TARDIS STUDY
SUBSTANTIAL PROTOCOL AMENDMENT
SUMMARY OF CHANGES VERSION 1.3

In the text below, protocol and information sheet changes, having implications for research design, conduct or participant safety, have been listed. Additional minor changes to text and formatting made to bring protocol, information sheets and consent forms up-to-date are not described below but can be viewed in the 'marked' version of the documents. The trial summary has been updated to reflect the changes in the protocol.

PROTOCOL VERSION 1.3: SUMMARY OF CHANGES

1. Title

Existing Protocol
Safety and efficacy of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial

Revised Protocol
Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke and transient ischaemic attack: a randomised controlled trial

2. Trial Background Information and Rationale

The trial background information has been revised and updated to reflect the current evidence. These changes are highlighted in the document with tracked changes.

3. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCTS

Aspirin and dipyridamole will also be considered as investigational medicinal products in addition to clopidogrel.

Revised Protocol

Description

Aspirin (Asp)

International Non-Proprietary Name (INN): Aspirin

Chemical Abstracts Series (CAS) number: 50-78-2

Dose: Loading dose 300mg, then 75mg od.

Route: Enteral (including via nasogastric tube – dispersible or crushed tablets can be used) or rectal route.

For chemical and pharmacological properties, see summary of medical product characteristics (SmPC) at http://www.medicines.org.uk/emc/.

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

Dipyridamole (Dip)

INN: Dipyridamole

CAS number: 58-32-2

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.

4. Packaging and labelling

This section has been revised and updated

Existing Protocol

Standard pharmacy supplies should be used as the IMP (clopidogrel) has marketing authorisation for use in stroke. Separate labelling and packaging details are not required 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.

Revised Protocol

Standard pharmacy supplies should be used as all IMPs have marketing authorisation and are to be used in accordance with such 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. The information on the label should include the trial name, EudraCT number, description of contents, batch number, expiry date, and quantity. There should be space for insertion of the trial number, name of the participant and the date of dispensing on the label (see appendix K). Under exceptional circumstances (e.g. out of hours) where labeled IMPs are not available, trial sites may choose to use ward stock without separate labeling if agreed locally and approved by the pharmacy.

5. Storage dispensing and return

This section has been revised and updated.

Existing Protocol

Standard pharmacy supplies will be prescribed and used.

Revised protocol

The IMPs must be stored in a secure location at room temperature (20°C to 25°C) with excursions permitted within 15°C to 30°C. 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. A sample label is provided (Appendix K).

6. Known side effects

Side effects for aspirin and dipyridamole have now been added.

Revised protocol

Known Side Effects

Aspirin

Adverse reactions

i. Bleeding:Aspirin prolongs bleeding time, and bleeding disorders, such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, gastrointestinal bleeding, haematoma and cerebral haemorrhage have been reported.
ii. Blood and lymphatic system disorders - anaemia, haemolytic anaemia, hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, pancytopenia, prolonged bleeding time, occult blood loss, elevated transaminase levels, agranulocytosis.
iii. Gastrointestinal disorders - gastrointestinal bleeding, erosions, perforations or ulceration, which can occasionally be major (may develop bloody or black tarry stools, severe stomach pain and vomiting blood), gastrointestinal irritation (mild stomach pain, heartburn, vomiting and nausea). Fatalities have occurred.
iv. Hepatic disorders - hepatitis (particularly in patients with SLE or connective tissue disease)
v. Renal and urinary disorders – disturbances of renal function
vi. Ear and labyrinth disorders - tinnitus.
vii. Hypersensitivity reactions - rhinitis, urticaria, purpura, Stevens-Johnson syndrome, angio-oedema, asthma, worsening of asthma, bronchospasm.

Interaction with other medicinal products:

i. Salicylates may enhance the effect of oral hypoglycaemic agents, phenytoin and sodium valproate.
ii. They inhibit the uricosuric effect of probenecid and may increase the toxicity of sulphonamides.
iii. Aspirin may potentiate the effect of heparin and increases the risk of bleeding with oral anticoagulants, antiplatelet agents and fibrinolytics.
iv. The risk of gastrointestinal ulceration and bleeding may be increased when aspirin and corticosteroids are co-administered.
v. Concurrent use of aspirin and other Non Steroidal Anti Inflammatory Drugs (NSAID) should be avoided. Use of two or more NSAID preparations increases the risk of serious gastrointestinal haemorrhage.
vi. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.
vii. Alcohol may enhance the gastro-intestinal side effects of aspirin.

viii. Patients using enteric-coated aspirin should be advised against ingesting antacids simultaneously to avoid premature drug release.
ix. Selective Serotonin Reuptake Inhibitors (SSRI) may increase risk of gastrointestinal bleeding if coadminstered.

Dipyridamole

Adverse reactions at therapeutic doses are usually mild.

i. Bleeding: In very rare cases, increased bleeding during or after surgery has been observed.
ii. Blood and lymphatic system disorders: Isolated cases of thrombocytopenia have been reported in conjunction with treatment with Dipyridamole.
iii. Gastrointestinal disorders: Vomiting, diarrhoea and symptoms such as nausea, dyspepsia. These tend to occur early after initiating treatment and may disappear with continued treatment.
iv. Cardiovascular: As a result of its vasodilating properties, dypridamole may cause hypotension, hot flushes and tachycardia. Worsening of the symptoms of coronary heart disease such as angina and arrhythmias may occur.
v. Central Nervous System Disorders: Dizziness, headache and myalgia may occur early after initiating treatment and may disappear with continued treatment.
vi. Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angio-odema have been reported.

