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

Short title: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke.

Acronym: TARDIS

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ABBREVIATIONS

Asp	Aspirin
ADR	Adverse Drug Reaction
AE	Adverse Event
BI	Barthel Index
Clop	Clopidogrel
CAS	Chemical Abstract Series
CI	Chief Investigator
CRF	Case Report Form
Dip	Dipyridamole
GCP	Good Clinical Practice
HTA	Health Technology Assessment
IDMC	Independent Data Monitoring Committee
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
INN	International Non-Proprietary Name
LMWH	Low Molecular Weight Heparin
LRN	Local Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
MR	Modified Release
mRS	Modified Rankin Scale
NIHR	National Institute of Health Research
NIHSS	National Institute of Stroke Health Scale
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSAID	Non Steroidal Anti Inflammatory Drugs
NSTEMI	Non ST Elevation Myocardial Infarction
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development
SmPC	Summary of Medical Product Characteristics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
STEMI	ST Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SRN	Stroke Research Network
TIA	Transient Ischaemic Attack
TMC	Trial Management Committee
TSC	Trial Steering Committee

SYNOPSIS

Title	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
Acronym	TARDIS
Short title	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke
Trial Summary	Recurrence is greatest immediately after stroke or TIA; existing prevention strategies (antithrombotic, lipid/blood pressure lowering, carotid endarterectomy) reduce, not abolish, further events. Dual antiplatelet therapy – aspirin & clopidogrel for coronary disease, aspirin & dipyridamole for stroke - is superior to aspirin monotherapy. Triple antiplatelet therapy reduces MI and death in patients with coronary disease. We have shown that it is feasible to give triple antiplatelet therapy (aspirin, clopidogrel, dipyridamole) to patients with ischemic stroke/TIA. We will assess the efficacy, safety, tolerability and feasibility of intensive (combined aspirin, dipyridamole and clopidogrel) versus guideline antiplatelet therapy (combined aspirin and dipyridamole or clopidogrel) given for 1 month in ~1000 patients (over ~4 years) with acute stroke/TIA (i.e. at high risk of recurrence) in the start-up phase of a large randomised controlled trial. This will seamlessly run into the main phase of the trial (total 4100 patients) over the next 5 years providing safety information from the start up phase allows. The primary outcome is ordinal stroke severity at 90 days. Secondary outcomes include safety, serious adverse events, vascular events, death and platelet function.
Chief Investigator	Professor Philip Bath
Primary Objective	The trial will assess ordinal stroke severity: 5-level ordinal stroke and TIA scale with stroke ordered by its severity using the modified Rankin Scale (mRS): fatal stroke / severe non-fatal stroke (mRS 2-5) / mild stroke (mRS 0,1) / TIA / no stroke-TIA, measured at 90 days.
Trial Design	International, collaborative, multicentre, parallel group prospective, randomised, open-label blinded-endpoint, controlled Phase III trial.
Setting	In the start-up phase, patients will be recruited from the UK Stroke Research Network Centres. Further expansion within the UK and overseas will occur in the main phase.
Sample size estimate	The start-up phase is sized to assess safety and will inform the sample size calculation for the main trial phase, which will assess the efficacy of intensive versus guideline therapy. Assuming the distribution in 5 level recurrent stroke/TIA outcome (stroke with mRS 6 =0.1%/ mRS 2-5 = 0.7%/ mRS 0-1 = 1.53%/ TIA = 3.57%), odds ratio of 0.68, alpha 5%, power 90%, losses to follow-up 2%, treatment crossovers 5% the total sample size for the whole

	study is 4100.
Number of participants	Start up: ~1000; main phase: 3100
Eligibility criteria	Adults at high risk of recurrent ischaemic stroke: 1. Acute high risk TIAs ≤48 hours of onset All TIAs must have limb weakness and/or dysphasia lasting at least 10 minutes. 2. Ischaemic, non cardioembolic stroke with limb weakness, dysphasia or hemianopia ≤48 hours of onset with neuroimaging to rule out alternative causes. 3. Meaningful consent, or consent from a relative, carer or legal representative if the patient is unable to give consent (e.g. in cases of dysphasia, confusion, or reduced conscious level).
Description of interventions	Intensive versus guideline antiplatelet therapy will be given for 28 to 30 days along with standard 'best care' (including lifestyle advice, BP and lipid lowering). Randomised patients will receive clopidogrel (loading dose 300 mg, then 75 mg daily), aspirin (loading dose 300 mg, then 75 mg daily), and dipyridamole (modified release 200 mg twice daily), or guideline antiplatelet therapy (aspirin and dipyridamole or clopidogrel, doses as above), .
Duration of study	8 years
Randomisation and blinding	Patients will be randomised through the trial website with stratification and minimisation. Outcome assessments are blinded.
Outcome measures	**Primary:** Ordinal stroke severity at 90 days. **Secondary:** Binary and ordinal outcomes of stroke, TIA, MI, acute coronary syndrome, composite vascular outcome, death. Also safety (ordinal bleeding events), tolerability and feasibility. Additional measures include laboratory measures (FBC and P-Selectin), clinical efficacy (NIHSS), function (mRS, BI), cognition (TICS), quality of life (EuroQoL, EQ-5D), mood (Zung), disposition, days at home and economic activity.
Statistical methods	Ordinal logistic regression on ordered categorical outcomes, binary logistic regression on binary outcomes, analysis of covariance (ANCOVA) on continuous data and Kaplan-Meier and Cox proportional hazards regression on time to event data. Analyses will be adjusted for randomisation/minimisation factors. Subgroup analyses will only be performed in the main trial phase

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1 TRIAL BACKGROUND INFORMATION AND RATIONALE

Stroke is devastating to patients, carers and society through high mortality (~1-in-3 patients by 1 year), morbidity (dependency in ~1-in-3 patients often needing long term care) and cost (6% of NHS spend). Both stroke incidence and prevalence will increase as the UK population ages. Following stroke or transient ischaemic attack (TIA), the risk of recurrence is high, especially immediately after the event (~10% over weeks) after which it falls (~40% by 5 years). Importantly, recurrent strokes are usually more severe than earlier events. The Government has emphasised stroke as a clinical 'marker' condition and has supported its research importance through funding the UK Stroke Research Network (PB is prevention Director, TR and HM are Local Research Network Directors for Trent and South-east respectively).

TIA ('mini stroke') is a sudden, focal neurologic deficit that lasts for less than 24 hours (typically 10 minutes to 1 hour), is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery. (A tissue-based definition [1] is not used since MR scanning is not universally available around the world in the participating sites.) TIAs are important because they are a key risk factor for subsequent stroke. Patients presenting with specific TIA features are at particularly high risk of a subsequent stroke, as assessed by the ABCD^2 score:[2] age $\geq$60 years (1 point); blood pressure $\geq$140/90 mmHg (1); clinical symptoms of unilateral weakness,(2) or speech impairment without weakness (1); duration $\geq$60 minutes,(2) or $\geq$10 minutes (1); and diabetes (1).[2] The score ranges from 0 to 7 and the risk of stroke over the next 90 days increases exponentially: score 0 - risk <1%, 1 – 2%, 2 – 4%, 3 – 4.5%, 4 – 8%, 5 – 12%, 6 – 17%, and 7 – 22%.[2] Other groups have now validated the score. An important caveat is that data for the training databases used to derive and validate the ABCD^2 score were collected up to 1998 and 2005 respectively so the absolute risk rates of stroke now are likely to be lower as enhanced secondary prophylaxis with antithrombotics, BP and lipid lowering are now standard practice.

The risk of recurrence can be reduced, but not abolished with life style changes, carotid endarterectomy (large artery stroke) and drug interventions: antihypertensives and statin therapy. While oral anticoagulants are established for cardioembolic stroke,[3] other patients with ischaemia (the majority) need antiplatelets.[4-5] These interventions are cost-effective. The archetypal antiplatelet, aspirin (inhibitor of cyclooxygenase), reduces recurrence (relative risk reduction, RRR) by 17% in patients with prior stroke or TIA.[6] Clopidogrel (adenosine diphosphate [ADP] receptor antagonist) was slight more efficacious than aspirin in CAPRIE.[7]. Importantly, the absolute difference in efficacy between A and C was highest in patients with prior stroke or MI.[8] Dipyridamole (inhibits red cell uptake of adenosine) reduced recurrence by 16% in comparison with placebo in ESPS II.[9] Evidence now suggests that stroke prevention is dependent on the number of antiplatelets, e.g. aspirin and dipyridamole reduces events by 23% in comparison to aspirin (or dipyridamole) alone without increasing the risk of bleeding, as seen in ESPS II and ESPRIT.[9-10] As with clopidogrel alone, the difference in efficacy between aspirin and dipyridamole versus aspirin alone was largest in patients with highest baseline risk.[11] Similarly, aspirin and dipyridamole was superior to aspirin in cardiac patients (CURE, CREDO) [12-13] but not in CHARISMA,[14] probably because the apparent benefit in those with prior stroke or MI (high risk of recurrence) was diluted by lack of efficacy in those with no previous vascular events (low risk). The risk of bleeding with aspirin and dipyridamole vs. aspirin was 30-40% higher in these 3 trials. The MATCH trial (aspirin and clopidogrel vs. clopidogrel) found that dual aspirin and clopidogrel also increased bleeding.[15-16]

On the basis of this information and taking account of the prices of branded clopidogrel and dipyridamole-ER (£37 and £10 per month respectively), NICE recommended in 2005 that

patients should take combined AD after ischaemic stroke or TIA (TA90). In late 2010, NICE updated its recommendation to aspirin and dipyridamole for TIA, and clopidogrel for ischaemic stroke (TA210), this taking account of the massive drop in price of clopidogrel (£3.40, as a generic, British National Formulary [BNF] 61) but lack of significant randomised data and license for clopidogrel in patients with TIA. Former and current guidelines have not recommended dual aspirin and clopidogrel because of increased bleeding.[17-18] The preference for dual aspirin and dipyridamole or clopidogrel alone over aspirin alone is also recommended by the European Stroke Organisation in its 2008 guidelines (Bath was Co-Chair of the Prevention section).[19] In contrast, the 2011 American Stroke Association secondary prevention guidelines still give equal recommendations for aspirin (50-325 mg daily) alone, dual aspirin and dipyridamole, and clopidogrel (75 mg daily) alone,[20] thereby ignoring the results of recent trials.[7, 9-10, 21]

