TARDIS STUDY
SUBSTANTIAL PROTOCOL AMENDMENT SUMMARY OF CHANGES VERSION 1.3 to 1.4

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 1.4: SUMMARY OF CHANGES

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Funding source: British Heart Foundation (start-up phase)

National Institute for Health Research Health technology Assessment Programme (main phase)

Other Investigators: Dr Nikola Sprigg has been added as Co-Chief Investigator

Addition of Kailash Krishnan as author.

1.1 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

1.1.1.1 Aspirin (Asp)

Existing protocol

Dose: Loading dose 300mg, then 75mg od

Revised protocol

Dose: Loading dose 300mg, then 50-150 mg per day. Aspirin may be given in combination with dipyridamole as Asasantin or equivalent.

1.1.1.2. Dipyridamole (Dip)

Existing protocol

Dose: 200mg modified release (MR), bd. Dysphagic patients with enteral access will take dipyridamole suspension 75mg tds. Patients with a headache from dipyridamole will have the dose weaned up from daily MR 200mg or standard release 75mg od to MR 200mg bd.

Fixed dose combinations of A and D can also be used, e.g. Asasantin Retard (Aspirin 25mg, Dipyridamole 200mg MR, bd)

Route: Enteral (including via nasogastric tube).

For chemical and pharmacological properties SmPC at http://www.medicines.org.uk/emc/.

The IMP is defined by active substance only, so all authorised brands in the UK can be used.

Revised protocol

Dose: 225 mg to 450 mg daily, including 200 mg modified release (MR) twice daily

Patients with a headache from dipyridamole will have the dose weaned up from daily MR 200mg or standard release 50 mg once daily to MR 200mg twice daily.

Fixed dose combinations of Aspirin and Dipyridamole can also be used, e.g. Asasantin Retard (Aspirin 25mg, Dipyridamole 200mg MR, twice daily

Route: Enteral (including via nasogastric tube). Dysphagic patients with enteral access will take dipyridamole suspension,dispersed capsules or crushed dipyridamole tablets 100mg four times daily.

For chemical and pharmacological properties SmPC at http://www.medicines.org.uk/emc/.

The IMP is defined by active substance only, so all authorised brands may be used.

1.1.1.3 Clopidogrel

Deleted "or rectal route" and "in the UK".

1.1.3 Storage, dispensing and return

Existing protocol

The IMP's must be stored in a secure location at room temperature (20° to 25°C) with excursions permitted with 15°C to 30° C.

Revised protocol

The IMP's must be stored in a secure location at room temperature (20°C to 25°C) in accordance with the relevant SmPC.

3.3 SELECTION AND WITHDRAWAL OF PARTICIPANTS

3.3.1 Recruitment

Existing protocol

3. TIA with limb weakness and/or dysphasia lasting between 10 minutes and <24 hours with no residual symptoms and presenting with any of the following
   a. ABCD2 score ≥4, or
   b. Crescendo TIA or
   c. Already on dual antiplatelet therapy

Revised protocol

3. TIA with limb weakness and/or dysphasia lasting between 10 minutes and <24 hours with no residual symptoms and presenting with any of the following

a. ABCD2 score ≥4;

b. Crescendo TIA

Patients who are on combined therapy aspirin+ dipyridamole or on monotherapy e.g aspirin alone, or clopidogrel alone, or dipyridamole alone, are eligible for recruitment.

Existing protocol

4. Ischaemic non cardioembolic stroke presenting with any of the following
a. Ongoing limb weakness and/or dysphasia of more than one hour duration
b. Resolved limb weakness of more than one hour duration with ongoing facial weakness
c. Ongoing isolated hemianopia of more than 1 hour duration with positive neuroimaging evidence to support the index event (e.g. ischaemic stroke in occipital lobe)
d. Resolved limb weakness and/or dysphasia between 24-48 hours after index event onset

Revised protocol

4. Ischaemic non cardioembolic stroke presenting with any of the following:
   a. Ongoing limb weakness of more than one hour duration; and/or

b. Dysphasia of more than one hour duration; and/or
c. Resolved limb weakness of more than one hour duration with ongoing facial weakness; and/or
d.Ongoing isolated hemianopia of more than 1 hour duration with positive neuroimaging evidence to support the new event (e.g. ischaemic stroke in the occipital lobe) and/or
e. Limb weakness that resolves between 24-48 hours after onset
f. Dysphasia that resolves between 24-48 hours after onset

Patients who are on combined therapy (aspirin+dipyridamole) or on monotherapy, e.g. aspirin alone, or clopidogrel alone, or dipyridamole alone, are eligible for recruitment.

