5, NICE guidelines CG67 May 2008).

The PODCAST trial offers a unique opportunity to test these target-based interventions for both cholesterol and BP lowering not only for preventing cognitive decline but also for reducing further cardiovascular events, as they are key secondary outcomes. Hence

patients should be offered the opportunity to participate in PODCAST as it addresses important questions raised by current guidelines.

What if a patient is 'scored' as having dementia?

The automatic email summarising the patient's scores for each clinic visit will also state if a patient possibly has dementia using the ACE-R score as an indicator. The message on the email is only there to advise and ultimately it is at the local PI's discretion if the patient requires referral to their GP for dementia follow-up.

When is the answer 'yes' to evidence of periventricular white matter lucency on the Baseline form?

Answer yes if the report mentions: periventricular white matter lucency, leukoaraiosis, white matter disease, white matter change, small vessel disease, small vessel ischaemia.

What is the allowed time lapse between pre-clinic bloods being taken and the actual clinic appointment?

The time allowed on the form is one month.

Is there an alert to inform the investigator when a patient's BP's and lipids are of concern?

Alert boxes and pop-ups are given to the doctor in the following cases:

- Guideline BP - alert if mean systolic BP **≥ 160** mmHg.
- Intensive BP - alert if mean systolic **≥ 125** mmHg.

- Guideline lipids - alert if **total cholesterol over ≥7** mmol/L.
- Intensive lipids - alert if **total cholesterol ≥ 4** mmol/L and/or **LDL-cholesterol ≥ 2** mmol/L.

The doctor in the hospital research clinic should act on alerts for patients in the intensive group, i.e. by increasing medication.

The doctor in the hospital research clinic should not change medication for patients in guideline groups with a BP (≥160 systolic) or lipid (≥7 total cholesterol) alert, but may feel, under a duty of care, that they should let the GP know so the GP can discuss further management changes with the patient.

This difference in response to an alert is critical since the trial is comparing intensive management, as delivered in the hospital clinic, with routine/guideline care, as delivered in the community.

What amendment requires participants to re-consent?

All participants at their next clinic visit due to changes such as the addition of a further clinic visit at 12 and 24 months, in addition to the telephone follow up.

Is Dementia an SAE or outcome?

Dementia is not an SAE, it is an outcome, ensure the correct form is completed.