CHANGES TO THE TARDIS PROTOCOL TO CREATE VERSION 1.2

The changes are listed in page order (except for the changes in the synopsis, which are reflected in the appropriate section later in the protocol). The changes are highlighted in yellow within the protocol.

1. Page 1 and 4. Changed long title to: Safety and efficacy of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial

Reason: Efficacy is the primary outcome and should be reflected in the title.

2. ISRCTN and sponsor reference numbers added to the title page

Reason: Update

3. Page 3. Abbreviations. Added "LMWH, Low Molecular Weight Heparin; TIA, Transient Ischaemic Attack"

Reason: Clarification.

4. Page 10. Investigational Medicinal Products (IMPs) (and Intervention, page 17). This section has been altered significantly and reference to the protocol is advised. Briefly, TARDIS is testing the addition of open-label clopidogrel (for one month) to standard antiplatelet treatment (aspirin and dipyridamole) for stroke and TIA. In the original CTA application we listed all three products as IMPs (aspirin, dipyridamole and clopidogrel), which was an error. The only IMP in this trial is clopidogrel because aspirin and dipyridamole are considered as standard, routine treatment. We have removed the IMP status from aspirin and dipyridamole as reflected in the revised CTA xml. file. This is now explicit in the protocol (and synopsis, page 5) and dose regimens for all three anti-platelet drugs have been further clarified. In particular, the treatment period of 1 month is defined as 30 days which is convenient to patient and researcher as clopidogrel is currently provided in a 30-tablet blister pack. However, the patent for clopidogrel will end before the end of the trial and if alternative suppliers provide smaller pack sizes (e.g. 28-tablet packs), then this length of treatment is sufficient. After the 30 day treatment period, patients will be expected to return to routine antiplatelet therapy, such as combined aspirin and dipyridamole as recommended by NICE. These changes are also reflected in the information sheets (versions 1.4) - descriptions and side effects of aspirin and dipyridamole have been removed as they are considered standard care.

5. Page 11. Packaging and labelling. Added: "but local sites can overlabel as they feel appropriate, in which case accountability logs for clopidogrel (batch numbers and expiry dates) should be recorded. Aspirin and dipyridamole are not IMPs as they are standard treatment for stroke and TIA; accountability logs for them are therefore unnecessary." This has also been added to page 23 (drug accountability)

Reason: Version 1.1 of the protocol highlighted that labelling was not necessary as aspirin, dipyridamole and clopigogrel are already licensed for use in stroke. However, sites involved in the trial may feel more comfortable labelling clopidogrel and recording accountability logs.

6. Page 12. Side effect list of aspirin and dipyridamole have been deleted

Reason: Aspirin and dipridamole are no longer considered as IMPs.

7. Page 13. Secondary endpoints. Added "incidence and type of infection".

Reason: Clopidogrel has antileucocyte properties and it is therefore worthwhile looking for incidence and type of infection

8. Page 14. Paragraph 1. Setting (and synopsis page 4). Removed “including hospitals in the Trent and South-East Stroke Local Research Networks”.

Reason: All hospital within the UKSRN will be considered for inclusion.

9. Page 14. Primary endpoint. The following has bee moved from the primary endpoint to secondary outcomes as there should only be one primary outcome (ordinal stroke severity): “The start-up phase will assess ordinal bleeding (fatal/major/moderate/minor/none) at 35 days (end of treatment) as adjudicated by an independent blinded panel”

10. Page 16. Inclusion criteria. Point 1. Added. "All strokes must have motor weakness or dysphasia at the time of randomisation.”

Reason: Requiring that these events have motor weakness or dysphasia decreases the chance of including patients with non-stroke diagnoses.

11. Page 16. Inclusion criteria. Point 2. Added. "All TIAs must have motor weakness or dysphasia lasting at least 10 minutes.”

Reason: Requiring that these events have motor weakness or dysphasia decreases the chance of including patients with non-TIA diagnoses.

