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

Short title: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke

Acronym: TARDIS

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ABBREVIATIONS

A	Aspirin
ADR	Adverse Drug Reaction
AE	Adverse Event
BI	Barthel Index
C	Clopidogrel
CI	Chief Investigator
CRF	Case Report Form
D	Dipyridamole
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
LMWH	Low Molecular Weight Heparin
LRN	Local Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
mRS	Modified Rankin Scale
NHS	National Health Service
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SmPC	Summary of Medical Product Characteristics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UKSRN	UK Stroke Research Network
TIA	Transient Ischaemic Attack
TMG	Trial Management Group
TSC	Trial Steering Committee

SYNOPSIS

Title	Safety and efficacy of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: 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, endarterectomy) reduce, not abolish, further events. Dual antiplatelet therapy – aspirin & clopidogrel (AC) for IHD, aspirin & dipyridamole (AD) for prophylaxis - 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 therapy (aspirin, clopidogrel, dipyridamole, ACD) to patients with ischemic stroke/TIA. We will assess the efficacy, safety, tolerability and feasibility of triple therapy versus dual therapy given for 1 month in 350 patients (over 3 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 (up to 5000 patients) over the next 5 years proving 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, cerebral emboli and platelet function.
Chief Investigator	Professor Philip Bath
Primary Objective	The trial will assess ordinal stroke severity at 90 days measured an ordinal outcome: mRS 6=fatal-5-4-3-2-1-0-TIA-no stroke; this approach allows for smaller sample sizes than for binary outcomes such as stroke/no stroke.
Trial Design	Multicentre parallel group prospective randomised open-label blinded-endpoint controlled trial.
Setting	In the start-up phase patients will be recruited from the UK Stroke Research Network. Further expansion within the UK and internationally will occur in the main phase.
Sample size estimate	The start-up phase is sized to assess safety, i.e. where the addition of Clopidogrel ***might be*** hazardous when added to AD; the key concern for antiplatelet agents relates to bleeding. The sample size calculation uses assumptions based on data from our recent pilot trial of ACD. Assuming bleeding rates for control (AD) is 15% and active (ACD) 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. The start-up phase will inform the sample size calculation for the main trial phase which will assess the efficacy of triple versus dual therapy; currently these are: control rate 10%, active/triple rate 7.5%, RRR 25%/ARR 2.5%, alpha 5%, power 90%, losses 5%, total sample 6,000; use of an ordinal scale for stroke should reduce this to ~4,500.
Number of participants	Start up: 350; main phase: 4150
Eligibility criteria	Adults at high risk of recurrent ischaemic stroke: 1. Acute non-cardioembolic ischaemic stroke (≤48 hours of onset); 2. Acute TIA (≤48 hours of onset) with one or more of: crescendo TIA (>1 TIA within 1 week), and/or admitted on dual antiplatelet therapy

	(aspirin/dipyridamole, aspirin/clopidogrel, clopidogrel/dipyridamole), and/or with an ABCD2 score ≥4. All TIAs must have motor weakness and/or dysphasia lasting at least 10 minutes. 3. Meaningful consent, or consent from a relative, carer or legal representative if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level).
Description of interventions	Open-label clopidogrel will be given for 28 to 30 days on top of routine aspirin/dipyridamole (to cover the period of maximum risk of recurrence) and standard 'best care' (including lifestyle advice, BP and lipid lowering). Randomised patients will receive either 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 dual antiplatelet therapy (aspirin/dipyridamole, doses as above), randomised 1:1. Dysphagic patients with enteral access will take crushed aspirin (or rectal aspirin), crushed or liquid dipyridamole (range 75 mg tds to 100mg qds), and crushed clopidogrel (if so randomised). Patients 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). Fixed dose combinations of aspirin and dipyridamole can also be used. At the discretion of the investigator, patients can take gastro-prophylaxis against upper gastrointestinal bleeding (proton pump inhibitor/histamine 2 receptor antagonist ± H. pylori eradication). After the 30 day treatment period, patients will be expected to return to routine antiplatelet therapy, such as combined aspirin and dipyridamole as recommended by NICE
Duration of study	8 years
Randomisation and blinding	Patients will be randomised by a computer 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 transcranial doppler for embolic events, 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	Kaplan-Meier and Cox proportional regression on dichotomous primary and secondary outcomes; ordinal logistic regression for ordered categorical variables. Analyses will be adjusted for randomisation/minimisation factors. Subgroup analyses will only be performed in the main trial phase

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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. Government has emphasised stroke as a '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).

The risk of stroke recurrence can be reduced substantially with life style changes, carotid endarterectomy (large artery stroke) and drug interventions: antihypertensives and statin therapy. While warfarin is established for cardioembolic stroke,[1] other patients with ischaemia (the majority) need antiplatelets.[2,3] These interventions are cost-effective. The archetypal antiplatelet, aspirin (A, inhibitor of cyclooxygenase), reduces recurrence (relative risk reduction, RRR) by 17% in patients with prior stroke or TIA.[4] Clopidogrel (C, adenosine diphosphate [ADP] receptor antagonist) was slight more efficacious than aspirin in CAPRIE (and comparable to A in those patients with prior stroke).[5] Dipyridamole (D, inhibits red cell uptake of adenosine) reduced recurrence by 16% in comparison with placebo in ESPS II.[6] Evidence now suggests that stroke prevention is dependent on the number of antiplatelets, e.g. AD reduces events by 23% in comparison to A alone without increasing the risk of bleeding, as seen in ESPS II and ESPRIT.[6,7] AC was superior to A in cardiac patients (CURE, CREDO) [8,9] but not in CHARISMA,[10] 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 AC vs. A was 30-40% higher in these 3 trials. The MATCH trial (AC vs. C) found that A also increased bleeding.[11,12] UK and European Guidelines, and NICE, each recommend the use of AD after stroke or TIA.[13,14]

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. Since risk falls quickly 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 C-based dual therapy has not proved effective/safe in long-term stroke prophylaxis, early and short-term use may be useful, at least after TIA/minor stroke, as suggested in FASTER (AC vs. A) and EXPRESS (before-after comparison of AC and A).[15,16] In FASTER, AC reduced stoke by absolute 3.7% (NS) and increased SICH by absolute 1% (NS) leading to a net absolute benefit of 2.7%;[15] hence, benefit may outweigh hazard with AC vs. A when used in patients at high risk of recurrence (figure 1).

