TARDIS – Working Practice Document – No: 002

Frequently Asked Questions

INCLUSION/EXCLUSIONS

At baseline, do both blood pressure measurements have to be in range: (systolic <185mmHg and Diastolic <110mmHg)?
Yes, two separate sets of blood pressure readings must be taken after consent.
If any one of the four measurements is outside the accepted range then this patient will be refused entry into the trial. Please do not use readings taken either on admission to the emergency room or ward.

If a patient has reduced hand grip only can they be randomised into TARDIS?
No, not unless they also have had at least 10 minutes dysphasia for TIA patients and dysphasia is still present for STROKES at randomisation, or if dysphasia has lasted over 24hours but resolved at randomisation
Hand weakness or numbness is not an eligibility criteria for TARDIS, limb weakness is (arm or leg).

Are there any situations when patients can go into other trials as well as TARDIS?
Concurrent uncoordinated co-enrolment of patients into two or more trials has the potential for introducing bias, e.g. when the treatments have a similar mechanism of action or cause similar adverse events.
Co-enrolment of patients into TARDIS and non-drug studies e.g. CLOTS, LUNS, CALM, is permitted since the interventions and trial aims are very different.
However, patients should not be enrolled into TARDIS if they are already in another acute (such as IST-3) or prevention trial. You cannot co-enrol into CADISS either.

Can patients be randomised into TARDIS following thrombolysis?
Yes, as long as patients are thrombolysed under licence, and are randomised 24 hours or more post-thrombolysis but still within 48hrs of stroke onset. Patients thrombolysed for stroke with full recovery in less than 24 hours from the onset of symptoms are eligible for inclusion as a Stroke, providing neuroimaging post thrombolysis excludes Intracerebral Haemorrhage.

Can patients who are nil by mouth be recruited?
Yes, provided they already have enteral access (e.g. NG tube/PEG tube) available at the time of randomisation. The loading doses need to be given as soon as randomisation has been completed *(but after bloods are taken).*

If I enrol a patient into TARDIS and they are a 'high risk' patient (e.g. they have HIV, hepatitis B or C), should I take their blood for the trial?
No.

Can patients be recruited if they have a rapidly improving event?
Yes, The patient can be recruited as a TIA, only if symptoms last less than 24hours and the patient has had at least 10 minutes limb weakness and/or dysphasia. Limb weakness and/or dysphasia must still be present for strokes at time of randomisation, unless these symptoms have lasted over 24hours and resolved between 24-48hrs

MEDICINAL PRODUCTS

If a patient is admitted on dual antiplatelet therapy can they be randomised?
If a patient has taken clopidogrel after onset of their TIA/stroke but prior to randomisation then they are only eligible for TARDIS if the site's randomisation choice is Triple vs Clopidogrel monotherapy. Otherwise they must not be recruited.

The following table shows allowed and disallowed antiplatelets before and after randomisation for TARDIS:

Before Stroke	
Allowed:	not on an antiplatelet, or on aspirin, or on dipyridamole, or on clopidogrel, or on aspirin + dipyridamole, or on aspirin + clopidogrel, or on clopidogrel + dipyridamole
Not allowed:	on aspirin + clopidogrel + dipyridamole
After stroke / before randomisation	
Allowed:	not on an antiplatelet, or on aspirin, or on dipyridamole, or on aspirin + dipyridamole
Not allowed:	on clopidogrel (if randomisation choice is Triple vs AD), or on any clopidogrel containing combination, or on aspirin + clopidogrel + dipyridamole
Not allowed:	*on dipyridamole (if randomisation choice is Triple vs C)*

Can a patient be recruited be recruited to TARDIS if they have received both Aspirin and Clopidogrel (after onset and before randomisation?

No. Aspirin alone is allowed in all cases after onset prior to randomisation. Participants may have received Clopidogrel alone prior to recruitment (depending on the randomisation choice for each site).

Do all IMPs for this trial need to be overlabelled?
The protocol states Standard pharmacy supplies should be used as all IMPs have marketing authorisation. Hospitals/pharmacies should choose their own supplier for the IMPs and should be packaged according to local policy. All IMPs for the TARDIS trial should be labeled separately and pharmacies at the recruiting centre must have a written procedure in place for dispensing trial medications. Labelling should in accordance with Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices (see appendix K). Under exceptional circumstances (e.g. out of hours) where labelled IMPs are not available, trial sites may choose to use ward stock without separate labeling if agreed locally and approved by the pharmacy.