The above data for stroke reflect long-term prophylaxis, a very different situation from the situation immediately after an event when the risk of recurrence is much higher. Conventional acute antiplatelet therapy is based on aspirin alone for ischaemic stroke reflecting the results of the IST-1 and CAST megatrials [22-23] but the effect size is small (absolute risk reduction ~1.1%); until recently the acute treatment of TIA had not been investigated. Since risk of recurrence falls quickly after stroke or TIA, intensive antiplatelet specific treatment is only likely to be needed for a short period so that the exposure-time to hazard (mainly bleeding) is limited. While clopidogrel based dual therapy has not proved effective/safe in long-term stroke prophylaxis, early and short-term dual therapy may be useful, at least after TIA/minor stroke, as suggested by trials (FASTER, EARLY, PRoFESS early [24-26]) and observational studies (EXPRESS, SOS [27-28]). In FASTER (n=392), 90 days of aspirin and clopidogrel (vs aspirin) showed a trend to reduced stoke by absolute 3.7% (not significant (NS)) and increased symptomatic intracerebral haemorrhage (sICH) by absolute 1% (NS) leading to a net absolute benefit of 2.7%[24] . Similarly, EARLY (n=543, acute ischaemic stroke/TIA) found a trend to reduced vascular events at day 90 with aspirin and dipyridmole (vs aspirin, NS) but no effect on functional outcome,[25] a pattern of observations also seen with aspirin and dipyridamole (vs clopidogrel) in the PRoFESS early subgroup (n=1,360, mild acute ischaemic stroke).[26]

In a meta-analysis of all trials comparing dual with mono antiplatelet therapy in acute patients with stroke or TIA (including CARESS, CHARISMA, CLAIR, FASTER, EARLY, ESPRIT, ESPS-2, MATCH and PRoFESS early [9-10, 14-15, 24-26, 29-30]), acute dual therapy versus monotherapy within 3 days of ictus significantly reduced subsequent vascular events,[24] stroke (ischaemic and haemorrhagic, **figure 1**), and composite vascular events (trend) (Geeganage & Bath; submitted *Stroke*). No significant differences were seen for MI, sICH, major bleeding or death (but there were few events, **table 1**). No heterogeneity existed in any analysis suggesting that the composition of dual and mono therapy was not of primary importance. None of the trials were large enough (each <1,400) to show individual significant differences in stroke or vascular events. Importantly, the magnitude of effect appeared to decline with time from ictus so trials recruiting early have greater reductions in their point estimates (albeit non-significant because of small sample size) than those recruiting later: range of odds ratio for stroke, early, OR 0.51 to 0.71 (EARLY, FASTER, PRoFESS early); later, OR 0.83 to 2.44 (CHARISMA, MATCH).

	Stroke, MI, Vascular death	Stroke,TIA, ACS, all death	Stroke recurrence	MI	sICH	Major bleed	Death

Odds Ratio	0.75	**0.71**	**0.67**	0.71	1.39	2.09	1.34
95% Confidence intervals	0.56-0.99	**0.56-0.91**	**0.49-0.93**	0.25-2.03	0.22-8.75	0.86-5.06	0.76-2.34

Table 1. Meta-analysis of 12 trials of dual vs mono antiplatelets in patients with acute ischaemic stroke/TIA. Data were obtained from trialists for patients recruited within 72 hours of ictus (Geeganage & Bath; submitted *Stroke*).

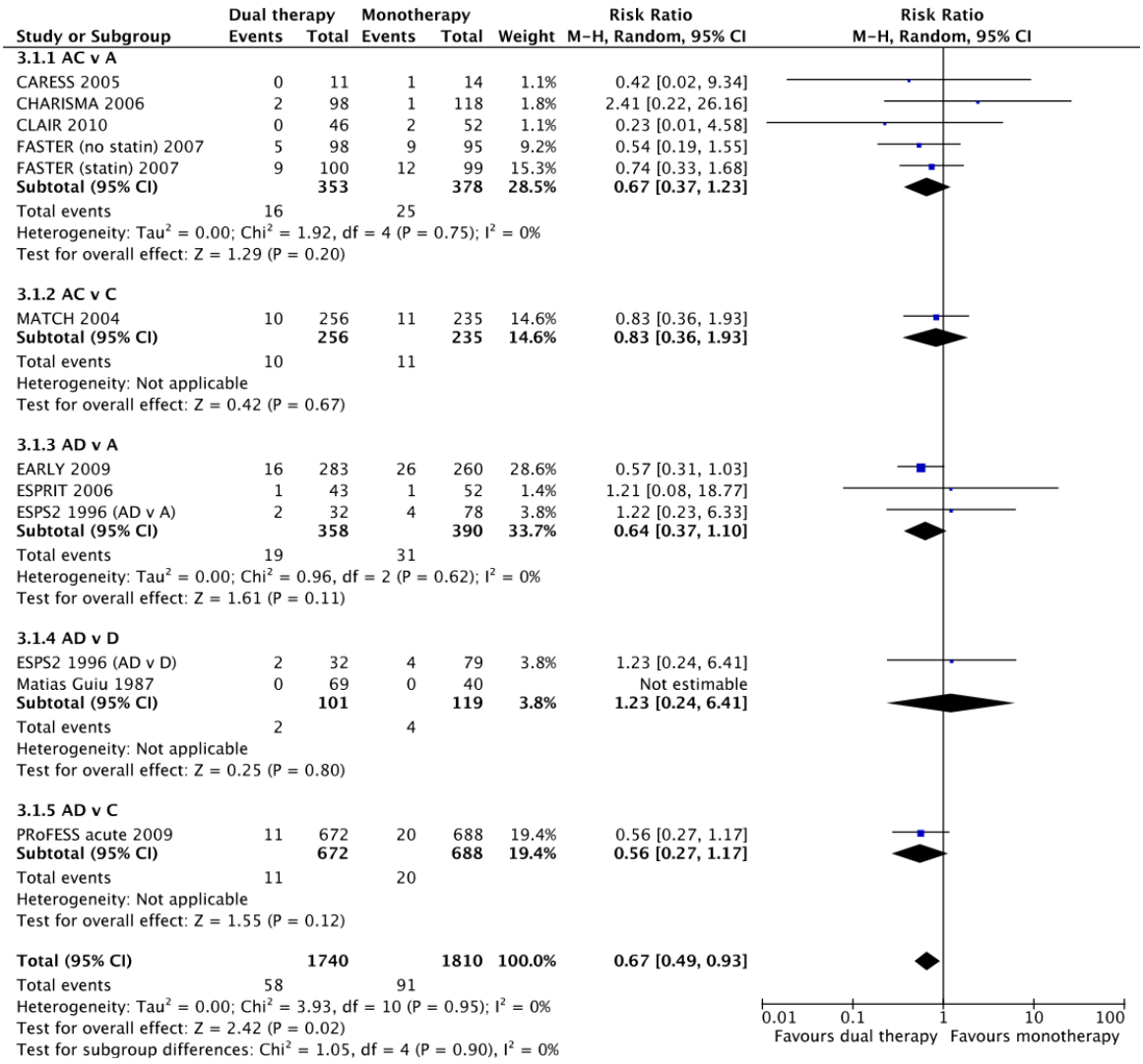


Figure 1. Meta-analysis of effect of dual versus mono antiplatelet therapy on stroke using data from 10 trials in patients with acute stroke or TIA. As compared with monotherapy, dual therapy reduced stroke: OR 0.67 (0.49-0.93). No heterogeneity was present suggesting that the composition of dual and mono therapy was less important than the number of antiplatelet agents (Geeganage and Bath; submitted *Stroke*).

Current stroke prevention is far from perfect: stroke is heterogeneous in type (ischaemic vs. haemorrhage; lacunar vs. cardioembolic vs. large artery), severity and outcome; treatments reduce, not abolish, events ('treatment failure'); and patients may be (relatively) insensitive to treatment ('treatment resistance', as identified for aspirin and clopidogrel [31]).

If aspirin and dipyridamole is superior to aspirin for long-term secondary prevention,[9-10, 32] and aspirin and clopidogrel is probably superior to aspirin in acute minor stroke/TIA,[24, 27] then triple antiplatelet therapy (aspirin+dipyridamole+clopidogrel) may be better still providing the risk of recurrence is high and bleeding does not become excessive. In this respect, the risk of bleeding when adding clopidogrel to aspirin and dipyridamole is likely to be similar to that when adding clopidogrel to aspirin since dual aspirin and dipyridamole does not increase bleeding over aspirin.[9-10] We have performed a series of 'proof-of-concept' laboratory and clinical studies investigating this approach.[33-37] In vitro studies found that triple therapy was most effective in inhibiting aggregation, platelet-leucocyte conjugation, and leucocyte activation.[33-35] In multiway crossover phase I and II trials comparing short-term administration of mono dual, and triple antiplatelet platelet therapies, the combination of aspirin and clopidogrel, with or without dipyridamole, was most potent in inhibiting platelet function ex vivo in both normal volunteers (n=11) and patients with previous stroke/TIA (n=11).[36-37]

In the only parallel group trial of triple therapy in patients with stroke, triple therapy was feasible to administer (vs. aspirin, phase II trial, n=17) for up to 24 months.[38] [The comparator of aspirin was chosen since this was the UK standard of care at trial start. The trial was stopped early on publication of ESPRIT [10] confirming the superiority of dual aspirin and dipyridamole over aspirin, i.e. it was unethical to continue patients on aspirin alone.] Predictably, there was a non-significant trend to increased bleeding with triple therapy vs aspirin. Although unintended, the patients were at low risk of recurrence (young/recruited months after the event/many lacunar strokes), a problem also seen in MATCH and CHARISMA.[14-15] Future trials of triple antiplatet therapy need to target patients at high risk of recurrence so that benefit is likely to outweigh hazard. We have also used chronic triple antiplatelet therapy in clinical practice in patients at high risk of recurrence, defined as recurrence on dual antiplatelet therapy.[39]

Short-term randomised controlled trials of triple antiplatelet therapy have been reported in patients with acute coronary syndromes or to cover stent insertion (25 studies, 17,383 patients) . In our published meta-analysis and in comparison with dual antiplatelet therapy, GP IIb/IIIa based triple therapy reduced Myocardial Infarction (MI) in Non ST Elevation MI (NSTEMI) patients (OR 0.70, 95% CI 0.56-0.88) and ST Elevation MI (STEMI) (OR 0.26, 95% CI 0.17-0.38) patients , and vascular events in NSTEMI (OR 0.69, 95% CI 0.55-0.86) and STEMI (OR 0.39, 95% CI 0.30-0.51) patients[40]. Death was also reduced after STEMI; major bleeding and transfusions were non-significantly increased and were few in number such that benefit outweighed hazard in absolute numbers of patients. The number of stroke events were too few to assess any trends, and insufficient or zero data were available for other antiplatelets (cilostazol, clopidogrel, dipyridamole)[40].

