APPLICANT'S CHECKLIST

CTIMP (Clinical trial of an investigational medicinal product)

REC Ref:	08/H1102/112	EudraCT No:	2007−006749−42
Short Title of Study:	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke		
CI Name:	Professor Philip M. W. Bath		
Sponsor:	University of Nottingham		

Please complete this checklist and send it with your application

- Send ONE copy of each document (except where stated)
- ALL accompanying documents must bear version numbers and dates (except where stated)
- When collating please do NOT staple documents as they will need to be photocopied.

Document	Enclosed?	Date	Version	Office use
Covering letter on headed paper	○ Yes ○ No			
NHS REC Application Form, Parts A&B	Mandatory			
Site−Specific Information Form (for SSA)	○ Yes ○ No			
Request form for authorisation from the MHRA (Annex 1 to ENTR/CT1) without enclosures	Mandatory			
Research protocol (6 copies)	Mandatory			
Investigator's brochure (3 copies)	○ Yes ○ No			
Summary C.V. for Chief Investigator (CI)	Mandatory			
Research participant information sheet (PIS)	Mandatory			
Research participant consent form	Mandatory			
Letters of invitation to participants	○ Yes ○ No			
GP/Consultant information sheets or letters	Mandatory			
Evidence of insurance or indemnity (non−NHS sponsors only)	Mandatory			
Letter from sponsor	○ Yes ○ No			
Letter from statistician	○ Yes ○ No			
Letter from funder	○ Yes ○ No			
Referees' or other scientific critique report	○ Yes ○ No			
Summary, synopsis or diagram (flowchart) of protocol in non−technical language	○ Yes ○ No			
Details of any Data Monitoring Committee	○ Yes ○ No			
Sample diary card/patient card	○ Yes ○ No			
Validated questionnaire	○ Yes ○ No			
Non−validated questionnaire	○ Yes ○ No			
Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.	○ Yes ○ No			

WELCOME TO THE NHS RESEARCH ETHICS COMMITTEE APPLICATION FORM

An application form specific to your project will be created from the answers you give to the following questions.

1. Is your project an audit or service evaluation?

○ Yes ◉ No

2. Select one research category from the list below:

◉ Clinical trials of investigational medicinal products
○ Clinical investigations or other studies of medical devices
○ Other clinical trial or clinical investigation
○ Research administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
○ Research involving qualitative methods only
○ Research limited to working with human tissue samples and/or data
○ Research tissue bank

If your work does not fit any of these categories, select the option below:

○ Other research

2a. Please answer the following questions:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA?	○ Yes	◉ No

2b . Please answer the following questions:

a) Does the study involve the use of any ionising radiation?	○ Yes	◉ No
b) Will you be taking new human tissue samples?	◉ Yes	○ No
c) Will you be using existing human tissue samples?	○ Yes	◉ No

3. Is your research confined to one site?

○ Yes ◉ No

4. Does your research involve work with prisoners?

○ Yes ◉ No

5. Do you plan to include in this research adults unable to consent for themselves through physical or mental incapacity?

◉ Yes ○ No

5a. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [x] Wales
- [x] Scotland
- [x] Northern Ireland

6. Is the study, or any part of the study, being undertaken as an educational project?

- ( ) Yes
- (•) No

NHS Research Ethics Committee NHS
Application form for a clinical trial of an investigational medicinal product

This form should be completed by the Chief Investigator, after reading the guidance notes. See glossary for clarification of different terms in the application form.

Short title and version number: (maximum 70 characters – this will be inserted as header on all forms)
Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke

Name of NHS Research Ethics Committee to which application for ethical review is being made:
South East Research Ethics Committee

Project reference number from above REC: 08/H1102/112
Submission date: 21/10/2008

PART A: Introduction

A1. Title of the research

Full title:	Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial
Key words:	ischaemic stroke, aspirin, dipyridamole, clopidogrel, secondary prevention, antiplatelet

A2. Chief Investigator

Title:	Professor
Forename/Initials:	Philip M. W.
Surname:	Bath
Post:	Professor of Stroke Medicine
Qualifications:	MBBS, MD, FRCP, FRCPath
Organisation:	University of Nottingham
Work Address:	Division of Stroke Medicine, City Hospital Campus Nottingham
Post Code:	NG5 1PB
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Telephone:	0115 8231765
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Mobile:	

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application

A3. Proposed study dates and duration

Start date:	01/03/2009
End date:	01/03/2017
Duration:	Years: 8 ; Months: 0

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☑ Publicly funded trial or scientific investigation
- ☐ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