An accountability log for all IMPs should be maintained by the pharmacy and/or the research team and should include the following information: hospital number, participant initials, trial number, date dispensed, brand manufacturer, batch number, expiry date, quantity dispensed, quantity returned and initials of personnel who dispense and check the log. This should be completed for every participant who is randomised into the study. Accountability

logs must be available for inspection during trial monitoring and/or audit and open to regulatory authorities inspection at any time.

Do all patients receive clopidogrel for the first month whichever arm they are randomised to?
No, recruits will only receive clopidogrel for a maximum of 30 days, if randomised to mono or triple therapy. If your hospital supply of clopidogrel contain blister packs of 28 tablets then this is acceptable.

Do patients only receive up to 90 days of trial treatment? If so, am I correct in assuming that all 3 months supply will be made by the hospital?
Trial treatment will be the 30 days (only) of antiplatelets supplied by the hospital, for any of the randomization arms.

How many days is aspirin 300mg loading dose given for? Or is this a single stat dose?
A single stat dose of 300mg aspirin is required to load on Day 0, day of randomisation, then 50-75mg per day thereafter. If the recruit has already been given 300mg on the same day as randomisation then do not re-load. However, if a recruit already took their usual dose of 75mg on the day of randomisation, but prior to randomisation then a top-up dose of 225mg would still be required. Basically all patients must receive 300mg aspirin on the day of randomisation (Day 0). Please disregard any aspirin given the day before.

How many days is clopidogrel 300mg loading dose given for? Or is this a single stat dose?
If a recruit is randomised to mono or triple therapy, a single stat dose of 300mg clopidogrel is required to load, then 75mg per day commencing the day after, for (28 or) 30 days depending on pack size. If the recruit has already been given 300mg on the same day as randomisation then do not re-load. However, if a recruit already took their usual dose of 75mg on the day of randomisation, but prior to randomisation then a top-up dose of 225mg would still be required. Basically all patients must receive 300mg clopidogrel on the day of randomisation (Day 0). Please disregard any clopidogrel given the day before.

Can Dipyridamole be weaned up if the participant has a headache?

Yes. Patients with a headache will have the dose weaned up from daily MR 200 mg or standard release 50 mg once daily to MR 200mg twice daily. If the patient cannot tolerate the dose of 450mg, you do not have to give it. However, do try in the first instance if the patient agrees rather than stopping the drug.

Can patients be recruited if not expected to be hospitalised for 30 days?
Yes, they should be given the trial medications to take home to complete the 30 days treatment period. If discharged before Day 7 or Day 35 follow-ups have been undertaken, then the patient should be brought back to the hospitals/clinic for their visits. *(see note on travel expenses)*

Can enteric coated aspirin be used?
Yes.

Which medications are classed as IMPs and what doses can be used?
For the first 30 days all antiplatelets taken will be treated as IMPs. From Days 31 to 90 (end of the trial), the patients will be on standard antiplatelet therapy, at the discretion of the treating physician, as per the latest NICE guidelines.

The MHRA approval details the following drug preparations and doses:

Aspirin:

Tablet, dose range 25mg to 300mg (enteral and oral use)
Dispersible tablet, dose range 75mg to 300mg (enteral and oral use)
Suppository, dose range 150mg – 300mg (rectal route)

Dipyridamole
Tablet, 25mg – 100mg, total dose per day 450mg (enteral and oral use)
Oral suspension, concentration 10mg/ml (equivalent to 50mg/5mls), total dose per day 400mg) (oral and enteral use)
Capsule (e.g. persantin retard), 200mg MR capsule, max dose 400mg daily

The above preparations will also allow Asasantin to be used, and also weaning dipyridamole from low dose to higher doses is allowed should the recruit suffer from a dipyridamole headache.

Clopidogrel
Tablet, 75mg, dose range 75mg to 300mg (enteral and oral use)

When weaning the patient on dipyridamole, do we have to reach the maximum dose of 450mg a day?
No, if the patient cannot tolerate this dose you do not have to give it. However, please do try in the first instance if the patient agrees, rather than stopping the drug.

If a patient stops their trial medications at any time, do they no longer continue in the trial?
If this happens for any reason, then the patient remains in the trial and is to be monitored for the complete 90 day period. Days 7 and 35 face-to-face follow-up visits still need to be done and any Outcomes or SAEs need recording up to Day 90.