Existing protocol

Note: Neuroimaging is essential for ischaemic stroke to exclude intracranial haemorrhage and/or non stroke diagnosis.

Revised protocol

Note: Neuroimaging is essential for ischaemic stroke to exclude intracranial haemorrhage and a non stroke diagnosis. If the patient received thrombolysis, a post-thrombolysis/pre- TARDIS scan needs to be done to exclude new thrombolysis associated bleeding prior to enrolment. Typically this is done routinely as 'standard of care', but if it is not done, then it must be done prior to enrolment.

5. Patients thrombolysed for stroke with full recovery in less than 24 hours from the onset of symptons are eligible for inclusion as a TIA providing neuroimaging post thrombolysis excludes intracranial haemorrhage.

Exclusion Criteria

Existing protocol* deleted

*9. Participant has taken clopidogrel or dipyridamole after the index event but prior to randomisation (aspirin is allowed between ictus onset and randomisation)

Revised protocol

Added 28. Patients who have not had post thrombolysis neuroimaging.

3.4.1.3. Comparators

Existing protocol

All participating sites will choose what comparators they wish to use for ischaemic stroke and TIA separately (e.g A1/B1 or A2/B3, or A3/B3). Sites will only be allowed to randomise patients to the group that they have previously chosen. Sites can however change this group during the trial, but will need to inform the coordinating centre so that the computerised randomisation system can be reprogrammed.

Revised protocol

All participating sites will choose what comparators they wish to use for ischaemic stroke and TIA separately (e.g A1/B1 or A2/B3, or A3/B3)). The randomisation choice will affect whether or not Clopidogrel or Dipyridamole can be given after onset and prior to randomisation. Aspirin is allowed in all choices. The principal investigator can change the choice of comparing groups on the database at any stage during the trial. This will however take 48 hours for the changes to take effect. The site will however need to inform the coordinating centre when making change.

The remaining decision is dependent on what the patient could be randomised to, and the general rule is they cannot have something that may confound the guideline group:

- ACD vs C vs AD A only before randomisation, i.e. no C or D
- ACD vs C A or C only before randomisation, ie. no D
- ACD vs AD A or D only before randomisation, i.e. no C

If the patient is given a 'confounding' antiplatelet after their event and before randomisation (e.g. dipyridamole in a site that has chosen clopidogrel), the patient may still be included, but randomisation will then only involve the appropriate comparisons.

3.4.1.4

Existing protocol

i. Dysphagic participants with enteral access may take crushed aspirin (or rectal aspirin), crushed or liquid dipyridamole (range 75 mg tds to 100mg qds), and crushed clopidogrel (if so randomised).
ii. Participants having a headache on dipyridamole will have the dose weaned up from daily MR 200mg or standard release 75 mg od to MR 200 mg bd (as in PRoFESS [47]). Fixed dose combinations of aspirin and dipyridamole can also be used.

Revised protocol

i. Dysphagic participants with enteral access may take dispersed or crushed aspirin (or rectal aspirin), crushed or suspension dipyridamole (100mg 6 hourly), and dispersed clopidogrel (if so randomised).
ii. Participants having a headache on dipyridamole will have the dose weaned up from daily MR 200mg or standard release 50 mg once daily to MR 200 mg twice daily (as in PRoFESS [48]). Fixed dose combinations of aspirin and dipyridamole can also be used.

3.4.5. Additional Blood Samples

Revised protocol

Blood sampling, as above, will be country dependent i.e. according to local regulations.

3.4.6. Scan Transfer and Storage

Existing protocol

The upload facility will transfer data using RC4-MD5 (128 bit) cipher encryption and anonymise the DICOM header of the images automatically once the scan and participant have been matched.