A5. Type of medicinal trial:

- ☐ Clinical trial of a non−authorised investigational medicinal product
- ☑ Clinical trial of an authorised product for a new indication, i.e. not in the Summary of Product Characteristics, (SmPC)
- ☐ Clinical trial of an authorised medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☐ Clinical trial of an authorised medicinal product used according to the SmPC
- ☐ Other

If Other, please specify:

A5a. Phase of medicinal trial: *(Tick one category only)*

- ○ Human pharmacology trial *with no evidence of potential benefit to the proposed participants* (Phase 1 or 1/2a)
- ○ Therapeutic exploratory trial in patients (Phase 2)
- ◉ Therapeutic confirmatory trial in patients (Phase 3)
- ○ Therapeutic use trial in patients (Phase 4)

Applicants must enclose a copy of the completed request for authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA). The application form is published as Annex 1 to the European Commission guideline ENTR/CT1 and can be obtained from the EudraCT website at http://eudract.emea.eu.int.

A6. Does this research require site−specific assessment (SSA)? (Advice can be found in the guidance notes on this topic.)

◉ Yes ○ No

If No, please justify:

If Yes, an application for SSA should be made for each research site on the Site−Specific Information Form and submitted to the relevant local Research Ethics Committee. Do not apply for SSA at sites other than the lead site until the main application has been booked for review and validated by the main Research Ethics Committee.

Management approval to proceed with the research will be required from the R&D office for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA. R&D applications in England, Wales and Scotland should be made using the Site−Specific Information Form.

PART A: Section 1

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

To perform a randomised trial assessing the efficacy, safety and tolerability of adding Clopidogrel to Aspirin and Dipyridamole in patients with recent stroke (caused by a blood clot in the brain) or TIA (mini−stroke) and who are at high risk of recurrence.

A8. What are the secondary research questions/objectives? *(If applicable, must be in language comprehensible to a lay person.)*

To further assess, in high risk patients with stroke/TIA, whether the addition of Clopidogrel to Aspirin and Dipyridamole:
(i) Is feasible to administer acutely and tolerable to take for 1 month,
(ii) Is superior in respect of surrogate markers assessed as emboli (blood clots) and platelet function
(iii) Improves functional outcome

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance?*(Must be in language comprehensible to a lay person.)*

Stroke is a devastating event to patients, carers and society. One third of patients need long term care and it cost 6% of NHS resources. Having survived a stroke, the risk of another one is high and the government has targeted research into stroke as a priority through creating the UK Stroke Research Network (UKSRN). The normal treatment for stroke caused by a blood clot is to use two types antiplatelet agents called ‘Aspirin’ and 'Dipryidamole' in combination with each other. They work by acting on cells in the blood called platelets and reduce the risk of another stroke by making the platelets less ‘sticky’. A third antiplatelet agent, Clopidogrel, is also liscensed for use in srtoke, but usually instead of Aspirin and Dipyridamole rather than in addition to them.

Evidence now suggests that reducing stroke recurrence is dependent on the number of antiplatelet agents used. For example, the combination of using aspirin and dipyridamole reduces the number of events by 23% in comparison to aspirin alone (ESPSII and ESPIRIT trials). However, other trials (e.g. MATCH) have shown that using Clopidogrel as dual therapy with Aspirin in the long term can increase your bleeding risk and therefore outweighing any benefit gained from reducing additional strokes. While Clopidogrel based therapy has not proven beneficial in the long term, recent evidence (EXPRESS and FASTER trials) has shown that short term use of Clopidogrel may be useful. In this study we want to find out if using three antiplatelet drugs (for one month) is better than using two (the current UK standard treatment) in preventing further strokes in patients who are at high risk.

A10−1. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order.

This section must be completed in language comprehensible to the lay person. It must also be self−standing as it will be replicated in any applications for site−specific assessment on the Site−Specific Information Form. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

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 (stroke caused by a blood clot) or TIA (mini−stroke) 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. We hypothesise that three antiplatelets will be better than two in preventing further strokes, providing it is not outweighed by increased bleeding risk.

Design:
− Randomised contolled trial − Patients with a recent stroke or TIA (within 48 hours) will be randomly assigned to receive either usual stroke treatment (dual therapy) or Clopidogrel in addition to this (tripletherapy) for 1 month. There is no placebo (dummy drug).