Trust Guidelines say 300mg of PR of aspirin should be given, is that acceptable?
For the TARDIS trial, we would prefer 150mg on alternate days, if the patient is unable to swallow.

In your protocol it is stated that 'patients will be recommended to take gastro-prophylaxis against upper gastrointestinal bleeding (proton pump inhibitor/histamine 2 receptor antagonist +/- H.pylori eradication) as is standard'.
Either a PPI or H2 antagonist may be used for gastro-protection at the Investigator's discretion. We record this information at baseline, day 7 and day 35 follow-up visits.

Is this going to be updated in light of the recent information regarding a possible interaction between PPIs and clopidogrel which may decrease clopidogrel's effectiveness? Most PPIs (but not pantoprazole) block cytochrome P450 2C19, one of the enzymes that converts clopidogrel to its active metabolite.
Ultimately it is up to the investigator but we suggest using H2 antagonist such as ranitidine rather than a PPI. We will record what the intention is, i.e. use PPI, H2 antagonist or nothing.

NICE guidelines state 300mg aspirin should be given to patients for the first two weeks. Can we continue this at our site?
No. If your site takes part in TARDIS then the doses given in the protocol must be agreed and followed by your investigators/medics.

Please ensure that all medics are aware that the recruit is in the Trial and that the new drug regime is made clear on the patient's drug card and TTO form. Also if the recruit is randomised to Triple antiplatelets, or clopidogrel monotherapy then the trial dose should be stopped after day 30. The actual antiplatelet regime after Day 30 is at the discretion of the treating physician in line with the NICE guidelines.

What are the temperature monitoring requirements for the IMPs?
The IMPs must be stored in a secure location at room temperature in accordance with the relevant SmPC. Depending on local arrangement; this may be at the local pharmacy, the research department or the ward. Only extreme deviations from storage conditions as defined by the SmPC should be discussed with the trial Coordinating Centre.

INVESTIGATIONS

How quickly should a CT head scan be performed?
For a stroke patient, CT or MRI is mandatory prior to randomisation, to rule out the possibility of haemorrhage. If the patient receives thrombolysis, a pre TARDIS scan to rule out intracranial haemorrhage is essential.

It is not mandatory in patients with clinical symptoms of TIA.

What images do we need to upload?
If uploading a CT scan the series were require are Axial:

- Plain, non-contrast
- Soft-tissue

If uploading a MRI scan the series we require are Axial:

- Gradient echo (T2*),
- FLAIR or T2
- Diffusion Weighted Imaging (DWI with ADC map)

All radiology scans ideally need to be uploaded anonymously as a DICOM file via the web site.

If you are unable to upload directly to the website, all radiology scans need to be sent to the TARDIS trials office. In this instance, please send a CD of the scan to the coordinating centre as soon as possible if this complies with local policy. Please see the latest WPD on Posting CT/MR scans for more information.

All clinical radiology undertaken until the Day 90 follow-up has been completed also need collecting and sending as soon as available.

Is it necessary for patients in the trial to have a carotid duplex scan?
The results of carotid duplex scanning are not required prior to recruitment. However, duplex scanning should be performed during the 30 day treatment phase (or, less ideally, during the follow-up period). The printed report of the carotid scan should be sent to the TARDIS Trials Office once available. Carotid information is important (as are the CT/MRI scans and results of an ECG) so that the likely aetiology of ischaemic stroke can be categorised (e.g. cardioembolic, large artery disease, lacunar/small vessel disease).

Please fax reports of carotid duplex scans to the TARDIS fax number at the Trial Office. In most cases, patients enrolled into TARDIS are likely to need a carotid duplex scan as part of their clinical care.

Naturally, patients with a primary haemorrhage do not need a carotid scan and would not be eligible for recruitment into TARDIS.

Which CT result do you write on the day 7 form?
We need the Local investigator's opinion and interpretation of the baseline CT/MRI scan reported on the day 7 form. Please also fax the report/result of the baseline scan to the TARDIS Trials Office fax number.

Do all sites have to take part in the P-selectin part of the trial?
Due to the high number of hospitals taking part in the trial, only specific high recruiting sites will be requested to take part. All blood tubes and postal boxes will be supplied by the Coordinating Site.