The proposed trial comes from members of the UK Stroke Research Network (SRN) Prevention Clinical Study Group (PB, SH, HM, GV) and is predicated on: (i) dual aspirin and dipyridamole is superior to aspirin after stroke; (ii) dual aspirin and dipyridamole or clopidogrel is the standard of care in the UK (NICE); (iii) dual aspirin and clopidogrel is superior to aspirin in patients with ischaemic heart disease (iv) some patients still 'fail' on aspirin and dipyridamole; and (v) Adding clopidogrel to aspirin may be useful in high risk patients, i.e. immediately after TIA/minor stroke. The results of our experimental medicine research (laboratory, phase I/II trials) and routine clinical use support this approach.[33-37] Hence, triple therapy may be better still in high risk patients providing benefit exceeds bleeding.[41]

1.1 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

1.1.1 Description

1.1.1.1 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.

1.1.1.2 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.

1.1.1.3 Clopidogel (Clop)

INN: Clopidogrel
CAS number: 113665-84-2
Dose: Loading dose 300mg, then 75mg od.
Route: Enteral (including via nasogastric tube – crushed tablets can be used) or rectal route.
For chemical and pharmacological properties see 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.

1.1.2 Packaging and labelling

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.

1.1.3 Storage, dispensing and return

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).

1.1.4 Known Side Effects

1.1.4.1 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.

1.1.4.2 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.

1.1.4.3 Clopidogrel

Adverse Reactions

i. Bleeding is the most common reaction reported and is mostly reported during the first month of treatment.Bleeding: some cases were reported with fatal outcome (especially intracranial,gastrointestinal and retroperitoneal haemorrhage); serious cases of skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding(conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), haematuria and haemorrhage of operative wound have been reported; cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with acetylsalicylic acid or clopidogrel with acetylsalicylic acid and heparin.

In addition to clinical studies experience, the following adverse reactions have been spontaneously reported. Within each system organ class (MedDRA classification), they are ranked under heading of frequency. "Very rare" corresponds to <1/10,000. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

ii. Blood and lymphatic system disorders: very rare; Thrombotic Thrombocytopenic Purpura (TTP) (1/200,000 exposed patients), severe thrombocytopenia (platelet count 30 $x10^9$/l), agranulocytosis, granulocytopenia, aplastic anaemia/pancytopenia, anaemia.
iii. Immune system disorders: very rare; anaphylactoid reactions, serum sickness
iv. Psychiatric disorders: very rare: confusion, hallucinations
v. Nervous system disorders: very rare; taste disturbances
vi. Vascular disorders: very rare; vasculitis, hypotension
vii. Respiratory, thoracic and mediastinal disorders: very rare; bronchospasm, interstitial pneumonitis
viii. Gastrointestinal disorders: very rare; pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
ix. Hepato-biliary disorders: very rare; acute liver failure, hepatitis
x. Skin and subcutaneous tissue disorders: very rare; angioedema, bullous dermatitis (erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis), rash erythematous, urticaria, eczema and lichen planus
xi. Musculoskeletal, connective tissue and bone disorders: very rare; arthralgia, arthritis, myalgia.
xii. Renal and urinary disorders: very rare; glomerulonephritis.

Investigations: very rare; abnormal liver function test, blood creatinine increase

Interaction with other medicinal products:

i. Clopidogrel should not be co-adminisrered with warfarin due to increased bleeding risk. Caution should also be taken with corticosteroids, NSAIDS, heparin and thrombolytics.
ii. Patients entered into clinical trials with clopidogrel have received a variety of concomitant medications including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

2 TRIAL PURPOSE AND OBJECTIVES

2.1 Purpose

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.

2.2 Primary Objective

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.

2.3 Secondary Objectives

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:
   ii. it is feasible to administer intensive therapy acutely and is tolerable to take for 1 month,
   iii. intensive therapy is superior in respect of surrogate markers such as platelet function.
   iv. intensive therapy improves functional outcome

3 TRIAL DESIGN

3.1 TRIAL /STUDY CONFIGURATION

3.1.1 Design

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

3.1.2 Setting:

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.

3.1.3 Trial Duration:

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).

Table 2a: Trial timeline: Start-up phase

Time (months)	-6-0	0	0.25	0.5	1	1.5	2	2.5	3	3.25	3.5
Protocol	+										
Approvals	+										
Trial materials	+										
Site identification/training		+	+	+	+	+	+	+			
Recruit participants		+	+	+	+	+	+	+	+		
Day 90 follow-up			+	+	+	+	+	+	+	+	
DMC reviews				+	+	+	+	+	+		+
TSC meeting	+	+		+	+	+	+	+	+		+
Investigator meeting	+	+			+				+		
Feasibility reviews					<	+	+	+	>		
Database clean		+							+	+	
Finalise SAP										+	
Analysis											+

Table 2b: Trial timeline: Main phase

Year	0†	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5
Further site identification	+	+	+	+	+	+	+	+	+			
Participant recruitment	+	+	+	+	+	+	+	+	+	+	+	
Day 90 follow-up	+	+	+	+	+	+	+	+	+	+	+	
DMC review		+		+		+		+		+		
TSC meeting	+		+		+		+		+		+	
Investigator meeting	+		+		+		+		+		+	
Publish protocol			+									
Database clean	+				+		+		+			
Data base close											+	
Analysis											+	+
Report writing											+	+

3.1.4 Primary outcome

5-level ordinal stroke and TIA scale with stroke ordered by its severity using the modified Rankin Scale (mRS): fatal stroke / severe non-fatal stroke (mRS 2-5) / mild stroke (mRS 0,1) / TIA / no stroke-TIA, measured at 90 days.; this approach allows for smaller sample sizes compared to binary outcomes such as stroke/no stroke.[42]

3.1.5 Secondary outcomes

Days 35 and 90
Binary stroke; binary myocardial infarction; ordinal myocardial infarction (fatal MI/non-fatal MI/no MI);[42] binary acute coronary syndrome; ordinal acute coronary syndrome (ACS - fatal/STEMI/NSTEMI/unstable angina/none); binary composite vascular outcome (non fatal MI & stroke, vascular death); ordinal composite vascular outcome;[42] composite stroke, TIA, acute coronary syndromes and all cause death, incidence and type of infection.

Day 90, all participants:
Function (mRS, Barthel Index); Cognition (telephone mini mental state, TICS and animal naming); quality of life (EuroQoL/EQ-5D and EuroQOL VAS [43]); Mood (Zung [44]); disposition (home, carer, residential, nursing home); discharge from hospital (timing) days at home; economic activity.

Tolerability: Proportion of patients completing 30 days of randomised treatment.

Feasibility: Recruitment rate per week.

3.1.6 Safety Outcomes

Days 7 and 35
Full blood count by local investigator

Days 7, 35 and 90:
Ordinal bleeding (fatal/major/moderate/minor/none[42]) as adjudicated by an independent blinded panel; death; binary major bleeding (fatal, symptomatic, causing fall in haemoglobin of ≥2g/l, or leading to transfusion of ≥2 units of blood/red cells);[45] binary minor bleeding (e.g. bruising)
binary bleeding; all bleeding, symptomatic intracerebral haemorrhage, major extracranial bleeding, binary serious adverse events,
ordinal adverse events (fatal/serious/other/none[42]);
thrombotic thrombocytopenic purpura; granulocytopenia.

3.2 Randomisation and Blinding

Patients will be randomised centrally using a secure internet site in real-time with stratification on index event (stroke/TIA) and country and minimisation on key prognostic/logistical baseline factors (age, gender, systolic blood pressure, cortical/lacunar syndrome, previous mono/dual antiplatelet, gastro-protection, use of low dose heparin, and time to randomisation, number of crescendo TIAs and ABCD2 score for TIAs and NIHSS and treatment with alteplase for strokes.) thereby maintaining concealment of allocation, minimising differences in key baseline variables, and improving statistical power.[46]

Multiple measures will be taken to reduce bias: internet data capture, real-time validation and concealment of allocation; blinded assessment of events, and adjudication of events, SAEs and neuroimaging; analysis by intention-to-treat; analyses adjusted for minimisation factors; adjustment for non-randomised treatment (e.g. statins, BP medications).

In the event that the website cannot be accessed, participants may be randomised by telephoning one of a series of emergency telephone numbers. These participants will be randomised without stratification or minimisation.

3.3 SELECTION AND WITHDRAWAL OF PARTICIPANTS

3.3.1 Recruitment

The initial approach will be from a member of the patient's usual care team (which may include the investigator or other members of the clinical research team).

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, but the consent forms and participant information sheets may not be available printed in other languages. It will be explained to the potential participant that entry into the trial is entirely voluntary and that their normal treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

3.3.2 Inclusion criteria

Adults at high risk of recurrent ischaemic stroke:

1. Age ≥50 years
2. Within 48 hours of ictus (24-48 hours if thrombolysed)
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

   Note: Neuroimaging is not necessary for transient ischaemic attack. Crescendo TIA is >1 TIA in one week and the onset time of last TIA is taken as time of ictus.