12. Page 16. Inclusion criteria. Point 2. Changed “(<48 hours of onset)” to “(≤48 hours of onset)”

Reason: Clarification. Minor change.

13. Page 16. Inclusion criteria: Point 2. Changed “ABCD2 score ≥5” to “ABCD2 score ≥4”

Reason: We want to include TIAs that are at high risk of recurrent stroke, which is quantified using the ABCD2 score. From a clinical perspective, high risk scores include all those with a score ≥4, and we feel that this should be reflected in the trial.

14. Page 16. Inclusion Criteria. Added: Point 3. “Meaningful consent, or consent from a relative, carer or legal representative if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level).”

Reason: Clarification

15. Page 16. Exclusion criteria. Point 1. Changed Age <40 to “Age <50. The patient information sheet has been changed accordingly to version 1.4.

Reason: The use of antiplatelet therapy is important in preventing stroke caused by atherosclerosis. Patients younger than 50 are more likely to have a different cause of their stroke and will therefore be excluded.

16. Page 16. Exclusion Criteria. Point 2 has been split into divided into points 2 and 3.

Reason: Minor change

17. Page 16. Exclusion criteria. Point 2 has been changed from: “Motor weakness lasting <30 minutes…” to “Motor weakness or dysphasia lasting <10 minutes…”

Reason: We only want to include TIAs that are at high risk of recurrent stroke, which is quantified using the ABCD2 score. The criteria used for limb weakness uses a cut-off of 10 minutes, to score 1 point. The ABCD2 score also involves patients with speech difficulties (e.g. dysphasia). These changes reflect the ABCD2 scoring system. The patient information sheet has been changed accordingly to version 1.4.

18. Page 16. Exclusion criteria. Added point 5: "Patients with definite need for treatment with clopidogrel (e.g. recent MI)"

Reason: Patients with a definite need for clopidogrel cannot be randomised into the trial which is made clear by adding this point.

19. Page 16. Exclusion criteria. Point 10 (was point 8 in version 1.1). Changed from "Definite need for, or currently on triple antiplatelet therapy or anticoagulation" to "Definite need for full dose oral (e.g. warfarin) or parental (e.g. heparin or glycoprotein IIb IIIa inhibitors) anti-coagulation. NB Low dose heparin for DVT prophylaxis is allowed".

Reason: The bleeding risk to patients on full dose anti-coagulation is too high for entry into the trial. However, patients on only prophylactic heparin may still benefit from triple antiplatelet therapy so will be allowed entry into the trial. The safety analyses will specifically look at this subgroup of patients.

20. Page 16. Exclusion criteria. Point 11 (was point 9 in version 1.1). Changed "Indication for, or received (in last week), thrombolysis" to "Received thrombolysis within the last 30 hours".

Reason: Antiplatelet drugs are usually started 24 hours after a patient has received thrombolysis for ischaemic stroke (as the effects of a thrombolytic agent have worn off by this time). Patients may therefore enter the trial as defined above.

21. Page 16. Exclusion Criteria. Changed "Pre-morbid dependency (mRS>3)" to "Pre-morbid dependency (mRS>2)".

Reason: For trial entry, it is important that patients are physically independent prior to their qualifying event, which is reflected in this change.

22. Page 16. Exclusion Criteria. Added:
    a. Point 14. Known haemoglobin less than 10g/dL
    b. Point 15. Known platelet count less than 100 x 10^9 /L
    c. Point 16. Known white cell count less than 3.5 x 10^9 /L

Reason: These are added as a safety measure to ensure that patients with significant anaemia, thrombocytopaenia or leucopenia are not entered in to the trial.

23. Age 16. Exclusion criteria. Deleted: "Planned surgery during first month post stroke (e.g. carotid endarterectomy)"

Reason: This was a duplication (in error), therefore removed

24. Page 17. Follow-up. Added "at 7±1 and"

Reason. A minor addition to the text. This visit with the patient was present in the previous version but just not in this paragraph. The table on page 19 has also been updated.