Do all sites have to take the other trial bloods i.e. serum/plasma/DNA?
Yes please, we would like all sites to take the serum and plasma samples at baseline and Day 7 follow-up visit. The DNA sample can only be taken if a separate DNA consent form has been signed (this must be consented and signed by an authorised physician, (not a nurse), as per the main consent form).

On the patient information sheet (independent physician information sheet) it states that samples will be destroyed, however on ethics B4 it says samples will be used in research studies both now and in the future
The precise tests on the frozen samples are yet to be determined, so the samples will be frozen until the tests are decided (hence the reason for stating 'future research' in the Ethics application). Once the samples have been tested, they will be destroyed, as stated in the information sheets.

ASSESSMENTS

Who will do the Day 7 and 35 assessments?
A member of the research team, authorised on the signature/delegation log, will ideally complete this at the researcher's facility. If the patient has been discharged then they need to return to clinic/hospital. There will be re-imbursement of up to £50 per patient for travel at this time point, to the recruiting site. Proof of actual travel expenses paid to recruit etc and data entry of the follow-up details must be completed prior to reimbursement. Any amount over £50 will be at the expense of the recruiting site.

Who is going to perform telephone follow-up?
Centres in the UK will have their telephone follow up performed by the Coordinating Centre in Nottingham. The 90-day Assessor will be separate from the clinical team managing TARDIS patients (so that they do not introduce any bias into follow-ups). Please make sure patients understand that they will not have previously met the 90-day assessor and that this person may not even be from the same hospital to which the patient was admitted.

What was the reasoning behind the choice of stroke scales used in TARDIS?
The primary outcome is assessed at 90 days using the modified Rankin Scale; a standard scale used in acute stroke trials.
A key secondary outcome is the Barthel Index, another standard scale.
Impairment will be measured at baseline and end of treatment using the NIHSS which has also been used in many acute trials and observational studies.

We use the same scale for other trials, can we just use their versions?
We ask that you just use our versions of these scales to avoid any discrepancy in the data.

SAEs

What qualifies as stroke extension?

Stroke is considered to extend if there is a progression of neurological symptoms or signs in the same vascular territory. It usually occurs within 72 hours of the index event. A period of

improvement or stabilisation for at least 24 hours after the qualifying stroke may occur, followed by neurological deterioration.

What is a recurrent stroke?

A stroke which occurs anytime in a different vascular territory following the index event or in the same vascular territory 72 hours after the qualifying stroke.

Can a recurrent stroke occur within 72 hours?

Yes, if the event occurs in a different vascular territory after the qualifying stroke.

Is a pacemaker an exclusion for recruitment to TARDIS?

A pacemaker inserted previously (e.g. for complete heart block) is not an exclusion to TARDIS. However, in this situation, it is important to exclude previous history of AF, definite need for anticoagulation and the presenting stroke is not cardioembolic in aetiology prior to enrolment.

What is death unattended?

"Death unattended" or "died unattended by a physician" means a death where a person dies of apparent natural causes and has no physician who can certify as being due to natural causes. There is no set amount of time and depends on the circumstances.

What is sudden cardiac death?

Sudden cardiac death is the unexpected death from a cardiac cause within a short period of time, usually within 1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal. It is often the result of a ventricular tachyarrhythmia that occurs secondary to a complex interplay between susceptible myocardium affected by cardiomyopathy ischemic or non-ischaemic and a transient trigger.

Finance

Will sites be paid for blood transfer and storage?
Centres will be asked to freeze blood, (serum and plasma and DNA sample) if they have the facilities to do so. Hospitals will need to supply their own blood and transfer tubes, have access to a centrifuge and freezer and be able to adequately label the samples. Labelling should be anonymised with full trial id, date taken and indicating what the sample contains. Once they have accumulated enough samples to transport, we will arrange and pay for courier pick up.

The P-selectin assays will be posted directly to Queen's Medical Centre, via Royal Mail in special pre-paid boxes supplied to each site taking part in this sub-study. Blood kits and Pre-Paid boxes for the P-selection blood samples, will be supplied by the Coordinating Centre.

Cost of sending CT or DVD
CT or MR images can be uploaded anonymously onto the website, as in ENOS, so there should be no additional material cost.

Who will pay for patient travel for follow-up visits, Days 7 and 35?
There will be re-imbursement of up to £50 per patient for travel. This will be made to the recruiting site after receipt of proof of expenditure i.e. expenses form signed by recruit, or taxi invoice. All data entry for this recruit must be completed prior to reimbursement. Any amount over £50 will be at the expense of the recruiting site.