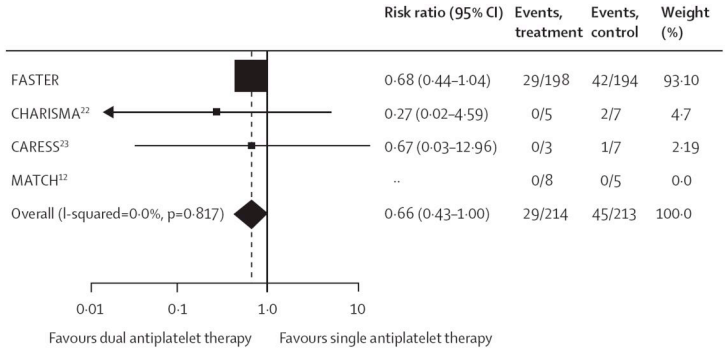

Figure 1. Meta-analysis of trials recruiting patients within 24 hours of stroke/TIA and comparing AC with monotherapy.[15] As compared with monotherapy, AC reduced the composite outcome of 'stroke, TIA, acute coronary syndromes and all cause death'.[15]

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 A and C [17]).

If AD is superior to A for long-term secondary prevention,[6,7,18] and AC is probably superior to A in acute minor stroke/TIA,[15,16] then triple antiplatelet therapy (ACD) 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 C to AD is likely to be similar to that when adding C to A since AD does not increase bleeding over A.[6,7] We have performed a series of 'proof-of-concept' laboratory and clinical studies investigating this approach.[19-23] In vitro studies found that triple therapy was most effective in inhibiting aggregation, platelet-leucocyte conjugation, and leucocyte activation.[19-21] In multiway crossover phase I and II trials comparing short-term administration of mono (A/C/D), dual (AC/AD/CD) and triple (ACD) platelet therapy, the combination of AC, with or without D, was most potent in inhibiting platelet function ex vivo in both normal volunteers (n=11) and patients with previous stroke/TIA (n=11).[22,23]

In the only parallel group trial of triple therapy in patients with stroke, ACD was feasible to administer (vs. A, phase II trial, n=17) for up to 24 months.[24] [The comparator of A was chosen since this was the UK standard of care at trial start. The trial was stopped early on publication of ESPRIT [7] confirming the superiority of AD over A, i.e. it was unethical to continue patients on A alone.] Predictably, there was a non-significant trend to increased bleeding with ACD vs A. 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.[10,11] Future trials of ACD need to target patients at high risk of recurrence so that benefit is likely to outweigh hazard. We have also used chronic ACD in clinical practice in patients at high risk of recurrence, defined as recurrence on dual antiplatelet therapy (either adding C to AD or D to AC).[25]

Short-term randomised controlled trials and observational studies (11 studies, 21618 patients) of triple antiplatelet therapy have been reported in patients with acute coronary syndromes or to cover stent insertion. In comparison with standard antiplatelet therapy, triple therapy reduced MI and vascular events (table, figure 2) [Bath, Geeganage, Wilcox, unpublished]; 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. No long term trials have been performed in IHD, and dipyridamole was not assessed since it is not used routinely after IHD.

OR (95% CI)	MI	Vascular	Major bleed	Transfusion
Trials (21, n=14,964)	0.62 (0.47-0.84)	0.63 (0.47-0.83)	1.24 (0.89-1.73)	1.37 (0.99-1.90)
Studies (11, n=21,695)	0.57 (0.35-0.91)	0.53 (0.34-0.82)	1.19 (0.76-1.88)	1.71 (0.61-4.80)

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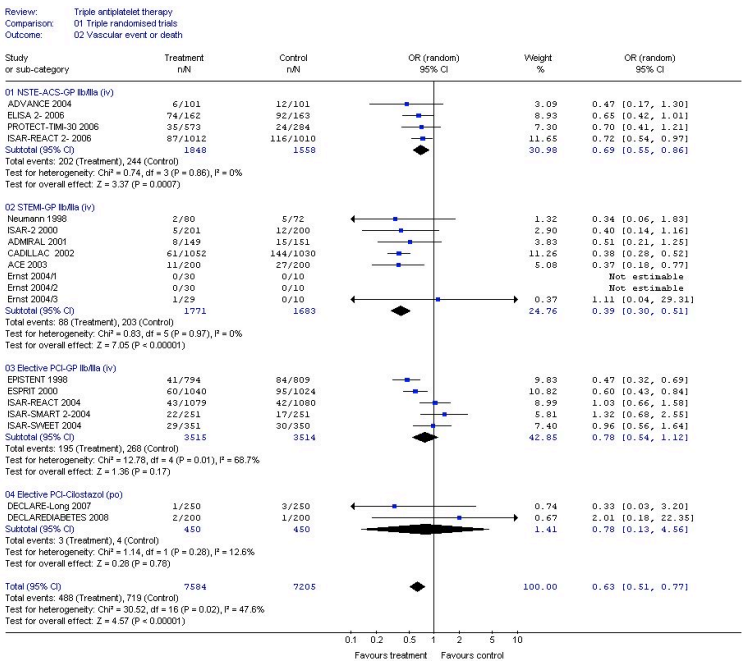
Figure 2. Meta-analysis of trials comparing triple with mono or dual antiplatelet therapy in patients with acute coronary syndromes, having stent insertion, or previous stroke. Triple therapy reduced myocardial infarction and all vascular events. [Bath, Geeganage, Wilcox, unpublished



DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Description

1. Clopidogel

Open-label clopidogrel will be given to 50% of randomised patients in addition to standard aspirin plus dipyridamole.

International Non-Proprietary Name (INN): clopidogrel

CAS number: 113665-84-2

Dose: Loading dose 300mg, then 75mg od (the LOAD study used a loading dose of 375mg).[26]

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

The IMP is defined by active substance only, so all authorised brands in the UK can be used. For chemical and pharmacological properties see summary of medical product characterisics (SmPC) at www.emc.medicines.org.uk.