Interaction with other medicinal products:

i. Dipyridamole increases the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should therefore be considered if use with dipyridamole is unavoidable.
ii. Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs.
iii. Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

TRIAL PURPOSE AND OBJECTIVES

7. PURPOSE

Existing Protocol

To perform a randomised trial assessing the efficacy, safety and tolerability of adding Clopidogrel to Aspirin and Dipyridamole in patients with recent ischaemic stroke or TIA and who are at high risk of recurrence. The study will comprise a start-up phase of 350 patients to then expand into a larger trial of 5000 patients assessing the efficacy, safety and health economics of this approach.

Revised Protocol

To perform a randomised trial assessing the efficacy, safety and tolerability of intensive antiplatelet therapy (Asp+Dip+Clop) versus guideline antiplatelet therapy (Asp+Dip or Clop) in patients with recent ischaemic stroke or TIA and who are at high risk of recurrence.

8. PRIMARY OBJECTIVE

Existing Protocol
To assess ordinal stroke severity at 90 days after short-term administration (1 month) of triple antiplatelet therapy (aspirin/clopidogrel/dipyridamole) versus standard dual therapy (aspirin/dipyridamole) in patients with very recent ischaemic stroke or TIA.

Revised Protocol
To assess ordinal stroke severity at 90 days after short-term administration (1 month) of intensive antiplatelet therapy versus guideline therapy in patients with very recent ischaemic stroke or TIA.

9. SECONDARY OBJECTIVE

Existing Protocol

1. To assess the safety of short-term administration (1 month) of triple antiplatelet therapy (aspirin/clopidogrel/dipyridamole) versus standard dual therapy (aspirin/dipyridamole) in patients with very recent ischaemic stroke or TIA.

2. To further assess, in high risk patients with stroke/TIA, whether the addition of clopidogrel to aspirin/dipyridamole:
   i. Is feasible to administer acutely and tolerable to take for 1 month,
   ii. Is superior in respect of surrogate markers such as emboli (with transcranial doppler) and platelet function.
   iii. Improves functional outcome

3. To assess whether ordinal outcomes are superior to binary events

Revised Protocol

1. To assess the safety of short-term administration (1 month) of intensive antiplatelet therapy versus guideline therapy in patients with very recent ischaemic stroke or TIA.

2. To further assess, in high risk patients with stroke/TIA, whether:
   iv. it is feasible to administer intensive therapy acutely and is tolerable to take for 1 month,
   v. intensive therapy is superior in respect of surrogate markers such as platelet function.
   vi. intensive therapy improves functional outcome

TRIAL DESIGN- TRIAL CONFIGURATION-SETTING

10. Design

Existing Protocol
Multicentre parallel group prospective randomised open-label blinded-endpoint controlled trial.

Revised Protocol
International, collaborative, multicentre, parallel group, prospective, randomised open-label, blinded-endpoint, controlled, Phase III trial.

11. Setting:

Existing Protocol
The trial comes from members of the SRN Prevention Clinical Study Group (PB, SH, HM, GV). Initially, 350 patients will be recruited from the UK Stroke Research Network. Each of the participating sites runs a stroke service with sufficient stroke/TIA patients to allow the planned recruitment rate (20+ centres x 0.6 patient/month [typical rate for academic stroke trials] x 12 months x 2.5 years = 360 patients). Expansion overseas and within the UK will occur for the main phase.

Revised Protocol
Initially, ~1000 patients will be recruited from the UK National Institute of Health Research (NIHR) Stroke Research Network (SRN) to the start-up phase. In the main phase, a further 3,100 participants from UK and overseas hospital-based stroke/TIA services will be recruited; UK participants (~2000) will be recruited from SRN sites (the trial is already adopted) including 55 sites who have been started-up and are recruiting in England and Scotland. These sites have dedicated SRN nurses to facilitate recruitment and follow-up. Philip Bath will run the trial from the University of Nottingham Stroke Trials Unit.

12. Trial Duration

Existing Protocol
The start-up phase will run for 3 years; months 0-3: development of trial systems (based on the internet site/database used in the ongoing ENOS trial) and training of LRN nurses at recruiting centres; months 4-31: patient recruitment; months 32-34: follow-up of the last recruited patients and data cleaning; months 35-36: analysis and report writing. There will then be a seamless transition from start-up to the main phase of the trial of the same design (as done with funding from BUPA Foundation to MRC for ENOS) so that recruitment does not stop. The main phase will last for an additional 5 years. Separate permission for funding from the appropriate bodies (e.g.HTA) will be sought for the second phase.

Revised Protocol
The start-up phase will run for ~4 years. If the start-up phase shows acceptable safety, there will then be a seamless transition to the main phase of the trial of the same design so that recruitment does not stop (**tables 2a, 2b**).

The main phase will recruit in the order of ~3,100 patients (depending on the rate and distribution of ordinal events) and will last an additional 5 years. Separate permission for funding from the appropriate bodies (e.g. HTA) is being sought for the main phase.

If the trial shows that intensive antiplatelet therapy is superior to guideline therapy (taking account of the balance between reduced stroke/vascular events and potentially increased bleeding), intensive antiplatelet therapy could be introduced rapidly for stroke prevention with immediate benefit to high risk

patients; each component is available now and licensed for secondary prevention. As the patent for clopidogrel has ended, NHS implementation of positive results will be based on generic costs, which will improve uptake and health economics.

A decision to proceed onto the main phase will be dependent on regular safety analyses during the start-up phase (by the Data Monitoring Committee), a successful funding application for the main phase, and the results of ongoing trials of dual antiplatelet therapy e.g. SPS-3 (Asp+Clop vs Asp), and ARCH (Asp+Clop vs. warfarin).