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

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

5. Informed consent from participant. If the participant is unable to give meaningful consent e.g. due to dysphasia, confusion, or reduced conscious level, proxy consent may be obtained from a relative, carer or legal representative .

.Exclusion criteria

1. Age<50
2. Isolated sensory symptoms or vertigo/dizziness or facial weakness
3. Isolated hemianopia without positive neuroimaging evidence
4. Intracranial haemorrhage
5. Baseline neuroimaging showing parenchymal haemorrhagic transformation (PH I/II) of infarct, subarachnoid haemorrhage or other non ischaemic cause for symptoms
6. Presumed cardioembolic stroke (e.g. history or current AF, myocardial infarction within 3 months)
7. Participants with contraindications to, or intolerance of, aspirin, clopidogrel or dipyridamole.
8. Participants with definite need for treatment with aspirin, clopidogrel or dipyridamole individually or in combination (e.g. aspirin and clopidogrel for recent MI/acute coronary syndrome)
9. Participant has taken clopidogrel or dipyridamole after the index event but prior to randomisation (aspirin is allowed between ictus onset and randomisation)
10. Definite need for full dose oral (e.g. warfarin, dabigatran) or medium to high dose parenteral (e.g. heparin) anti-coagulation. NB Low dose heparin for DVT prophylaxis is allowed
11. Definite need for glycoprotein IIb-IIIa inhibitors
12. Received thrombolysis within the last 24 hours
13. No enteral access
14. Pre-morbid dependency (mRS>2).
15. Severe high BP (BP>185/110 mmHg).
16. Haemoglobin less than 10g/dL
17. Platelet count more than 600 x 10^9/L or less than 100 x 10^9/L
18. White cell count more than 30 x 10^9/L or less than 3.5 x 10^9/L
19. Major bleeding within 1 year (e.g. peptic ulcer, intracerebral haemorrhage).
20. Planned surgery during 3 month follow-up (e.g. carotid endarterectomy)
21. Concomitant STEMI or NSTEMI.
22. Stroke secondary to a procedure (e.g. carotid or coronary intervention)
23. Coma (GCS<8)
24. Non-stroke life expectancy<6 months
25. Dementia
26. Participation in another drug or devices trial concurrently or within 30 days. (participants may take part in observational studies or non-drug or devices trials)
27. Geographical or other factors that may interfere with follow-up e.g. no fixed address or telephone contact number, not registered with a GP, or overseas visitor.
28. Females of childbearing potential, pregnancy or breastfeeding

3.3.3 Removal of participants from therapy or assessments

Participants may be withdrawn from therapy or assessments either at their own request or at the discretion of the Investigator (e.g. for reasons of safety or new information becoming available on the trial medication or condition being treated). The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

3.3.4 Informed consent / assent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. If participants are not competent to consent, e.g. due to dysphasia or confusion, relatives will be invited to give consent. These approaches are standard practice in acute stroke trials. However, all attempts should be made to take further informed consent from the participants should

their condition improve. A doctor knowledgeable about the trial will gain consent. Third party consent by an experienced, independent clinician would also be accepted in the event that no relatives were available. The Investigator will explain the details of the trial and provide a Participant / Relative/Independent Physician Information Sheet, ensuring that the individual providing consent has sufficient time to consider patient participation in the trial. The Investigator will answer any questions that the participant / relatives have concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. The Investigator will keep the original, the participant will keep one copy, and a second will be retained in the participants's hospital records.

Should there be any subsequent amendment to the protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form, which will be signed by the participant.

3.4 TRIAL TREATMENT AND REGIMEN

3.4.1 Intervention

The trial will compare intensive versus guideline antiplatelet therapy. Guidelines for secondary prevention of recurrent stroke may vary at local trial centres depending on local, national and international guidelines, and cost.

3.4.1.1 Intensive antiplatelet group

Participants in the intensive antiplatelet group will receive Asp+Dip+Clop triple therapy for 28-30 days (to cover the period of maximum risk of recurrence) along with standard 'best care' (including lifestyle advice, BP and lipid lowering). 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.

3.4.1.2 Guideline antiplatelet group

Patients randomised to the guideline group will receive one of the following antiplatelet therapies depending on local policy and guidelines:

A. For ischaemic strokes: Asp and Dip dual therapy or Clop monotherapy.
B. For TIAs: Asp and Dip dual therapy or Clop monotherapy.

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.

3.4.1.3 Comparators

The trial will compare the following intensive versus guideline antiplatelet therapies.

A. For ischaemic stroke:
   1) Asp+Clop+Dip : Clop: Asp+Dip (2:1:1)
   2) Asp+Clop+Dip : Clop (1:1)
   3) Asp+Clop+Dip : Asp+Dip (1:1)

B. transient ischaemic attack:
   1) Asp+Clop+Dip : Clop : Asp+Dip (2:1:1)
   2) Asp+Clop+Dip : Clop (1:1)
   3) Asp+Clop+Dip : Asp+Dip (1:1)

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.

3.4.1.4 Notes on treatment

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.
iii. At the discretion of the investigator, participants can take gastro-prophylaxis against upper gastrointestinal bleeding (proton pump inhibitor/histamine 2 receptor antagonist $\pm$ H. pylori eradication) according to local practice and policy.[48]
iv. After the 30 day treatment period, participants will be expected to return to guideline antiplatelet therapy, such as combined aspirin and dipyridamole or clopidgrel as recommended by local, national or international guidelines. [Note: PRoFESS (aspirin/dipyridamole vs. clopidogrel) enrolled 8,113 (40%) of patients within 10 days, and ~1000 patients within 2 days of onset, so it is feasible to administer dipyridamole acutely and is apparently safe.].
v. Study drugs may be stopped around procedures that become necessary after enrolment (however, this may constitute a protocol violation/deviation).

3.4.2 Baseline Measures

Pre-morbid modified Rankin Scale (mRS); stroke impairment (NIHSS); full blood count (part of routine clinical care); haemodynamics and ECG. Stroke type will be categorised according to modified TOAST criteria.[49]

3.4.3 Follow-up

Face-to-face interview at 7±1 and 35$\pm$3 days. Central telephone follow-up will be performed at 90$\pm$7 days by an assessor blinded to outcome.

As stroke is the primary outcome, vascular events a key secondary outcome, and bleeding the main hazard, ascertaining these events is vitally important. All participants will be asked specifically about Serious Adverse Events (SAE) and Outcome events at every follow up. We will also triangulate this information from GPs and local researchers, especially between day 35 and 90. Such information will be obtained centrally by the coordinating centre from the GPs and by the local researchers from their hospital electronic systems.

3.4.4 Platelet Function

Platelet expression of P-selectin will be used to monitor platelet effects in participants. Blood will be taken from all participants at baseline & day 7±1, fixed (to allow batching of samples), posted to Nottingham using pre-purchased blood sample containers, and P-selectin measured using a standardised assay [Heptinstall; patent pending (PTC/GB2008/050169)] with blinding to participant and treatment identity. P-selectin has been demonstrated to provide a robust means of identifying individual compliance with, and resistance to, aspirin, dipyridamole and clopidogrel; measurements will also be used to look for associations between successful platelet inhibition and clinical outcome. The analyses will be conducted at the Division of Cardiovascular Medicine at Queen's Medical Centre, Nottingham. All measurements are performed by flow cytometry and are subject to strict

quality control

3.4.5 Additional Blood Samples

Tertiary questions in TARDIS include assessing the effects of the interventions on blood biomarkers and whether a participant's genotype alters response to the interventions. For example, the *CYP2C19* genetic variant is a major determinant of prognosis in young participants who are receiving clopidogrel treatment after myocardial infarction, and may be significant in ischaemic stroke.[50-52] Several blood biomarkers are surrogate markers of outcome, such as S-100.[53] However, whether they and other blood factors (to be identified during the course of the trial) are also markers of the efficacy of interventions has yet to be determined.

Centres should have appropriate storage facilities including access to a centrifuge and freezer. In addition to the full blood counts, the following blood samples are required for blood biomarkers and genetic analysis:

Genetics blood test sample
- 4mls EDTA. Frozen whole (i.e. no centrifugation)
- anytime from baseline to Day 35

Baseline:
- 4mls EDTA. Centrifuge to collect and freeze plasma.
- 6mls clotted sample. Centrifuge to collect and freeze serum

Day 7±1:
- 4mls EDTA. Centrifuge to collect and freeze plasma.
- 6mls clotted sample. Centrifuge to collect and freeze serum

(See table 3, page 24 for a tabulated summary of all blood samples)

If the centre concerned does not use blood bottles containing EDTA, then their bottles usually used for FBC samples is sufficient (this will contain appropriate anticoagulant). Blood samples should be anonymised and labeled with the centre number, participant number and initials (C999/9999/ZZ), day and date of sample (Day 7 or 35, dd/mm/yyyy), stored locally in a freezer at -20°C (or lower if possible at -60°C to -80°C) and accounted for using the TARDIS Blood Sample Freezer Log. The TARDIS Coordinating Centre will arrange transfer of blood samples to Nottingham for analysis. Blood samples will be destroyed once analysis is completed, this being dependent on the trial's completion date.

A separate consent form will allow the participant/relative to opt-in to the genetic sub-study. Participants may continue in the main trial even if they or their next-of-kin elect not to consent to the genetics sub-study. The participant or next-of-kin may request destruction of the genetic samples at any time after consent and prior to creation of an anonymised database. An important aim of the genetic analyses is to determine whether polymorphic differences in candidate genes explain resistance to antiplatelets (pharmacogenetic analysis). The exact genetic analyses to be performed are undefined at present and will depend on relevant scientific information available at the time of laboratory analysis and prior to sample destruction.

3.4.6 Scan Transfer and Storage

Baseline and subsequent clinical or research CT and/or MR brain scans should be sent electronically (ideally) using the secure internet web upload facility provided on the TARDIS website (www.tardistrial.org/). Scans should not be anonymised prior to upload as certain fields such as study date, birth date and sex are essential to ensure that the scan is matched to the correct participant. 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. The DICOM header attributes that are

anonymised are a subset of those specified in the 'Basic Application Level Confidentiality Profile' of the DICOM standard 3.15; namely the institution name, institution address, referring physician, referring physician's address, Patient name, patient identifier, date of birth, other patient id, other patient names and patient's address attributes.