25. Page 18. Subheadings for 'Transcranial Doppler and Platelet Function' made clearer and moved to page 18 (from page 15) under section 'Trial Treatment and Regimen'. 'Additional Blood Samples' and 'Scan Transfer and Storage' also moved to this section.

Reason: A minor change to the protocol layout.

26. Page 18. Replaced "identical Nicolet/EME" with "commercial"

Reason: Not all sites will have the same make of TCD machine.

27. Page 18. Platelet Function. Added: "using pre-purchased blood sample containers"

Reason: clarification.

28. Page 18. Additional Blood Samples. Added "For example, the *CYP2C19* genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarction, and may be significant in ischaemic stroke."

Reason: A minor addition to the protocol; an example of a genetic variant that could be useful in genetic analysis in TARDIS.

29. Page 19. Scan Transfer and Storage. Added: "Data that are sent to the TARDIS Coordinating Centre are validated before anonymisation" and "Reports on brain imaging and carotid imaging performed at local centres will be faxed to the TARDIS Coordinating Centre".

Reason: It is vital that gathering patient data is accurate and valid. It is not possible to validate brain images (usually in a DICOM format) before the patient details have been removed. We therefore have to check that the images we receive correspond to the correct patient. This will normally be done automatically when the patient files are uploaded electronically. In a few cases, this information will have to be posted to the TARDIS coordinating centre where we will ensure that the data is anonymised after validation. An extra box on the consent form (version 1.4) has been added to reflect this practice.

Page 20. Statistics. Methods. Added "The effect of the intervention on the primary outcome will be performed within the following subgroups of subjects:

a) By age - ≤ 75 years, > 75 years.
b) By sex – male, female.
c) By stroke/TIA
d) By stroke sub-type – lacunar, posterior fossa, cortical
e) By stroke severity – severe, moderate/mild; NIHSS≤10,>10
f) By baseline systolic blood pressure – > 160 mmHg), 140-160 mmHg, <140.
g) By treatment delay - > 24 hours, ≤ 24 hours.
h) By patients enrolled into TCD substudy.
i) By patients enrolled into P-selectin substudy.
j) By patients on antiplatelet therapy at randomisation - mono, dual;
k) Aspirin naïve vs aspirin
l) By heparin - none, unfractionated, LMWH
m) By number of TIAs in the last week
n) By thrombolysis - yes, no
o) By ABCD2 score - 4, >4"

Reason: Predetermined subgroup analyses should be stated in the protocol.

30. Page 22. Participant removal from the study due to adverse events**.** Added: "Should the participant discontinue any trial medications due to, for example, an adverse event, they will remain in the study until the end of the trial at day 90 (±7), as completeness of follow-up is

essential. However, should they wish to do so, any participant is free to withdraw from the trial at any time and without giving reason."

Reason: Clarification

31. Page 26. Added: "the UKSRN Prevention Clinical Studies Group".

Reason: Additional information on trial approvals.

32. Page 28. Appendices A to H added.

Reason: The appendices contain material that is used in the trial. Specifically:

Appendix A: Definitions
Appendix B: NIHSS
Appendix C: Glasgow Coma Score
Appendix D: Rankin Scale (modified)
Appendix E: Barthel Index
Appendix F: EuroQOL
Appendix G: Cognitive Testing
Appendix H: Zung Depression Rating Scale (short)
Appendix I: Trial Flow
Appendix J: Trial Timeline

33. Consent form, Version 1.4. Added:

a. "I agree that information regarding my clinical scans can be sent to the TARDIS Coordinating Centre in Nottingham where it will be anonymised and stored"
Reason: Explained in point 29 above

b. "I understand that my anonymised data can be shared with other research groups (e.g. Antithrombotic Trialists' Collaboration) after publication of TARDIS"
Reason: This point has already been discussed in the original ethics application. Nonetheless, we felt that it should also be explicit in the consent process.