Clopidogrel treatment is for 1 month; the loading dose is received on day 0 (baseline, day of randomisation) and 75mg on days 1 to 30. This is convenient as clopidogrel is currently provided in a 30-tablet blister pack. However, the patent for clopidogrel will end before the end of the trial and if alternative suppliers provide smaller pack sizes (e.g. 28-tablet packs), then this length of treatment is sufficient. After the 30 day treatment period, patients will be expected to return to routine antiplatelet therapy, such as combined aspirin and dipyridamole as recommended by NICE. At the discretion of the investigator, patients can take gastro-prophylaxis against upper gastrointestinal bleeding (proton pump inhibitor/histamine 2 receptor antagonist ± H. pylori eradication).

Concomitant Antiplatelet Therapy

Aspirin and dipyridamole are considered as routine therapy for ischaemic stroke and TIA hence they are not considered as IMPs. However, for the purposes of the trial, the following regimens should be instituted. All randomised patients will receive aspirin and dipyridamole as this is standard treatment.

a. Aspirin

Dose: Loading dose 300mg (whether or not already on aspirin), then in the range 25mg bd to 81mg od.

- This is compatible with NICE guidelines 2004. A protocol violation will occur if 300mg aspirin is continued beyond the loading dose.
- 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 or gastrostomy – dispersible or crushed tablets can be used) or rectal route (150mg suppository alternate days can be used as an alternative if necessary).

b. Dipyridamole

Dose: 200mg modified release (MR), bd.

- Dysphagic patients with enteral access will take dipyridamole suspension (range 75mg tds to 100mg qds) or crushed standard release dipyridamole (100mg qds); the effective daily doses of dipyridamole have ranged between 75mg tds (ESPS1) and 200mg MR bd (ESPS2 and ESPRIT).
- 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. The manner in which this is achieved is left to the discretion of the investigator.
- 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 or gastrostomy).

Packaging and labelling

Standard pharmacy supplies should be used as the IMP (clopidogrel) has marketing authorisation for use in stroke. Separate labelling and packaging details are not required but local sites can overlabel as they feel appropriate, in which case accountability logs for clopidogrel (batch numbers and expiry dates) should be recorded. Aspirin and dipyridamole are not IMPs as they are standard treatment for stroke and TIA; accountability logs for them are therefore unnecessary.

Storage, dispensing and return

Standard pharmacy supplies will be prescribed and used.

Known Side Effects

1. **Clopidogrel**
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.

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.
Immune system disorders: very rare; anaphylactoid reactions, serum sickness
Psychiatric disorders: very rare: confusion, hallucinations
Nervous system disorders: very rare; taste disturbances
Vascular disorders: very rare; vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders: very rare; bronchospasm, interstitial pneumonitis
Gastrointestinal disorders: very rare; pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders: very rare; acute liver failure, hepatitis
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
Musculoskeletal, connective tissue and bone disorders: very rare; arthralgia, arthritis, myalgia.
Renal and urinary disorders: very rare; glomerulonephritis.
General disorders and administration site conditions: very rare; fever.
Investigations: very rare; abnormal liver function test, blood creatinine increase

Other concomitant therapy: clopidogrel should not be co-adminisrered with warfarin due to increased bleeding risk. Caution should also be taken with corticosteroids, NSAIDS, heparin and thrombolytics. 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.

TRIAL PURPOSE AND OBJECTIVES

Purpose

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

A secondary hypothesis is that ordinal vascular outcomes will be superior to binary events;[27] the trial is the first to be designed using these outcomes, this allowing both the frequency and severity of events to be assessed in one measure. Ordinal outcomes include bleeding, adverse events, stroke, MI, composite vascular events, and take the generic form: fatal event/non-fatal severe event/mild event/no event.[27] Conventional binary outcomes will also be measured.

Primary Objective

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

Secondary Objectives

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

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

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

TRIAL DESIGN

Design: Multicentre parallel group prospective randomised open-label blinded-endpoint controlled trial.

We will perform a phase III randomised controlled trial of short-term administration (1 month) of triple antiplatelet therapy (aspirin/clopidogrel/dipyridamole) versus standard dual therapy (aspirin/dipyridamole [6,7,18]) in patients with acute ischaemic stroke or TIA. Philip Bath will run the trial from the University of Nottingham Stroke Trials Unit. The results of our experimental medicine research (laboratory, phase I/II trials) and routine clinical use support this approach.[19-23] The proposed trial is predicated on: (i) aspirin/dipyridamole is superior to aspirin after stroke; (ii) aspirin/dipyridamole is the standard of care in the UK (NICE); (iii) aspirin/clopidogrel is superior to aspirin in patients with ischaemic heart disease; and (iv) Some patients still 'fail' on aspirin/dipyridamole; and (v) Adding clopidogrel to aspirin may be useful in high risk patients, i.e. immediately after TIA/minor stroke. Hence, aspirin/clopidogrel/dipyridamole may be better still in high risk patients providing benefit exceeds bleeding.[28]

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

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

If the start-up phase shows acceptable safety, the trial will be expanded to the main phase which will recruit in the order of 5000 patients (depending on the rate and distribution of ordinal events). If this shows that aspirin/clopidogrel/dipyridamole is superior to aspirin/dipyridamole (taking account of the balance between reduced stroke/vascular events and potentially increased bleeding), then aspirin/clopidogrel/dipyridamole could be introduced rapidly for stroke prevention with immediate benefit to high risk patients; each component is available now and licensed for secondary prevention. The patent for clopidogrel will end before the end of the trial so 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 (aspirin/clopidogrel vs aspirin), and ARCH (aspirin/clopidogrel vs. warfarin). The approach of running a start-up and then main phase is routine in academic stroke trials, including 3 MRC trials: IMAGES, IST-3, and ENOS [PB is chief investigator].

Primary endpoint

The trial will assess ordinal stroke severity at 90 days assessed as a level ordinal outcome: mRS 6=fatal-5-4-3-2-1-0-TIA-no stroke; this approach allows for smaller sample sizes than for binary outcomes such as stroke/no stroke.[27]

Secondary endpoints

Secondary outcomes at 35 and 90 days: Binary stroke; ordinal stroke (fatal stroke/non-fatal stroke/no stroke);[27] binary myocardial infarction; ordinal myocardial infarction (fatal MI/non-fatal MI/no MI);[27] binary composite vascular outcome (non fatal MI & stroke, vascular death); ordinal composite vascular outcome;[27] composite stroke, TIA, acute coronary syndromes and all cause death,[15] incidence and type of infection.