If centres are unable to use the web upload facility, encrypted and anonymised scans can be copied on a CD/DVD and sent via recorded delivery to the TARDIS ICC. The password for de-encryption, site and participant number, participant initials and scan date should be communicated separately via email. The data will be unencrypted at the TARDIS ICC and uploaded to the database as described above.

If centres are unable to send the scans by the above methods, they will be advised to contact the TARDIS ICC, who will help them with the process. Under exceptional circumstances, for centres where the only method of transferring images is by films/hardcopies, centres will be advised to send anonymised films via recorded delivery. These will be digitised at the TARDIS ICC.

All digital brain image data will be stored on secure computer servers owned and maintained by the Information Services, University of Nottingham, with access restricted both physically (locked server rooms) and by password. Access for adjudication, analysis and archiving will be by login, password and PIN numbers.

Anonymised imaging data shall be adjudicated by trained neuroradiologists who may be based at the Coordinating Centre or elsewhere. The adjudication systems have been designed to ensure the highest levels of data security and participant confidentiality, and will be further enhanced if future technological advances permit it. The enhancements to the current system may include the use of e-Science and Grid technologies (e.g. NeuroGrid, www.neurogrid.ac.uk/) if they prove to be superior to current systems.

Reports from radiologists on clinical carotid imaging will also be collected (ultrasound, MRA or CTA). Reports on brain imaging and carotid imaging performed at local centres will be faxed to the TARDIS ICC.

3.4.7 Expected duration of participant participation

Participant participation and assessments are summarised in the table below (**table 3**):

	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

3.4.8 Co-enrolment into other studies

Uncoordinated co-enrollment of patients into two or more trials has the potential for introducing bias, e.g. when the treatments have a similar mechanism of action, potentially share adverse events or have common outcomes. Patients should not be enrolled into this trial if they are already in another drug or devices trial. Patients can be co-enrolled into non-drug or devices trials or observational studies.

3.4.9 Compliance

At each scheduled visit, compliance with the IMPs will be assessed on direct questioning or by reviewing medication charts. Patients stopping a drug because of adverse events will carry on with the remaining therapy and follow-up assessments with analysis by intention-to-treat.

3.4.10 Protocol Violations and Deviations

The study should be conducted in accordance with the approved protocol and that changes to that protocol will only be made to protect the safety, rights, or welfare of the subject.

3.4.10.1 Protocol Violation

A protocol violation is a major deviation from the trial protocol where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria, or where deviations from the protocol could affect the trial delivery or interpretation significantly.

The following baseline characteristics constitute a protocol violation

1. Randomisation > 48 hours from onset of symptoms
2. Participant less than 50 years of age
3. For ischaemic stroke:
    a. No cranial imaging results available prior to randomisation
    b. Isolated sensory symptoms, vertigo or dizziness or facial weakness as presenting symptoms of the index event
4. For TIAs:
    a. Limb weakness and/or dysphasia lasting less than 10 minutes
    b. ABCD2 score <4 and not a crescendo TIA and not on dual antiplatelet therapy
5. Failure to obtain appropriate consent prior to randomisation
6. Pre-morbid dependency (mRS) >2
7. Participant unable to swallow and does not have enteral access
8. Baseline cranial imaging shows parenchymal haemorrhagic transformation (PH I/II)
9. Subarachnoid haemorrhage
10. Intracerebral haemorrhage
11. On anticoagulation therapy except low dose low molecular weight heparin
12. Participant has taken dipyridamole or clopidogrel following the index event and prior to stroke randomisation
13. Thrombolysis less than 24 hours prior to randomisation
14. Presumed cardioembolic stroke or history of atrial fibrillation
15. Concomitant STEMI or NSTEMI
16. Baseline SBP reading >185 mm Hg or DBP > 110 mm Hg
17. Major bleeding within one year prior to randomisation
18. Planned surgery within the 3-month follow-up period
19. Randomising event was secondary to a surgical procedure
20. Glasgow Coma Score < 8
21. Known history of dementia
22. Known probable life expectancy of less than 6 months

23. Unavailable for follow-ups
24. Female patient of childbearing potential, pregnant or breastfeeding at randomisation
25. Patient receiving treatment that they are not randomised to.

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

1. Subsequent randomisation into another drug or devices trial
2. Patient does not receive 5 days of randomised treatment in the first seven days and 16 days in the next 3 weeks
3. Failure to complete SAEs where appropriate
4. Failure to complete outcomes where appropriate
5. Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:
    a. 7-day follow-up: >7 days past the due date
    b. 35-day follow-up: >7 days past the due date
    c. Hospital event form: >30 days past the due date
    d. 90-day follow up: >30 days past the due date

3.4.10.2 Protocol Deviation

A Protocol Deviation is a minor deviation from the protocol that affects the conduct of the trial in a minor way. This includes any deviation from the trial protocol that is not listed as a Protocol Violation. Examples of Deviations are given below but this is not exhaustive.

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

1. Failure to switch to standard treatment following completion of treatment period
2. Patient receives more than 400mg daily of dipyridamole
3. Patient receives >75mg of aspirin or clopidogrel after Day 0
4. Non-receipt of Day 7 or Day 35 Full Blood Count
5. No blood pressure measurements at baseline, D7 or D35 follow-ups
6. Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:
    a. 7-day follow-up: >1day past the due date
    b. 35-day follow-up: >3days past the due date
    c. Hospital event form: >7days past the due date
    d. 90-day follow-up: >7 days past the due date

3.4.10.3 Review of Protocol Violations and Deviations

Protocol Violations will be reviewed annually by both the Data Monitoring Committee (using unblinded data) and the Trial Steering Committee (with blinding to treatment assignment).

The list of protocol violations and deviations will be updated, as necessary, in a working practice document which will be uploaded and available on the trial website.

3.5 TRIAL MANAGEMENT

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. The sponsor contact details are

Mr Paul Cartledge

Head of Research Grants and Contracts
Research Innovation Services
King's Meadow Campus,
Lenton Lane
Nottingham NG7 2NR UK

3.5.2 Coordinating Centre

The Stroke Trials Unit (STU), part of the University of Nottingham's Clinical Trials Unit (which has provisional registration), will co-ordinate the trial. STU will have overall responsibility for the conduct of the trial and will be responsible for provision of trial materials, collation and analysis of data and reporting of the final results. They will act as the International Coordinating Centre, UK National Coordinating Centre, the primary point of contact for UK centres, and the secondary point of contact for non-UK centres. The contact details are

Stroke Trials Unit
Division of Stroke Medicine
University of Nottingham
Clinical Science Building
City Hospital campus
Nottingham, NG5 1PBUK
Tel: +44 115 8230210
Fax: +44 115 8230273

3.5.3 Trial Steering Committee (TSC)

The TSC will provide overall supervision, as per their charter, and ensure that the trial is conducted in accordance with the principles of the ICH GCP and the relevant regulations. Any amendments to the trial will be agreed by the TSC. The TSC will provide advice to the investigators on all aspects of the trial. The composition of the TSC is given on the Trial website.

3.5.4 Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) will monitor efficacy and safety as per their charter. As well as outcome measures, the DMC will also review recruitment, baseline data, balance in baseline factors between the treatment groups, completeness of data, compliance to treatment, co-administered treatments, and outcome by sub groups. They will also review all serious adverse events (both adjudicated and unadjudicated) and protocol violations. The DMC will usually meet at least yearly by teleconference; the chairman will receive 6 monthly updates from the statistician. The composition and charter of the DMC is given on the trial website (www.tardistrial.org).

3.5.5 Outcome and event adjudication

There will be 2 adjudication committees:

- Independent Events (vascular outcomes, SAE)
- Neuroimaging adjudication

4 STATISTICS

A medical statistician will support the TSC with analyses. An interim analysis will be done during the start-up phase, blinded to treatment allocation, to demonstrate feasibility of the trial.

4.1 Methods

Analysis will be performed using ordinal logistic regression for ordered categorical variables, binary logistic regression for binary outcomes, ANCOVA on continuous data and Kaplan-Meier and Cox proportional hazards regression on time to event data. Analyses will be adjusted for randomisation/minimisation factors.

Safety analyses will be reviewed 6 monthly during the start-up phase by the independent Data Monitoring Committee.

The effect of the intervention on the primary outcome will be performed within the following subgroups of subjects:

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

Patients in the UK will be 'flagged' for death with the NHS Information Centre (Medical Research Information Service-MRIS) so that vital status can obtained for all patients.

4.2 Sample size and justification

4.2.1 Start-up phase

The start-up phase was sized to assess safety, i.e. where intensive antiplatelet therapy *might be* hazardous compared to guideline therapy; the key concern for antiplatelet agents relates to bleeding. The sample size calculation [54] used assumptions based on data from our pilot trial of triple antiplatelet therapy.[55] Assuming bleeding rates for Asp+Dip was 15% and Asp+Dip+Clop was 30%, alpha 5%, power 90%, losses to follow-up 3%, total sample size = 320 rounded to 350. Analyses will, in reality, be performed using ordinal approaches to improve statistical power.[42]

4.2.2 Main phase

The start-up phase informs the sample size calculation for the main phase which will assess the efficacy of intensive versus guideline therapy. Assuming the distribution in 5 level recurrent stroke/TIA outcome (stroke with mRS 6 =0.1%/ mRS 2-5 = 0.7%/ mRS 0-1 = 1.53%/ TIA = 3.57%), odds ratio of 0.68, alpha 5%, power 90%, losses to follow-up 2%, treatment crossovers 5% the total sample size for the whole study is 4100.

4.3 Definition of populations analysed

4.3.1 Safety Set

All randomised participants.

4.3.2 Intention-to-Treat (ITT) efficacy set

All participants in the Safety Set, and who took at least one treatment dose. Participants in the ITT will be defined prior to database lock.

4.3.3 Per Protocol Set (PPS) efficacy set

All participants in the ITT, and who are deemed to have no ***protocol violations***
Participants in the PPS will be defined prior to database lock.

