26th September 2012

Professor Philip Bath
University of Nottingham
United Kingdom

Dear Professor Bath,

Re: TARDIS - Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack (TIA): a randomised controlled trial

The ASTN Executive Committee reviewed the above mentioned study. It was noted that the following document was provided: clinical study protocol TARDIS Protocol Version 1.3 (20/12/2011)

The comprehensive review was led by A/Professor Mark Parsons.

A/Professor Mark Parsons declared that he had no conflict of interest with the study.

Study design

The trial is an investigator driven, international, collaborative, multicentre, parallel group prospective, randomised, open-label blinded-endpoint, controlled Phase III trial.

Trial objective

The trial will assess the effects of intensive anti-platelet therapy against standard guideline-directed anti-platelet therapy on stroke severity at 90 days.

Comments on inclusion criteria

1. The inclusion criteria are pragmatic and broad in nature. For the TIA group high risk patients are included. The definition is more than 10 minutes but less than 24 hours of limb weakness and /or dysphasia. In addition, high risk TIA patients are defined as reaching an $ABCD^2$ score of > 4 or having had more than 1 TIA in the past week or already on dual anti-platelet therapy. The ABCD2 score is popularity as time goes on but there is not another clinical scale that can replace it. DWI might be better as a marker of high risk but is not practical in many countries.

2. In terms of the stroke group, they must have one of the following: ongoing limb weakness and/or dysphasia for more than one hour; or resolved limb weakness of more than one hour duration with ongoing facial weakness; or ongoing isolated hemianopia of more than 1 hour with positive imaging. It is noted that the last group is the only group where positive imaging for stroke is required. The other category is resolved limb weakness and/or dysphasia lasting between 24 and 48 hours.

Comments on Study Design and Outcome Measures:

1. This study investigates triple antiplatelets (Aspirin+ Clopidogrel + Dipyridamole) verses guideline-directed antiplatelet therapy in patients at high risk of recurrent stroke. The primary outcome at 90 days is somewhat different to the traditional stroke/no stroke measure. There are 5 categories:

1. Fatal stroke;
2. Severe to fatal stroke with Modified Rankin Scale (mRS) 2-5;
3. Mild stroke outcome mRS 0-1
4. TIA;
5. No stroke or TIA.

Sample size has been calculated based on categorical outcomes. It has been argued that the 5 categories allow for more power than a dichotomous outcome of stroke or no stroke. This has been estimated at 4100 patients which includes a 1000 start-up phase. It is a probe design, with no placebo supplied by a company. It follows that an open-label blinded endpoint allows for patients to be randomised to aspirin with a loading dose + Clopidogrel with a loading dose + Dipyridamole, or Aspirin + Dipyridamole, or Clopidogrel alone.

2. There are three choices for the intervention. The randomisation strategy is pragmatic as the centres are allowed to choose which strategy they prefer to use. This is based on uncertainty around the guidelines for antiplatelet therapy and non-cardio embolic stroke and TIA. Centres can choose to be in the randomisation group where A+C +D compared to C alone or A+D. Of note, centres can also to be A+C +D vs C alone, or A+C +D vs A+D. In addition, the study also allows centres to change to a different choice throughout the study.

3. It was not completely clear in the protocol about the definition of premorbid mRS <2 – is this before or after the initial event? If patients with relatively severe stroke (at baseline) are included, they may well have an mRS 2-5 as a result of the original stroke (not from any recurrent stroke). It is noted that the statistical analysis section provision have been made to adjust for baseline variables including NIHSS <10 or >10.

Comments about workload of the study:

From reviewing the protocol table of procedures the study does not look overly onerous. Assessments take place at day 3, day 7, day 35 and day 90 and separate visits should not take long.

Summary

In summary, the committee have some questions regarding the inclusion criteria (the premorbid mRS exclusion needs to be clarified in particular). Perhaps it may be better to have no choice about the randomisation (i.e. A + C + D vs A + D vs C randomised 1:1:1). More rigorous imaging based criteria could be considered but might not be practical for a large study.

Recommendations:

The ASTN committee recommends that TARDIS is a high quality, relatively low intensity study which is appropriate in the ASTN context. The ASTN executive committee is pleased to formally endorse this study for Australian stroke research centres.

Kind regards,

Associate Professor Bernard Yan

ASTN Chairman on behalf of the ASTN Executive Committee