Secondary outcomes at 90 days: Function (mRS, Barthel Index); cognition (TICS/animal naming); quality of life (EuroQoL/EQ-5D [29]); mood (Zung [30]); disposition (home, institution, dead); days at home; economic activity, all as in ENOS.[31] [These outcomes will be used in the main trial phase hence their presence in the start-up phase.]

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

Feasibility: Recruitment rate per week.

Safety measures at 35 and 90 days: The start-up phase will assess ordinal bleeding (fatal/major/moderate/minor/none[27]) at 35 days (end of treatment) 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);[32] binary minor bleeding (e.g. bruising); binary all bleeding; symptomatic intracerebral haemorrhage; major extracranial bleeding; binary serious adverse events; ordinal adverse events (fatal/serious/other/none [27]); full blood count (at 35 days); thrombotic thrombocytopenic purpura; granulocytopenia.

Safety

The trial will be the first ever to prospectively test the use ordinal outcomes (stroke, MI, vascular events) and safety measures (bleeding, adverse events) in vascular prophylaxis.[27] A retrospective analysis of existing published trials [27] and specific assessments of triple antiplatelet therapy,[33] [Bath, Geeganage, Wilcox, unpublished] hormone replacement therapy [34] and anticoagulation [35] suggest these outcomes are more efficient statistically and provide information on both events and their severity.

The principal hazard with antiplatelet therapy is major bleeding.[28] Whilst the addition of dipyridamole to aspirin does not increase bleeding (ESPS II and ESPRIT [6,7]), adding clopidogrel to aspirin does by ~30-40% (CURE, CREDO, CHARISMA, FASTER [8-10,15]). So, adding clopidogrel to aspirin/dipyridamole might increase major bleeding by a similar degree. Hence, we will monitor bleeding very closely in the proposed trial. Nevertheless, we believe that the absolute increase in bleeding will be smaller than the absolute decrease in stroke thereby pushing the balance between efficacy and hazard towards benefit as seen with mono and dual therapy in patients with clinical vascular disease.

Randomisation and Blinding

Patients will be randomised by computer with stratification (stroke/TIA) and minimisation (age, sex, systolic blood pressure, cortical/lacunar syndrome, previous mono/dual antiplatelet, gastro-protection) thereby maintaining concealment of allocation, facilitating matching of key prognostic variables at baseline, and improving statistical power.[36]

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).

SELECTION AND WITHDRAWAL OF PARTICIPANTS

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, the participant information sheets, and consent forms, but the consent forms and information sheets will 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.

Inclusion criteria

Adults at high risk of recurrent ischaemic stroke:

1. Acute non-cardioembolic ischaemic stroke (≤48 hours of onset). All strokes must have motor weakness or dysphasia at the time of randomisation.
2. Acute TIA (≤48 hours of onset) with one or more of: crescendo TIA (>1 TIA within 1 week), and/or admitted on dual antiplatelet therapy (aspirin/dipyridamole, aspirin/clopidogrel, clopidogrel/dipyridamole), and/or with an ABCD2 score ≥4. All TIAs must have motor weakness and/or dysphasia lasting at least 10 minutes.
3. Meaningful consent, or consent from a relative, carer or legal representative if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level).

Exclusion criteria

1. Age<50;
2. Motor weakness or dysphasia lasting <10 minutes;
3. Pure sensory, vertigo or dizziness, speech or visual disturbance symptoms without weakness or dysphasia;
4. Patients with contraindications to, or intolerance of, aspirin, clopidogrel or dipyridamole;
5. Patients with definite need for treatment with clopidogrel (e.g. recent MI)
6. Pre-morbid dependency (mRS>2);
7. No enteral access;
8. Parenchymal haemorrhagic transformation (PH I/II), subarachnoid haemorrhage or other non ischaemic cause for weakness;
9. TIA not fulfilling inclusion criteria
10. Definite need for full dose oral (e.g. warfarin) or parental (e.g. heparin or glycoprotein IIb IIIa inhibitors) anti-coagulation. NB Low dose heparin for DVT prophylaxis is allowed.
11. Received thrombolysis within the last 30 hours;
12. Presumed cardioembolic stroke (e.g. AF, recent MI, or other conditions need for anticoagulation);
13. Severe high BP (BP>185/110 mmHg);
14. Known haemoglobin less than 10g/dL
15. Known platelet count less than 100 x 10^9/L
16. Known white cell count less than 3.5 x 10^9/L
17. Bleeding within 1 year (e.g. peptic ulcer, intracerebral haemorrhage);
18. Planned surgery during 3 month follow-up (e.g. carotid endarterectomy).
19. Concomitant acute coronary syndrome;
20. Stroke secondary to a procedure (e.g. carotid or coronary intervention);
21. Coma (GCS<8)
22. Non-stroke life expectancy<6 months;
23. Dementia
24. Participation in another drug trial concurrently or within 30 days. (Patients may be randomised into observational studies or non-drug trials)
25. Not available for follow-up e.g. no fixed address, overseas visitor
26. Females of childbearing potential, pregnancy or breastfeeding

[Note: Clopidogrel will be stopped around procedures that become necessary after enrolment].

Removal of participants from therapy or assessments

Participants may be withdrawn from the trial 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.

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 patients 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. 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 Information Sheet, ensuring that the participant has sufficient time to consider participating or not. 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 participant will keep one copy of this, the Investigator will keep one, and a third will be retained in the patient's hospital records.
Should there be any subsequent amendment to the final 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.

TRIAL TREATMENT AND REGIMEN

Intervention

Open-label clopidogrel will be given for 30 days on top of routine aspirin/dipyridamole (to cover the period of maximum risk of recurrence) and standard 'best care' (including lifestyle advice, BP and lipid lowering).

Randomised patients will receive either clopidogrel (loading dose 300 mg,[8] then 75 mg daily), aspirin (loading dose 300 mg,[37] then 75 mg daily), and dipyridamole (modified release 200 mg twice daily [6]), or dual antiplatelet therapy (aspirin/dipyridamole, doses as above), randomised 1:1. Please also see the IMP section on page 10.