Revised protocol

The upload facility will encrypt the data during transfer and anonymise once the scan and participant have been matched. Data transfer occurs via the SSLv3 or TLSv1 protocol, using RSA key exchange and a minimum of 128 bit cipher encryption (DES-CBC3-SHA, IDEA-CBC-SHA, RC4-SHA1 or RC4-MD5 cipher suites). A copy of the non-anonymised scan data will be kept securely to allow resolution of data errors, until 1 year after the end of the trial.

3.4.7. Expected duration of participant participation

Existing protocol

	Day 0	**Day 3±1**	**Day 7±1**	**Day 35±3**	**Day 90±***
Randomisation	**+**				

Safety assessments		+	+	+	+
Tolerability assessments		+	+	+	+
Bloods					
FBC	+		+	+	
P-Selectin	+		+		
Genetics/EDTA† sample	+				
Serum and plasma	+		+		
Clinical Efficacy					
Impairment (NIHSS)	+		+	+	
Function (mRS & BI)					+
Cognition, QoL & Mood					+

Table 3:*Day 90 assessment done by telephone questionnaire. †or anticoagulant provided in the hospital's usual FBC blood tubes. FBC, Full Blood Count; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Score; BI, Bartel Index; QoL, Quality of Life

Revised protocol- Genetics/EDTA sample on Day 0 and ¶

	Day 0	**Day 3±1**	**Day 7±1**	**Day 35±3**	**Day 90±***
Randomisation	+				
Safety assessments		+	+	+	+
Tolerability assessments		+	+	+	+
Bloods					
FBC	+		+	+	
P-Selectin	+		+		
Genetics/EDTA† sample	+				
Serum and plasma	+		+		
Clinical Efficacy					
Impairment (NIHSS)	+		+	+	
Function (mRS & BI)					+
Cognition, QoL & Mood					+
Transcranial Doppler¶	+	+			

Table 3:*Day 90 assessment done by telephone questionnaire. †or anticoagulant provided in the hospital's usual FBC blood tubes. FBC, Full Blood Count; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Score; BI, Bartel Index; QoL, Quality of Life
¶ Not in the main phase of the trial

The following baseline characteristics constitute a protocol violation

Revised protocol

26.Patients who do not have a post thrombolysis scan.

3.4.10.1 Protocol violation

Existing protocol

4b. ABCD2 score <4 and not a crescendo TIA and not on dual antiplatelet therapy.

Revised protocol

4b. ABCD2 score <4 and not a crescendo TIA and not on dual antiplatelet therapy or monotherapy antiplatelets.

3.4.10.2. Protocol Deviation

Existing protocol

The following practice during the trial constitutes a 'protocol deviation'

2. Patient receives more than 400mg daily of dipyridamole

Revised protocol

The following practice during the trial constitutes a 'protocol deviation'

3. Patient receives more than 450 mg dipydridamole daily

3.5. TRIAL MANAGEMENT

Existing protocol

3.5.1. Sponsor

The University of Nottingham is the trial sponsor in the UK and will delegate responsibility for design and conduct of the trial to the Chief Investigator via our Sponsor/Chief Investigator agreement.

Revised protocol

3.5.1. Sponsor

Sponsorship of the trial is undertaken in each participating country. The University of Nottingham will hold a contract with each sponsor.

The University of Nottingham is the trial sponsor in the UK but not in other countries and will delegate responsibility for design and conduct of the trial to the Chief Investigator via our Sponsor/Chief Investigator agreement.

6.3 DATA PROTECTION

Existing protocol

Personal information (e.g. name and address of patients and secondary contacts) about trial participants will be held at local centres and will be passed onto the Coordinating Centre, Nottingham, UK and to National Coordinating Centres for centres situated outside the UK.

Revised protocol

Personal information (e.g. name, date of birth, address of patients and secondary contacts) about trial participants will be held at local centres and will be passed onto the Coordinating Centre, Nottingham, UK and to National Coordinating Centres for centres situated outside the UK.

Existing protocol

The personal patient information will be deleted at the end of the trial.

Revised protocol

Except the trial ID number and date of birth all other personal patient information will be deleted at the end of the trial.

Appendix J

Updated Trial inclusion flow chart included. Item 3 "already on dual antiplatelet therapy" updated to "already on mono/dual antiplatelet therapy".

Appendix K

Sample labels updated.