4.3.4 Analyses

All efficacy analyses will be assessed using the ***ITT***; the robustness of the primary analyses will be assessed in the ***PPS***. Safety summaries will be performed on the ***Safety Set***. Major protocol deviations will lead to exclusion of a participant from the ***PPS***.

4.4 Health economic analysis

The impact of intensive antiplatelet therapy with aspirin, dipyridamole and clopidogrel on quality of life will be assessed using the EuroQoL. A full health-economic analysis will only be performed after completion of the main phase of the trial.

5 ADVERSE EVENTS

5.1 Definitions

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant
6. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may have been felt to jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All serious adverse events will be assessed for expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

5.2 Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship

incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator or delegate as "improbable", "possible", "probable", or "definite" is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

5.3 Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All serious adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator or delegate shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners. All SAEs will be reported to the Stroke Trials Unit, University of Nottingham.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring. Where it is the partner of a trial participant, consent will be obtained for this observation from both the partner and her medical practitioner. All serious adverse events will be recorded and reported to R&D and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

5.4 SUSARs

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, complete the CIOMS form and send to the MHRA.
- Shall inform the REC using the reporting form found on the NRES web page within seven days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

5.5 Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator. 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.

6 ETHICAL AND REGULATORY ASPECTS

6.1 ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

6.2 RECORDS

6.2.1 Drug accountability

Hospitals/pharmacies should choose their own supplier for the trial medications. As is common with stroke trials, medication can be dispensed and kept on the relevant ward or department ready for use as soon as the patient is randomised. It may be kept as 'ward stock' or as separate trial medication according to the practices of the randomising hospital (see Section 1.1.3).

6.2.2 Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database may also use their age. CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number and NHS number (UK patients), and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.' All paper forms should be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

6.2.3 Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

6.2.4 Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g., MHRA).

6.3 DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

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. This is necessary for the coordination and execution of the blinded 90 day follow up assessments, which will be carried out centrally for each country. Patient information will be held on a database in Nottingham but will be separated from all clinical information; the latter remain anonymous (identifiable only by initials, trial number and age). Computer data will be backed up regularly to an off-site secure repository (to enable disaster recovery). Personal patient information will be used only for the purposes of the TARDIS trial and will not be passed on to third parties. The personal patient information will be deleted at the end of the trial.

Trial paperwork will be anonymised, scanned and stored on a digital archiving system. This is with the exception of consent forms and patient details form. This will comply with the Data Protection Act and confidentiality rules, as outlined above.

Where permissible, the TARDIS Coordinating Centres may use central databases to obtain additional follow-up information on patients enrolled into the trial. In England and Wales, this will involve use of the NHS Information Centre (MRIS), database. When information will

be gathered on patients in this way, it will be clearly stated in the country specific patient/relative information sheets.

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

7 QUALITY ASSURANCE & AUDIT

7.1 INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

7.2 TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); serious adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

7.3 TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

7.4 RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

7.5 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and the Independent Data Monitoring Committee (IDMC) as appropriate in making this decision.

During the period of recruitment into the study, the trial statistician will perform interim analyses on major outcome events and supply these, in strict confidence, to the members of the Data Monitoring Committee, along with any other analyses that the committee may request. In the context of TARDIS, the balance between safety and efficacy will be considered.

With respect to safety the following outcomes in particular will initiate discussion for recommending early stopping or continuation of the study:

- The primary outcome ('shift' in modified Rankin Scale in patients having a recurrent stroke event or TIA)
- Combined outcome of fatal or non-fatal stroke or major bleeding
- The overall rate of symptomatic intracranial haemorrhage

With respect to efficacy, the committee will conduct formal interim analyses based on the following outcome.
Combined outcome of fatal or non-fatal stroke or major bleeding ‡ event .

In making any decision, the committee will consider the overall internal and external evidence, the multiplicity of testing and the possibility that the trends in the data might be reversed with longer follow-up or increased recruitment.

In the light of these analyses, the IDMC will advise the Chairman of the Trial Steering Committee (TSC) and Sponsor (via the Chief Investigator) if, in their view, the randomised comparisons in TARDIS have provided both

(i) "proof beyond reasonable doubt" that for all, or for some, specific types of patient, treatment is clearly indicated or clearly contraindicated, and
(ii) evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of any other relevant trials.[56-57]

On the basis of information supplied by the IDMC, the TSC can then decide whether to modify intake to the study (or to seek extra data). Unless this happens, however, the TSC, the collaborators, and the central administrative staff (except the unblinded statistician) will remain ignorant of the interim results.

Further details and updates to the DMC charter will be made available via the TARDIS website (www.tardistrial.org). Investigators are advised to refer to the trial website for an up to date DMC charter.

If a trial is discontinued for any of the above reasons, participants will go back to receiving standard care from their GPs.

7.6 STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files. Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

8 PUBLICATION AND DISSEMINATION POLICY

Data and results will be shared as follows:

8.1 Presentation

The main trial results will be presented to the investigators, and to funding bodies, and at major international and national scientific meetings, in the name of the trial and investigators i.e. 'TARDIS Investigators'.

8.2 Publication

The main results from the trial will be written by a 'Writing Committee' and published in quality peer-reviewed journal(s) in the name of the investigators, i.e. TARDIS Investigators. The writing committee will consist of as a minimum, the Chief Investigator, lead imaging and SAE adjudicators, statistical consultant and trial statistician.

Secondary publications will be published as 'Person(s), for the TARDIS Investigators', where the person(s) are those who conceived, designed, and analysed or interpreted the data, and/or wrote the paper for the publication.

Abstracts will be presented as 'TARDIS Investigators, person(s)', where the person(s) act as a contact point for the trial.

National and/or local investigators may present or publish data relating to their country or site once the main trial findings have been published. All papers will be approved by the TSC and all abstracts by the Chief Investigator.

8.3 Sharing of data

Anonymised subsets of data may be shared with other research groups and projects (e.g. Cochrane Collaboration, antithrombotic collaboration) once the main trial findings have been published, and following agreement by the Trial Steering Committee. A contract will be set up between the University of Nottingham (as represented by the Chief Investigator) and groups which are receiving the data.

9 USER AND PUBLIC INVOLVEMENT

The trial has been discussed with, and is supported by, the UK Stroke Research Network Prevention Clinical Studies Group, the Nottingham Stroke Users Research Committee. Their comments have been incorporated into the design. One member will be a member of the Trial Steering Committee.

10 STUDY FINANCES

10.1 Funding source

The start-up phase of the study is funded by The British Heart Foundation. Funding is being sought for the main phase from the United Kingdom Health Technology Assessment (HTA).

10.2 Participant stipends and payments

Participants will not be paid to participate in the trial. Travel or mileage/parking expenses will be offered for hospital visits.

11 SIGNATURE PAGE

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

Trial Pharmacist: (name)_____

Signature:_____

Date: _____

Appendices

Appendix A: Definitions

Bleeding Events

1. **Major bleed**:[45] All major bleeds will constitute a serious adverse event.
   - Fatal bleeding, and/or
   - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
   - Bleeding causing fall in haemoglobin of 2 g/l (1.24 mmol/l) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

2. **Moderate bleed**: Moderate bleeds may or may not constitute a serious adverse event depending on other criteria as determined by the investigator.
   - Not major, and
   - Bleeding causing fall in haemoglobin <2 g/l (1.24) mmol/l) and ≥ 1g (0.62 mmol/l), and leading to no transfusion, or transfusion of only 1 unit of whole blood or red cells.

3. **Minor bleed**: Minor bleeds usually do not constitute a serious adverse event.
   - Not major or moderate, and
   - Comprising bruising, ecchymoses, gingival bleed or similar other type of bleeding
   - Fall in haemoglobin of less than 1g/l (0.62 mmol/l).

Other Clinical Events

4. **Stroke**: A clinical syndrome characterised by rapidly developing clinical symptoms and/or signs of focal (and at times global) loss of cerebral function with symptoms lasting ≥ 24 hours or leading to death, with no apparent cause other than that of vascular origin'.[58]

5. **TIA**: A sudden focal neurological deficit of the brain or eye, presumed to be of vascular origin and lasts less than 24 hours.

NB. TIAs and stroke usually present with 'negative' symptoms (e.g. loss of motor power, loss of speech) as opposed to symptoms that are 'positive' in nature such as parasthesia or limb jerking, which will usually have an alternative underlying cause.

6. **Recurrent Stroke**: A stroke defined as above occurring after the qualifying stroke **or a** progression of neurological symptoms or signs (increase in NIHSS score >4) in the same vascular territory as the index event.
7. **Neurological Deterioration**: An increase in NIHSS score by 4 points or more than the baseline value.

8. **Symptomatic Intracerebral Haemorrhage (SICH):** Any haemorrhage with neurological deterioration as defined above, or intracerebral haemorrhage leading to death. The haemorrhage must be the predominant cause of the neurological deterioration.[59]

9. **Bleeding on CT/MRI head scans**: [60-61]
   a. *Haemorrhagic Infarct (HI):* petechial infarction without space occupying effect.
      i. HI1 - small petechiae
      ii. HI2 - more confluent petechiae
   b. *Parenchymal Haemorrhage (PH):* haemorrhage with mass effect.
      i. PH1 - <30% of the infarcted area with mild space occupying effect
      ii. PH2 - >30% of the infarcted area with significant space occupying effect.