Dysphagic patients with enteral access will take crushed aspirin (or rectal aspirin), crushed or liquid dipyridamole (range 75 mg tds to 100mg qds), and crushed clopidogrel (if so randomised). Patients 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 [38]). Fixed dose combinations of aspirin and dipyridamole can also be used. At the discretion of the investigator, patients can take gastro-prophylaxis against upper gastrointestinal bleeding (proton pump inhibitor/histamine 2 receptor antagonist $\pm$ H. pylori eradication).[39] After the 30 day treatment period, patients will be expected to return to routine antiplatelet therapy, such as combined aspirin and dipyridamole as recommended by NICE. [Note: PRoFESS (aspirin/dipyridamole vs. clopidogrel) enrolled 8,113 (40%) of patients within 10 days, and ~600 patients within 2 days of onset, so it is feasible to administer dipyridamole acutely and is apparently safe.]

Baseline Measures

Pre-morbid modified Rankin Scale (mRS); impairment (NIHSS); full blood count (part of routine clinical care); haemodynamics and ECG. Stroke type will be categorised according to modified TOAST criteria.[40]

Follow-up

Face-to-face interview at 7±1 and 35$\pm$3 days post randomisation, i.e. end-of-treatment plus time to allow for clopidogrel washout. Central telephone follow-up will be performed at 90$\pm$7 days by an assessor blinded to outcome (as done in ENOS [31] and as will be done in the main trial phase).

Data from two substudies will power substudies within the future main trial:

Transcranial Doppler

TCD recordings will be performed from the middle cerebral artery (MCA) at baseline and day 3±1 using commercial TCD systems e.g. Pioneer digital systems using a 2MHz transducer. One hour recordings will be stored digitally and transferred on DVD to London for analysis [by Markus, as before [41]] with blinding to patient and treatment identity. We will use similar recording protocols to those successfully used in the CARESS study (Markus CI).[41] Embolic signals will be identified using standard consensus criteria with an intensity threshold of 7dB.[42]

Platelet Function

Platelet expression of P-selectin will be used to monitor platelet effects in patients. Blood will be taken from all patients at baseline & day 7±1, fixed (to allow batching of samples), posted by Royal Mail 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 patient 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

Additional Blood Samples

Tertiary questions in TARDIS include assessing the effects of the interventions on blood biomarkers and whether a patient's genotype alters response to the interventions. For example, the *CYP2C19* genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarction, and may be significant in ischaemic stroke.[43-45] Several blood biomarkers are surrogate markers of outcome, such as S-100.[46] 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.

These blood measures are optional although the power of statistical analyses of them will depend on the number of patients who contribute blood samples. Centres who wish to participate in the blood biomarker study should have appropriate storage facilities including access to a centrifuge and freezer. In addition to the full blood counts (mandatory), the following blood samples are required for blood biomarkers and genetic analysis:

Baseline:

- 4mls EDTA. Frozen whole (i.e. no centrifugation)
- 4mls EDTA. Centrifuge to collect and freeze plasma.
- 8mls clotted sample. Centrifuge to collect and freeze serum

Day 7±1:

- 4mls EDTA. Centrifuge to collect and freeze plasma.
- 8mls clotted sample. Centrifuge to collect and freeze serum

(See page 19 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 (identify them with the centre number, patient number, patient initials, and date of sample) and stored locally in a freezer at -20^{o}C (or lower if possible at -60^{o}C to -80^{o}C) and accounted for using the 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.

The consent forms allows the patient/relative to opt-in to the genetic sub-study. Patients may continue in the trial if they or their next-of-kin elect not to consent to the genetics sub-study. The patient 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.

Scan Transfer and Storage

Baseline CT and/or MR brain scans should be sent electronically over the web, on a CD or DVD, or by film (the latter two mailed to the TARDIS Coordinating Centre in Nottingham). Ideally, investigators should use the secure internet upload facility provided on the TARDIS website which includes automatic anonymisation of images. If films are posted, these will be digitised and the resulting data, along with that submitted on CD/DVD, will be anonymised. Data that are sent to the TARDIS Coordinating Centre are validated before anonymisation. All digital brain image data will be stored on computer servers for analysis and archiving. The systems have been designed to ensure the highest levels of data security and patient 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 if they prove to be superior to current systems. The use of e-Science infrastructure within the MRC NeuroGrid project (or similar) for the TARDIS imaging data could: ensure more reliable, secure and confidential archiving of the imaging data; connect sites for rapid and secure flow of data; enable distributed data analysis with image analysis tools; enhance collaborative working between members of the research team; and, improve the power and applicability of studies. Information on routine 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 Coordinating Centre.

Expected duration of participant participation

The table below summarises the assessments for each patient in the trial:

	Day 0	Day 3±1	Day 7±1	Day 35±3	Day 90±7*
Randomisation	+				
Safety		+	+	+	+
Tolerability		+	+	+	+
Transcranial Doppler**	+	+			
Bloods					
FBC	+		+	+	
P-Selectin**	+		+		
EDTA† sample**	+				
Serum and plasma**	+		+		
Clinical Efficacy					
Impairment (NIHSS)	+		+	+	
Function (mRS & BI)					+
Cognition, QoL & Mood					+

*Day 90 assessment done by telephone questionnaire. **In selected centres. †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

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 trial. Patients can be co-enrolled into non-drug trials.

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.

TRIAL MANAGEMENT

The trial will be run from the Stroke Trials Unit (STU), University of Nottingham. STU has considerable experience in running phase II and phase III stroke trials and is coordinating the international multicentre MRC-funded ENOS trial (www.enos.ac.uk/). A Trial Steering Committee (independent chair, grant applicants, patient – see below) will oversee the study meeting annually; the Trial Management Committee will run the trial on a day to day basis and meet twice monthly (with support by the trial statistician). The independent Data Monitoring Committee (chair Prof Ian Ford) will assess unblinded data after each 50 patients have been enrolled and followed for at least 1 week.

PB will manage the project; PB, TR, GV HM (and colleagues from UKSRN) will provide patients; SH will analyse platelet measures; HM will analyse TCD data.

