TARDIS STUDY
SUBSTANTIAL PROTOCOL AMENDMENT
SUMMARY OF CHANGES FROM
VERSION 1.4 to 1.5

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

PROTOCOL VERSION 1.5: SUMMARY OF CHANGES

Page 1-61 Update version from 1.4 to 1.5 and date 28/2/14 throughout.

Page 2 Change of statistician from Aimee Houlton to Miss Katie Robson

Page 5 Addition of eligibility criteria to include "or positive imaging on MR diffusion".

Description of interventions. Dosing updated from "Aspirin (loading dose 300 mg, then 75 mg daily), and dipyridamole (modified release 200 mg twice daily)."

To "aspirin (loading dose 300 mg, then 50-100 mg daily), and dipyridamole (between 225 and 450 mg daily), or guideline antiplatelet therapy (aspirin and dipyridamole or clopidogrel, doses as above)."

Update Duration of Study from "8 years" to "5 years".

Page 12 Aspirin dosing updated from "Loading dose 300mg, then 75mg daily"

To "Loading dose 300mg, then 50-100 (including 75) mg daily".

Dipyradimole dosing wording added "up to a maximum dose of 450mg daily, over a few days".

Section 1.1.3, Storage, dispensing and return
Wording changed from: "The IMPs must be stored in a secure location at room temperature (20°C to 25°C) in accordance with the relevant SmPC. Depending on local arrangement, this may be at the local pharmacy, the research department or the ward. Following recruitment and randomisation into the trial, the study treatment should be prescribed on the drug chart and the IMPs dispensed by the principal investigator/qualified designee. 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."

To: "The IMPs must be stored in a secure location 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. Minor deviations should be discussed with local pharmacy and any action documented. Following recruitment and randomisation into the trial, the study treatment should be prescribed on the drug chart and the IMPs dispensed by the principal investigator/qualified designee. 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 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."

Page 14 **Section 1.1.4.3** – "intracranial, gastrointestinal" deleted.

Page 18 **Section 3.3.2**, Inclusion criteria has been edited to include new sentences below:

"Already on dual antiplatelet therapy with aspirin and Dipyradimole"

"Positive neuroimaging evidence to support the new event, ischaemic stroke on MR diffusion imaging".

Added "Notes: 1. Patients who are on monotherapy e.g. aspirin alone, or clopidogrel alone, or dipyridamole alone, are eligible for recruitment. Similarly, patients who are on combined therapy aspirin+ dipyridamole, are eligible for recruitment if they fulfil the above criteria.
2. Patients with posterior fossa events are eligible if they fulfil the above criteria."

Page 19 Added inclusion criteria:
"f. Positive neuroimaging to support the new ischaemic event with MR diffusion.
g. Already on combined dual antiplatelet therapy (aspirin + dipyridamole)

Page 20 **Exclusion criteria**. New exclusion added "Patients on aspirin and clopidogrel prior to the underlying event".

Section 3.4.1.1 Intensive. Updated from "Clop will be given as a loading dose of 300 mg,[12] then 75 mg daily, Asp as a loading dose of 300 mg,[22] then 75 mg daily, and Dip modified release 200 mg twice daily [9] for 28-30 days."
To Asp "loading dose of 300 mg then 50-100 (including 75) mg daily". Updated Dip to "between 225 and 450mg daily".

Page 21 **Section 3.4.1.2 Guideline antiplatelet Group.** Updated from "Asp as a loading dose of 300 mg, then 75 mg daily, and Dip modified release 200 mg twice daily for 28-30 days."
To "Asp as a loading dose of 300 mg, then 50-100 (including 75) mg daily, and Dip between 225 and 400 mg daily; including modified release as 200 mg twice daily (or 150 mg thrice daily) for 28-30 days".

Section 3.4.1.3 Comparators. Added "prior to randomisation".

Changed
"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"

To
"ACD vs C - A or C only before randomisation, i.e. no D in the guideline group

ACD vs AD - A or D only before randomisation, i.e. no C in the guideline group"

Section 3.4.1.4 Notes on Treatment. Added "150 mg thrice daily".

Page 24 **Section 3.4.7.** Removed reference to TCD, as not in the main phase of the trial.

Page 25 **Protocol violations**
Wording changed from
"Participant has taken dipyridamole or clopidogrel following the index event and prior to stroke randomisation"

To
"Participant has taken dipyridamole between the index event and prior to stroke randomisation, where clopidogrel is the control treatment."

New wording added:
"13. Participant has taken clopidogrel between the index event and prior to stroke randomisation, where AD is the control treatment."

Page 26 New wording added:

"28. Patient does not receive the correct loading dose."

Page 27 **Co-ordinating Centre**. "Division of Stroke" updated to "Stroke, Division of Clinical Neuroscience".

Page 28 **Section 4.1 Methods.** "Data Linkage and Extract Service, Health and Social Care Information Centre (HSCIC)" updated from "Medical Research Information Services (MRIS)".

Page 35 **Section 10.1 Funding source**. Updated to include main phase funder "National Institute for Health Research Health Technology Assessment Programme".