Note: patients with PH should not be enrolled

10. **ABCD^2 Scoring Criteria [62-63]**

A	Age ≥ 60 years	1 point
B	Blood pressure ≥ 140/90 mm Hg	1 point
C	Clinical features	
	Unilateral weakness	2 points
	Speech disturbance§ without weakness	1 point
D	Duration	
	≥ 60 minutes	2 points
	10–59 minutes	1 point
D	Diabetes	
	Presence of diabetes mellitus*	1 point

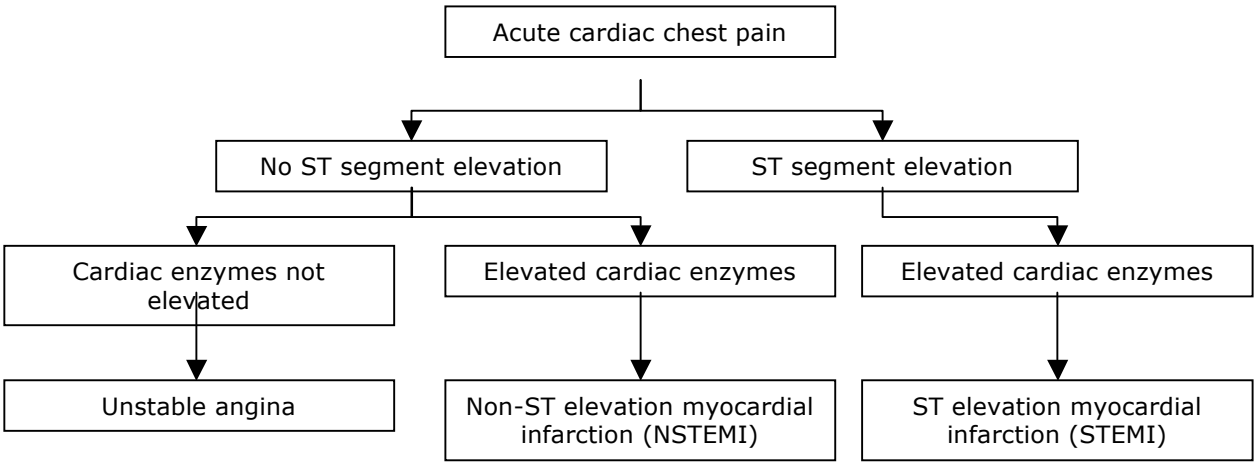
§ Speech disturbance defined as either dysarthria or dysphasia or both
* Diabetes defined as requiring either oral medication or insulin
Note: patients with ABCD^2 <4 should not be enrolled

11. **Criteria for acute, evolving or recent Myocardial Infarction (MI):**[64]Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:
1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
(a) ischaemic symptoms;
(b) development of pathologic Q waves on the ECG;
(c) ECG changes indicative of ischemia (ST segment elevation or depression); or
(d) coronary artery intervention (e.g., coronary angioplasty).
2. Pathologic findings of an acute MI.

12. **Unstable Angina**

Although there is no universally accepted definition of unstable angina, it has been described as a clinical syndrome between stable angina and acute myocardial infarction.

The diagram below will help distinguish between the types of acute coronary syndromes in patients presenting with acute cardiac chest pain:



Appendix B: The National Institutes of Health Stroke Scale (NIHSS)

All investigators should gain sufficient training and certification to measure NIHSS.

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort). (Please also see http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf for pictures associated with this score)

1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

0 = **Alert;** keenly responsive.

1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond.

2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).

3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

0 = **Answers** both questions correctly.

1 = **Answers** one question correctly.

2 = **Answers** neither question correctly.

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

0 = **Performs** both tasks correctly.

1 = **Performs** one task correctly.

2 = **Performs** neither task correctly.

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

0 = **Normal.**

1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.

2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.

0 = **No visual loss.**

1 = **Partial hemianopia.**

2 = **Complete hemianopia.**

3 = **Bilateral hemianopia** (blind including cortical blindness).

4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.

0 = **Normal** symmetrical movements.

1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling).

2 = **Partial paralysis** (total or near-total paralysis of lower face).

3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).

5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime,

but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds.

1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.

2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.

3 = **No effort against gravity;** limb falls.

4 = **No movement.**

UN = **Amputation** or joint fusion, explain: _____

5a. Left Arm

5b. Right Arm

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

0 = **No drift;** leg holds 30-degree position for full 5 seconds.

1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed.

2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity.

3 = **No effort against gravity;** leg falls to bed immediately.

4 = **No movement.**

UN = **Amputation** or joint fusion, explain: _____

6a. Left Leg

6b. Right Leg

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.

0 = **Absent.**

1 = **Present in one limb.**

2 = **Present in two limbs.**

UN = **Amputation** or joint fusion, explain: _____

8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.

0 = **Normal;** no sensory loss.

1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.

2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.

0 = **No aphasia;** normal.

1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.

2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.

3 = **Mute, global aphasia;** no usable speech or auditory comprehension.

10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.

0 = **Normal.**

1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty.

2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.

UN = **Intubated** or other physical barrier,
explain:_____

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

0 = **No abnormality.**

1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.

Reference[65]

Appendix C: Glasgow Coma Score

Eye movement

1 = None
2 = To pain
3 = To speech
4 = Spontaneous

Verbal response

1 = None
2 = Incomprehensible
3 = Inappropriate
4 = Confused
5 = Orientated

Motor response

1 = None
2 = Extension
3 = Flexor response
4 = Withdrawal
5 = Localises pain
6 = Obeys commands

Score out of 15 (range 3 – 15)

Reference[66]

Appendix D: Modified Rankin Scale (mRS)
All investigators should gain sufficient training and certification to measure mRS.

0 No symptoms at all
1 No significant disability, despite symptoms; able to carry out all usual duties and activities
2 Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3 Moderate disability; requiring some help, but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6 Dead

Score 0 to 6 (range 0-6)

Reference [67-68]

Appendix E: Barthel Index

Task	Criteria	Score
Bowels	Incontinent	0
	Occasional accident (once per week)	5
	Continent	10
Bladder	Incontinent, or catheterised and unable to manage alone	0
		5
	Occasional accident (maximum once per 24 hours)	10
	Continent	
Grooming	Needs help with personal care	0
	Independent face/hair/teeth/shaving (implements provided)	5
Toilet use	Dependent	0
	Needs some help, but can do something alone	5
	Independent (on and off, dressing, wiping)	10
Feeding	Unable	0
	Needs help cutting, spreading butter, etc.	5
	Independent	10
Transfer (bed to chair and back)	Unable, no sitting balance	0
	Major help (one or two people, physical), cab sit	5
	Minor help (verbal or physical)	10
	Independent	15
Mobility	Immobile	0
	Wheelchair independent, including corners	5
	Walks with help of one person (verbal or physical)	10
	Independent (but may use any aid: for example stick)	15
Dressing	Dependent	0
	Needs help but can do about half unaided	5
	Independent (including buttons, zips, laces, etc.)	10
Stairs	Unable	0
	Needs help (verbal, physical, carrying aid)	5
	Independent	10
Bathing	Dependent	0
	Independent (or in shower)	5

Score out of 100 (range 0-100)

Reference[69]

Appendix F: EuroQOL

Group 1 [70]
I have no problems in walking about
I have some problems in walking about
I am confined to bed

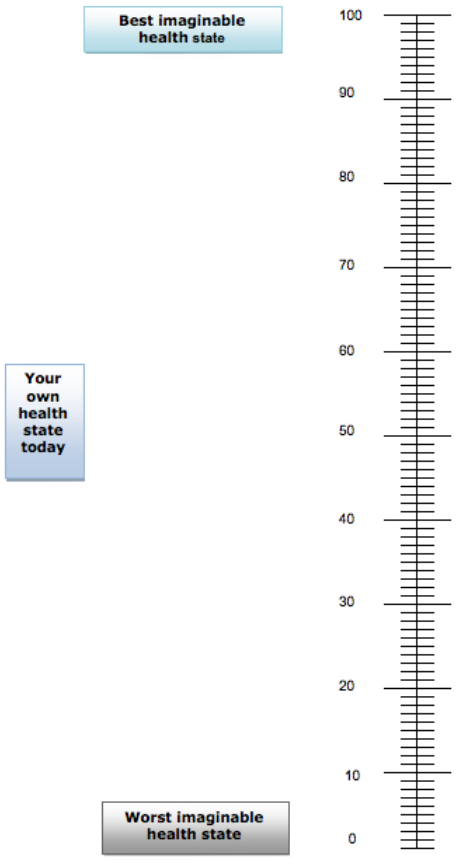
Group 2
I have no problems with self care
I have some problems with washing or dressing
I am unable to wash or dress myself

Group 3
I have no problems performing my usual activities (e.g. work, study, housework, family or leisure activities
I have some problems performing usual activities
I am unable to perform my usual activities

Group 4
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Group 5
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Health state today by visual analogue scale (best imaginable to worst imaginable)



Appendix G: Cognitive Testing

TICS-M[71] – Adjusted for the TARDIS Trial

Please note that this test is designed for telephone use. In the event follow up is done in person the entire test must be completed verbally, i.e. the memory words must not be shown to the patient.

Question and Instructions		Score
Orientation: Please ask them what day, date etc it is		**7**
Day		☐
Date		☐
Month		☐
Season		☐
Year		☐
Age		☐
Telephone Number (code+number)		
Registration		**10**
I am going to read you a list of 10 words. Please listen carefully and try to remember them. When I am done, tell me as many as you can in any order. Ready?		
Cabin		☐
Pipe		☐
Elephant		☐
Chest		☐
Silk		☐
Theatre		☐
Watch		☐
Whip		☐
Pillow		☐
Giant		
Attention and Calculation		**6**
Please take away 7 from 100. Now continue to take 7 away from what you have left over until I ask you to stop		
93		☐
86		☐
79		☐
72		☐
65		☐
Count backwards Please count back 20-1		
No mistakes		☐
Comprehension, Semantic and Recent Memory		**5**
What do people use to cut paper?	Scissors	☐
What is the prickly green plant found in the desert?	Cactus	☐
Who is the Prime Minister?	Correct surname	☐
Who is the reigning monarch?	E,QE,QE2	☐
What is the opposite direction to east? t	West	☐
Language/Repetition		**1**
Please listen carefully and repeat No ifs ands or buts'		☐
Score only if exactly right		
Delayed Recall		**10**
Please repeat as many of the 10 words I asked you to remember earlier		
Cabin		☐
Pipe		☐

Elephant	☐
Chest	☐
Silk	☐
Theatre	☐
Watch	☐
Whip	☐
Pillow	☐
Giant	☐

Total Score (1 point for each correct answer) **/39**

Verbal Fluency

Letter

I'd like you to generate as many words as possible beginning with the letter 'P'. You have got a minute. Are you ready?

Write down each word and score 1 mark for each word. Do not score repetitions.

Animals

I'd like you to generate as many animals as possible, any kind of animal, beginning with any letter, it doesn't matter'. You've got a minute. Are you ready?