STATISTICS

Methods

Ordinal logistic regression for ordered categorical variables; Kaplan-Meier and Cox proportional regression on dichotomous primary and secondary outcomes. Analyses will be adjusted for randomisation/minimisation factors. Safety analyses will be performed 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 - ≤ 75 years, > 75 years.
b) By sex – male, female.
c) By stroke/TIA
d) By stroke sub-type – lacunar, posterior fossa, cortical
e) By stroke severity – severe, moderate/mild; NIHSS≤10,>10
f) By baseline systolic blood pressure – > 160 mmHg), 140-160 mmHg, <140.
g) By treatment delay - > 24 hours, ≤ 24 hours.
h) By patients enrolled into TCD substudy.
i) By patients enrolled into P-selectin substudy.
j) By patients on antiplatelet therapy at randomisation - mono, dual;
k) Aspirin naïve vs aspirin
l) By heparin - none, unfractionated, LMWH
m) By number of TIAs in the last week
n) By thrombolysis - yes, no
o) By ABCD2 score - 4, >4

Losses to follow-up: 3%. Patients in the UK will be 'flagged' for death with the Office for National Statistics so that vital status can obtained for all patients.

Health economic assessment: The impact of aspirin/clopidogrel/dipyridamole on quality of life will be assessed using EuroQol,[29] and disposition and economic activity recorded at 90 days. A full health-economic analysis will only be performed as part of the main trial.

Sample size and justification

The start-up phase is sized to assess safety, i.e. where the addition of clopidogrel ***might be*** hazardous when added to aspirin/dipyridamole; the key concern for antiplatelet agents relates to bleeding. The sample size calculation [47] uses assumptions based on data from our recent pilot trial of aspirin/clopidogrel/dipyridamole.[33] Assuming bleeding rates for control (AD) is 15% and active (ACD) 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.[27] [The start-up phase will inform the sample size calculation [47] for the main trial phase; currently these are: control rate 10%, active/triple rate 7.5%, RRR 25%/ARR 2.5%, alpha 5%, power 90%, losses 5%, total sample 6,000; use of an ordinal scale for stroke [27] should reduce this to ~4,500.[35]]

ADVERSE EVENTS

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

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 jeopardize the patient or 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.

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 “unlikely”, “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.

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.

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 7 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

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.

ETHICAL AND REGULATORY ASPECTS

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.

RECORDS

Drug accountability

Hospitals/pharmacies should choose their own supplier for clopidogrel. 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. Once a patient is randomised the drugs should be prescribed. As the drugs are supplied by the hospital, there is no specific labelling used but local sites can overlabel as they feel appropriate, in which case accountability logs for clopidogrel (batch numbers and expiry dates) should be recorded. Aspirin and dipyridamole are not IMPs as they are standard treatment for stroke and TIA; separate accountability logs are therefore unnecessary. A sample label is provided (Appendix K).

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 date of birth. 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 or NHS number, 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.

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.

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).

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 the UK, this will involve use of the NHS Medical Research Information Service, Office of National Statistics (ONS) 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.

QUALITY ASSURANCE & AUDIT

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.

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); 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.

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.

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.

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 Data Monitoring Committee as appropriate in making this decision.

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.

PUBLICATION AND DISSEMINATION POLICY

Results from the trial will be published in peer-reviewed scientific medical journals.

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.

STUDY FINANCES

Funding source

This study is funded by The British Heart Foundation.

SIGNATURE PAGE

Chief Investigator: (name) PHILIP BATT

Signature:

Date: 25 JUNE 2009.

Appendices

Appendix A: Definitions

Bleeding Events

Major bleed:[32] 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.

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 of less than 2 g/l (1.24 mmol/l), and leading to no transfusion, or transfusion of only 1 unit of whole blood or red cells.

Minor bleed: Mild bleeds cannot constitute a serious adverse event.

- Not major or moderate, and
- Comprising bruising, ecchymoses, gingival bleed or similar other type bleeding.

Other Clinical Events

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 for more than 24 hours or leading to death, with no apparent cause other than that of vascular origin'.[48]

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.

Recurrent Stroke: A stroke defined as above occurring greater than 72 hours after the qualifying stroke if the event is in the same vascular territory, or occurring at any time after the qualifying stroke if the event occurs in a different vascular territory.

Extension of Initial Stroke: A progression of neurological symptoms or signs in the same vascular territory within 72 hours of the qualifying stroke.

Neurological Deterioration: An increase in NIHSS score by 4 points or more than the baseline value.

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.[49]

Bleeding on CT/MRI head scans: [50,51]

Haemorrhagic Infarct (HI): petechial infarction without space occupying effect.

HI1 - small petechiae

HI2 - more confluent petechiae

Parenchymal Haemorrhage (PH): haemorrhage with mass effect.

PH1 - <30% of the infarcted area with mild space occupying effect

PH2 - >30% of the infarcted area with significant space occupying effect.

Note: patients with PH should not be enrolled

ABCD^2 Scoring Criteria [52,53]

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

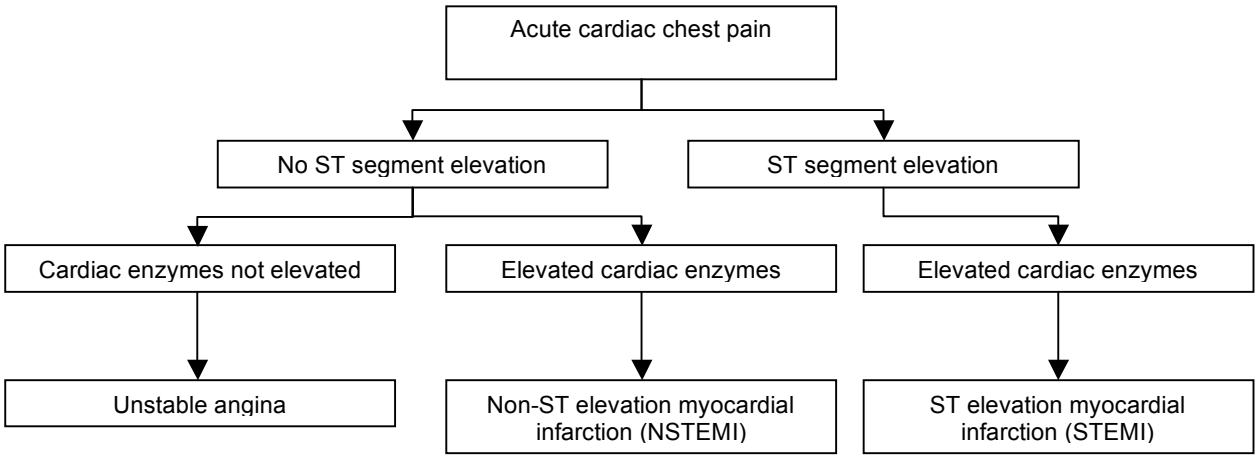
§ Speech disturbance defined as either dysarthria or dysphasia or both
* Diabetes defined as requiring either oral medication or insulin
Note: patients with ABCD^2 <5 should not be enrolled

Acute Coronary Syndromes

Criteria for acute, evolving or recent Myocardial Infarction (MI):[54]
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.