Funding / expenses paid to local investigator team etc.
There are only a few costs associated with this academic trial, and these will be NHS costs i.e. the cost of additional clopidogrel and of blood bottle usage.

Patient travel will be reimbursed as already described. There is also a payment of £50 to the investigators for their time spent recruiting and completing forms, once all queries have been resolved, documentation received and data entry performed.

OTHER QUESTIONS

How current does the Investigator's GCP or NIHSS training have to be?
All staff taking part in the trial, and on the signature/delegation log must have proof of GCP training within the last 2 years as a maximum. The rules are not absolutely clear on the matter of training, however we feel that this should be re-done so that your training is current for this trial.

There are web-based NIHSS training programmes, and we would expect researchers to be competent in undertaking these assessments.

For the purposes of TARDIS, what is an acute stroke unit, and what is a rehabilitation unit?
An Acute Stroke Unit (ASU) is defined as a 'high-dependency nursing unit (or area) caring only / mainly for patients with acute stroke and providing close monitoring of neurological and vascular signs', a definition used in the TAIST trial. Similarly, a Stroke Rehabilitation Unit (SRU) is defined as a 'dedicated rehabilitation unit (or area) caring only / mainly for patients with recent stroke and providing multidisciplinary therapy (e.g. physiotherapy, occupational therapy, speech & language therapy)'. In some hospitals, the ASU and SRU co-exist.

When do you fill out the day 7 for?
The day 7 form should be completed on the 7th day (+/- 1 day). The day of randomization is classed as Day 0. Entry onto the website should be done as soon as possible afterwards. If done outside the trial timeline then this is a deviation of protocol and a Trial File Note should be raised to indicate why this happened.

When do you fill out the day 35 form?
The Day 35 form should be completed on the 35th day (+/-3days) and should again be entered onto the website as soon as possible afterwards. If done outside the trial timeline then this is a deviation of protocol and a Trial File Note should be raised to indicate why this happened.

Do we have to freeze the genetic sample at -70^{0}C?
Ideally, but -20^{0}C will be adequate.

Can the recruit go to their GP to have their Day 7 and Day 35 bloods taken?
No. As well as taking bloods, a clinical consultation is required, which must be done by an investigator at enrolling sites who is on the Site Signature/Delegation Log. As a last resort if failed attempts have been made to take the FBC at the visit then the GP surgery may be asked to help.

If a recruit needs an endarterectomy during the trial period (90 days), is the recruit taken off the trial?
No. If an elective endartarectomy is known about prior to randomisation, then the patient cannot be recruited.

If it is decided that the patient needs a carotid endarterectomy after being randomised, then

they will remain in the study and follow-up visits performed. The antiplatelet medications will be stopped according to normal practice prior to surgery, and re-started later. The day 90 follow-up will also be completed by the Coordinating Centre.

A proportion of our patients will go on to need carotid endarterectomy following carotid doppler, and our vascular surgeons suggest that clopidogrel is stopped at least 1 week prior to surgery. Ideally, we would wait until the doppler was done but in most cases, the doppler cannot be carried out before the 48 hour onset.
As above, if someone is known at the time of considering TARDIS to have severe stenosis (and therefore likely to need surgery) do not randomise. If the carotid status is unknown then consent/randomise; if subsequently surgery is needed, stop the clopidogrel temporarily (when the surgeon requests) and then please restart afterwards.

Is an ECG mandatory prior to randomisation?
No, this is not mandatory, but preferable. However, if there is evidence that this is likely to be a cardioembolic event then please do not randomise this patient. Do not randomise any patients who have a history of AF or PAF.

How long do the medical records need to be retained?
The trial records need to be kept for 7 years after publication of the trial results. Therefore if a particular hospital wishes to destroy medical records before that time, they need to be copied and retained with the other trial records. A 'retention of sticker' label needs to be added to the cover of the medical notes (current date being 2025 to cover the 5-year extension period).

Can we go back and add information to an SAE as it becomes known?
At the moment, you are unable to update the SAE data on the website. Please inform us of any additions/changes, using the 'Data Correction form' on the website and we will update the trial information as necessary.

Do you need the CT/MR scan report printout?
Yes, please fax all radiology reports for all participants as soon as available to the Coordinating Centre.

Publication rights and names
Publication of the primary results will be in the name of the TARDIS Investigators. All Principal Investigators will be listed in the acknowledgements.