Write down each word and score 1 mark for each animal named. Do not score repetitions.

Total score _____

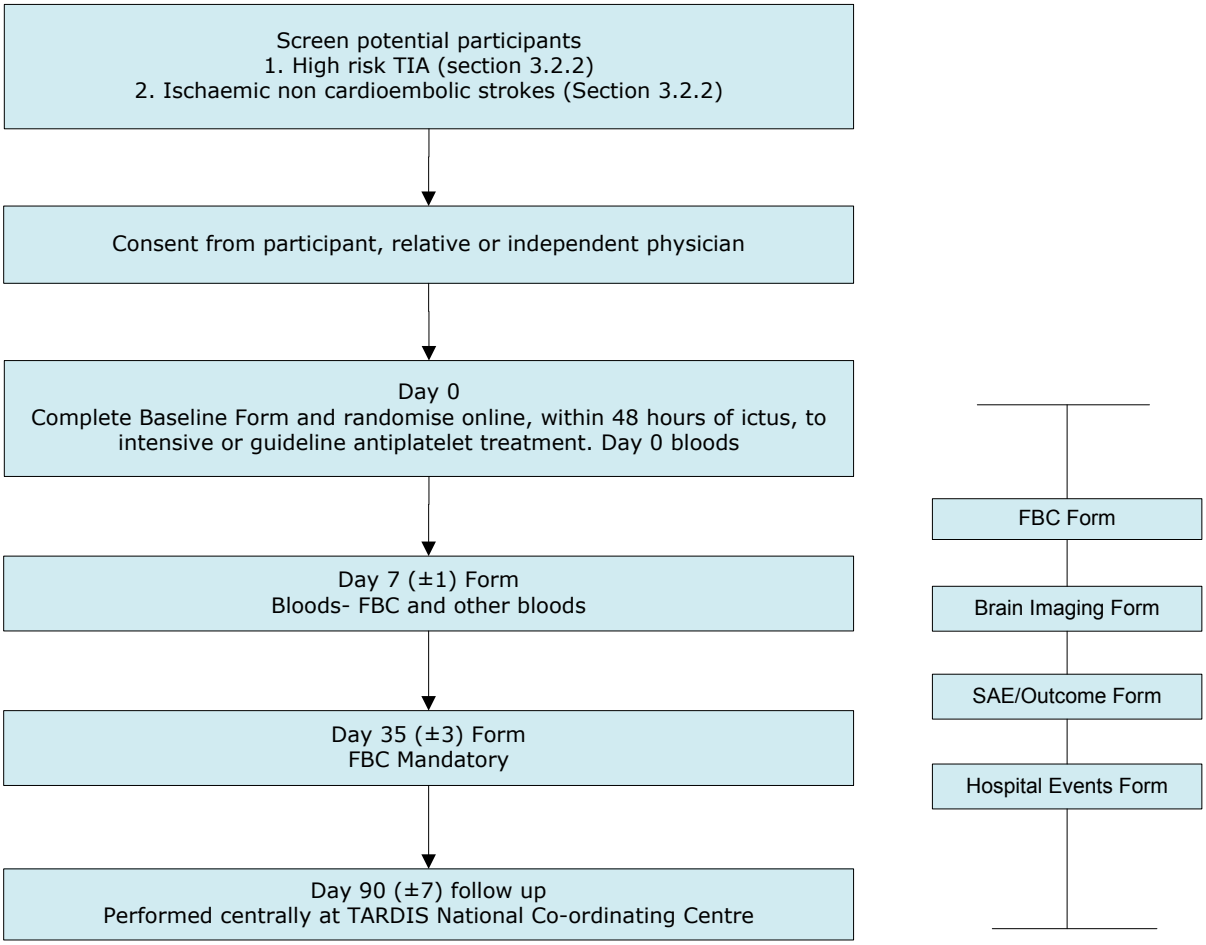
Appendix H: Zung Depression rating Scale (short)

	Seldom or never	Some of the time	Good part of the time	Most of the time
I feel down-hearted and blue	☐	☐	☐	☐
Morning is when I feel best	☐	☐	☐	☐
I have trouble sleeping at night	☐	☐	☐	☐
I can eat as much as I used to	☐	☐	☐	☐
I get tired for no reason	☐	☐	☐	☐
I find it difficult to make decisions	☐	☐	☐	☐
I feel hopeful about the future	☐	☐	☐	☐
I feel that I am useful and needed	☐	☐	☐	☐
My life is somewhat empty	☐	☐	☐	☐
I still enjoy the things I used to do	☐	☐	☐	☐

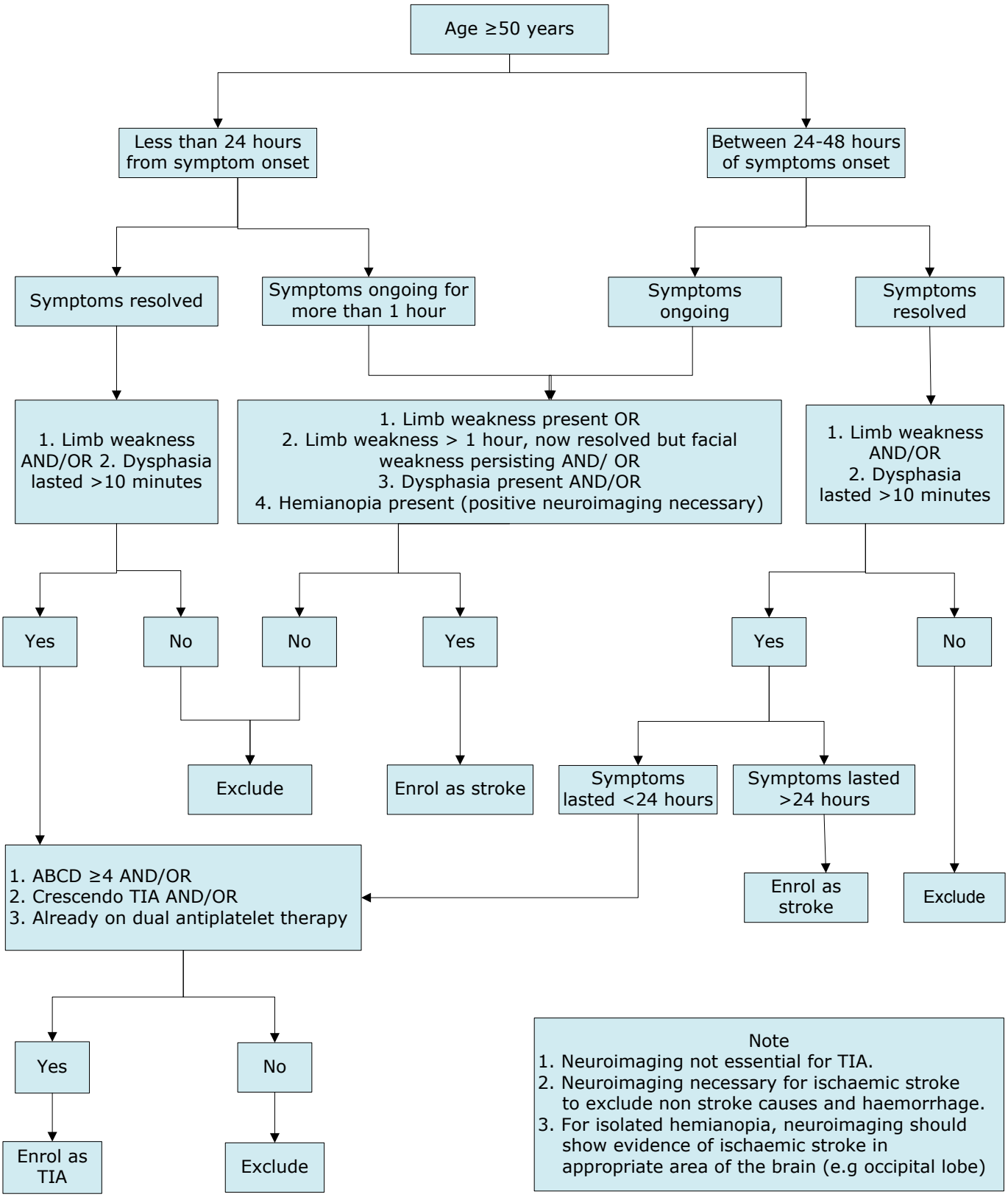
Reference[44]
Zung IDS Index = 100 x Total / 40

Depression => 70

Appendix I: Trial Flow



APPENDIX J: Trial inclusion flow chart



APPENDIX K: Sample Labels

CLOPIDOGREL LOADING DOSE (taken on day 0, day of randomisation):

Eudract no: 2007-006749-42
TARDIS STUDY
4 x Clopidogrel 75mg tablets

Take Four tablets as a loading dose.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

Or

Eudract no: 2007-006749-42
TARDIS STUDY
1 x Clopidogrel 300mg tablet

Take one tablet as a loading dose.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

CLOPIDOGREL (days 1 to 30)

Eudract no: 2007-006749-42
TARDIS STUDY
30 x Clopidogrel 75mg tablets

Take ONE tablet DAILY.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

ASPIRIN LOADING DOSE (taken on day 0, day of randomisation):

Eudract no: 2007-006749-42
TARDIS STUDY
4 x Aspirin 75mg tablets

Take Four tablets as a loading dose.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

Or

Eudract no: 2007-006749-42
TARDIS STUDY
1 x Aspirin 300mg tablet

Take one tablet as a loading dose.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

ASPIRIN (days 1 to 30)

Eudract no: 2007-006749-42
TARDIS STUDY
30 x ASPIRIN 75mg tablets

Take ONE tablet DAILY.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

DIPYRIDAMOLE (days 0-30):

Eudract no: 2007-006749-42
TARDIS STUDY
60 x DIPYRIDAMOLE 200 mg tablets

Take two tablets daily.

Name……..Date……
BN……EXP……
Clinical Trial use only Investigator Prof P Bath
KEEP OUT OF THE REACH OF CHILDREN
Do not store above 25^0c
Pharmacy Dept, City Hospital Campus, NUH, Hucknall Rd, Nottm NG5 1PB 0115 9691169.

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