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) [55]

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.

Appendix C: Glasgow Coma Score [56]

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)

Appendix D: Modified Rankin Scale (mRS) [57,58]

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)

Appendix E: Barthel Index [58,59]

Task	Criteria	Score
Bowels	Incontinent	0
	Occasional accident (once per week)	5
	Continent	10
Bladder	Incontinent, or catheterised and unable to manage alone	0
	Occasional accident (maximum once per 24 hours)	5
	Continent	10
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)

Appendix F: EuroQOL [60]

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

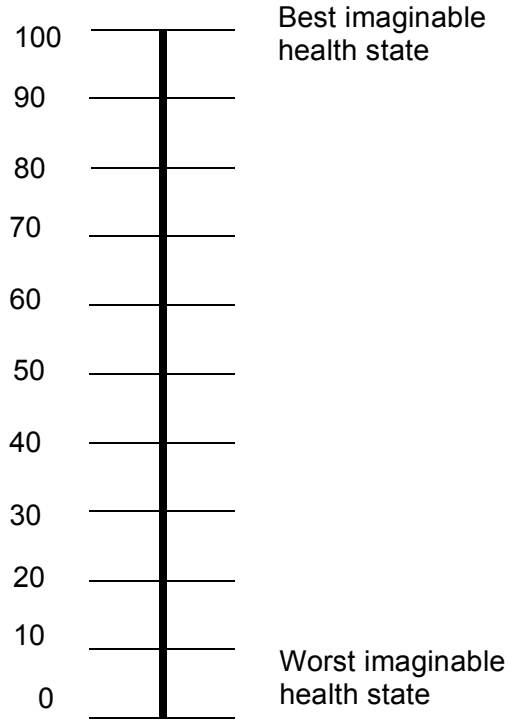
Group 2
I have no problems with self care
I have some problems with washing or dressing
I am unable to wash or dress myself

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 [61]

TICS-M – 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.

Orientation:

1(a). What day of the week is it?	Day	☐
(b). What is today's date?	Date	☐
	Month	☐
	Year	☐
(c). What season are we in?	Season	☐
2. What is your age?	Age	☐

Registration/ Free Recall:

3. I am gong 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	☐

Now tell me the words you can remember

Attention/Calculation:

4. Please take away 7 from 100	93	☐
Now continue to take 7 away from what	86	☐
you have left over until I ask you to stop	79	☐
	72	☐
	65	☐
5. Please count backwards from 20 to 1	No mistakes	☐

Comprehension, Semantic and Recent Memory:

6. What do people usually use to cut paper?	Scissors	☐
7. What is the prickly green plant found in the desert?	Cactus	☐
8. Who is the head of state now?	Correct Name	☐
9. What is the opposite direction to east?	West	☐

Language/Repetition:

10. Please listen carefully and repeat this: "No ifs, ands or buts	Exactly right	☐

Delayed Recall:

11. Please repeat as many of the 10 words I asked you to remember earlier	Cabin	☐
	Pipe	☐
	Elephant	☐
	Chest	☐
	Silk	☐

Theatre ☐
Watch ☐
Whip ☐
Pillow ☐
Giant ☐

Score 1 point for each correct answer. Maximum score = 39

Score _____

Concentration (from MMSE)
Spell WORLD backwards (or language specific equivalent)

Score _____out of 5

Verbal Fluency

Now you have 1 minute to name as many animals as you can think of. Ready? Start now!

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

Total score _____

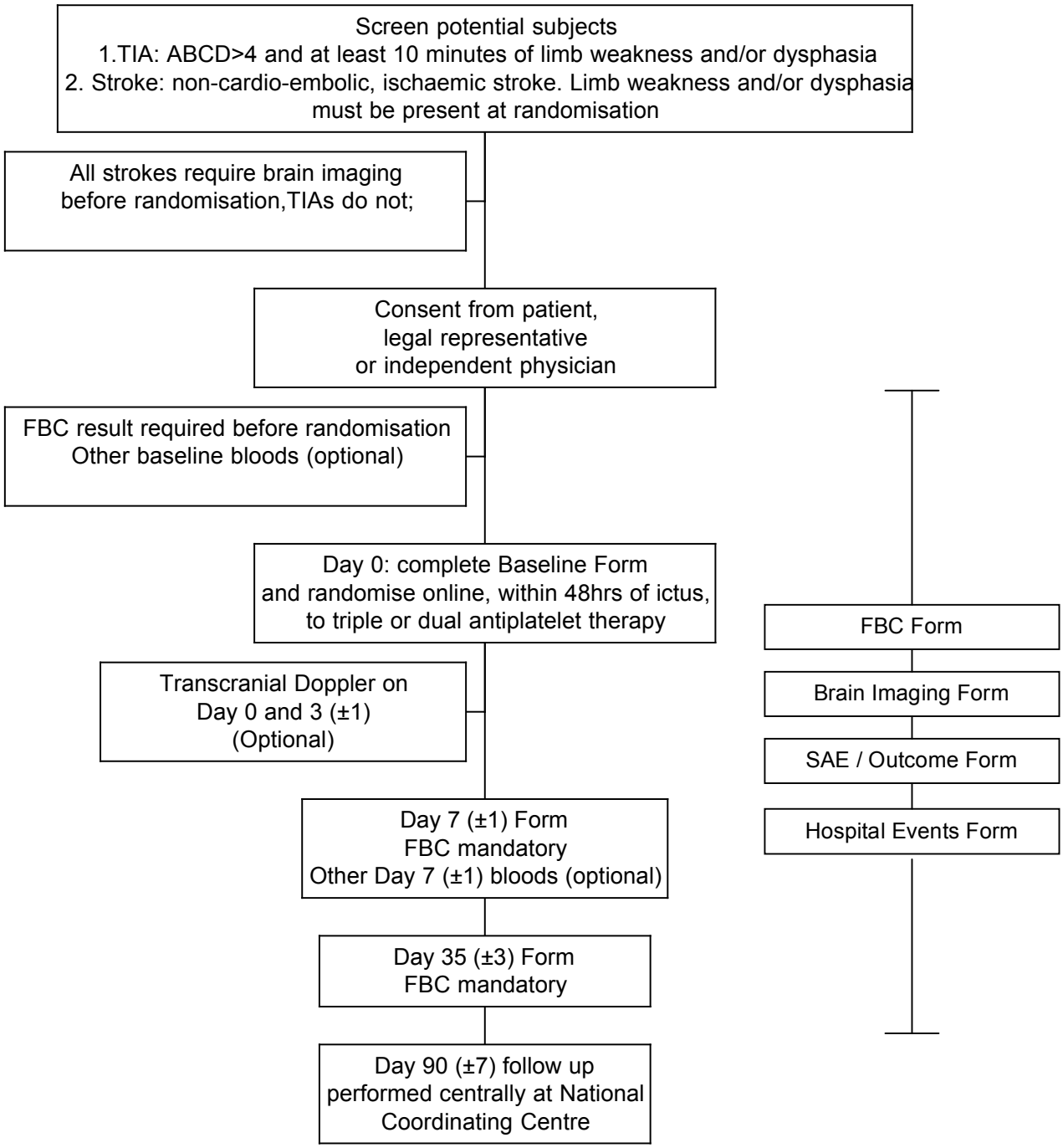
Appendix H: Zung Depression rating Scale (short) [30]

With scores:	Seldom or never	Some of the time	Good part of the time	Most of the time
I feel down-hearted and blue	1	2	3	4
I have trouble sleeping at night	1	2	3	4
Morning is when I feel best	4	3	2	1
I can eat as much as I used to	4	3	2	1
I get tired for no reason	1	2	3	4
I find it difficult to make decisions	1	2	3	4
I feel hopeful about the future	4	3	2	1
I feel that I am useful and needed	4	3	2	1
My life is somewhat empty	1	2	3	4
I still enjoy the things I used to do	4	3	2	1

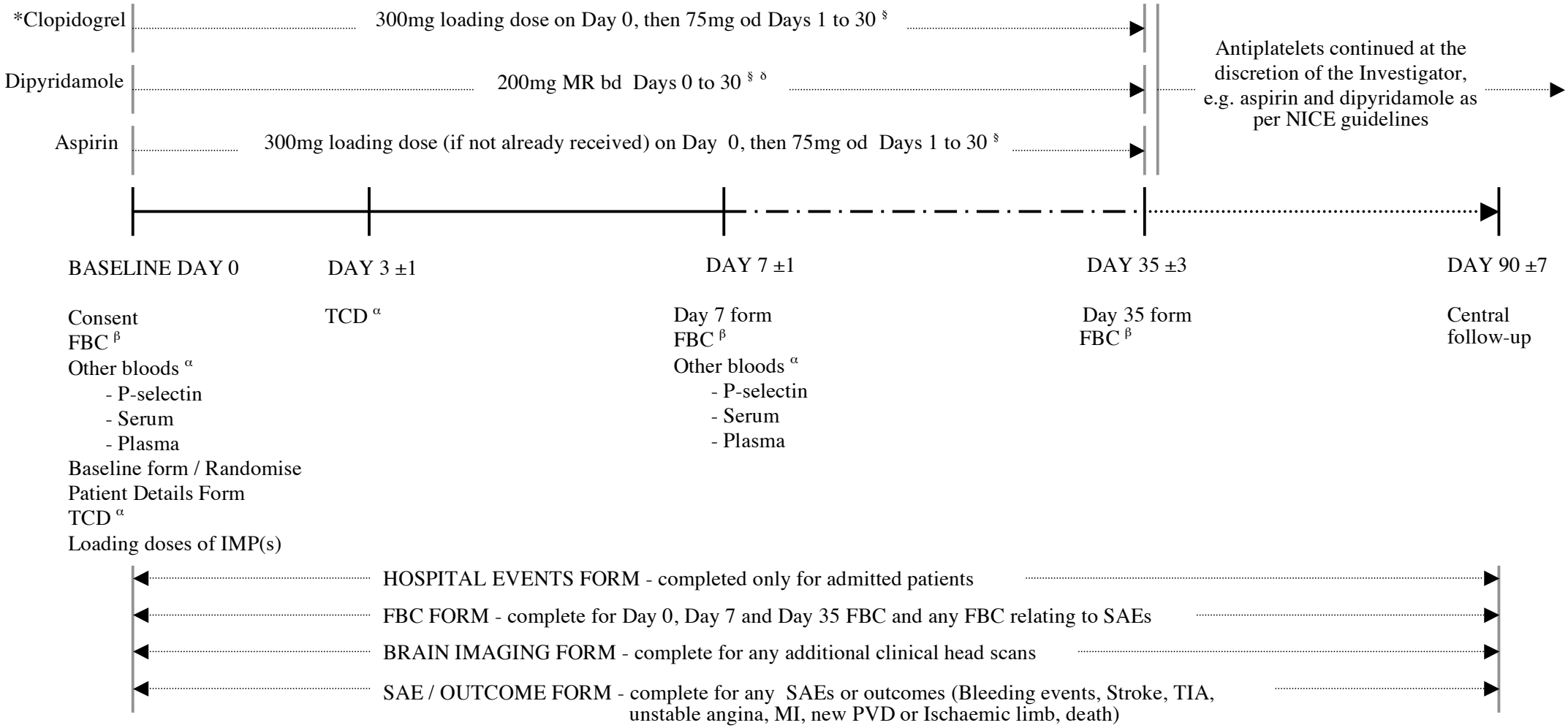
Short Zung IDS Index = 100 x Total / 40

Depression => 70

Appendix I: Trial Flow



Appendix J : Trial Timeline



* Given to 50% of randomised patients

§ If dysphagic, then administer drugs via NG/PEG; clopidogrel, aspirin and standard release dipyridamole can be crushed, or use liquid dipyridamole at a dose range of 75mg tds to 100mg qds. Dispersible aspirin (via NG/PEG) or aspirin suppositories (rectal, 150mg alternate days) can be given. NB Patients must have enteral access at trial entry

δ Patients with dipyridamole headache can reduce the dose (e.g. 200mg MR od, or 75mg od) and then wean up to a total of 400mg daily (e.g. 200mg MR bd)

β Mandatory at each centre

α In selected centres only

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.

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