– Blinded Outcome Assessment – the person making the final assessments does not know what treatment the patient received which helps prevent bias.
– Multi–centre

Methodology:
The following measures will be taken from the patient in hospital (or they will be brought to the researcher's facility if the patient has been discharged):

– Safety: At each time point, (day 2, day 7, day 35 and day 90) medication tolerability and side effects will be assessed.

– Clinical Efficacy – In order to see if the treatment improves a patient's outcome, a standrard neurological examination will be performed at baseline and at 35 days, along with questions about side effects and any adverse events. There will also be questions on their function, mood and quality of life at day 90. The day 90 assessment will be performed by telephone questionnaire.

– Transcranial Doppler (TCD). This is a machine that enables us to look at the flow of blood through vessels in the brain (using ultrasound waves). It is completely painless and can be done at the bedside. It involves placing a probe on the outside of the head for about one hour. It will also detect the presence of any blood clots
(emboli) travelling in the blood vessels. It will be done twice – on the day of enrolment and on Day 2 in selected centers only.

– Blood tests. Blood will be taken for a full blood count (to measure for anaemia) since the main risk of triple therapy is bleeding. This will be done on day 0, at day 7 and day 35. An additional blood test of platelet function (called P–selectin) will also be done on day 0 and day 7. Also a blood test for genetic analysis (which
will assess the relationship between genes, stroke risk and platelet resistance) and for stroke 'biomarkers'.

Summary of visits for the patient:
1. Baseline visit (Day 0) – patient consent gained and enrolled into the trial. Blood tests are taken as described along with baseline medical history and examination. This will usually take place in the hospital ward (and potentially the outpatient clinic). In selected centres only, and for those patients who agree, TCD will be performed (explained above).
2. Day 2 – In selected centres only, and for those patients who agree, TCD will be performed.
3. Day 7±1 – Many patients will still be in hospital at this stage, so the research team can see them as an inpatient to take blood as described and assess safety and tolerability of the trial drugs. For patients already discharged (or never admitted if a TIA), transport will be arranged to assess them at the researcher's facility or the trial medic or nurse can visit the patient at home. Transport will be paid for by the investigators and reimbursed from the Trial Coordinating Centre.
3. Day 35±3 – A larger proportion of patients will have been discharged home at this stage. Transport will therefore be arranged and paid for in order to make assessments of safety, drug tolerance, impairment and blood tests (full blood count only). Patients may also be seen at home if appropriate. Some patients will still be in hospital and assessments will be made there.
4. Day 90±7 – Assessment will be performed by a designated 'follow–up coordinator' using a telephone–based questionnaire. They will contact the patients GP first to ensure the patient still lives at the same address. If necessary the initial treating consultant's secretary may need to be contacted to establish the patient’s final discharge destination. If there is no response from the expected place of residence, a postal questionnaire will then be sent out. If the patient cannot answer the questions due to the nature of their stroke, then we will ask their main carer to answer on their behalf. The questionnaire is standardised and contains questions that have all been validated in previous research studies. These include questions on current ability (modified Rankin score and the Bartel Index) quality of life (EuroQoL questionnaire), depression (Zung depression scale) and cognition (TICS score).

The patient has finished in the trial after the 90 day assessment.

The start up phase will take 3 years to complete, recruiting 350 patients. This will seamlessly run into the main phase (if safety analyses allow) recruiting up to 5000 patients over the next 5 years.

A10–2. In which parts of the research have patients, members of the public or service users been involved?

- [x] As user–researchers
- [ ] As members of a research project group
- [ ] As advisor to a project
- [ ] As members of a departmental or other wider research strategy group
- [ ] None of the above

Please provide brief details if applicable:

A10–3. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

○ Yes ◉ No

A12. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care.*(These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material.)*

Additional Intervention	**Average number per participant**		**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**
	Routine Care	Research		
Imaging Investigations (not radiation)	0	2	1 hour	Transcranial doppler. This is a painless ultrasound probe placed on the outside of the head to detect blood flow and embolic events within the cerebral circulation.
Venepuncture	5–10	3	5–10 mins	Approximately 20mls (4 teaspoons) required at baseline for a full blood count, P–selectin assay, EDTA, serum and plasma samples. Approx 20mls required on day 7 for for a full blood count, P–selectin assay, serum and plasma samples.3–5mls for full blood count on day 35.

A13. Give details of any non–clinical research–related intervention(s) or procedure(s).*(These include interviews, non–clinical observations and use of questionnaires.)*

Additional Intervention	**Average number per participant**	**Average time taken** (mins/hours/days)	**Details of additional intervention or procedure, who will undertake it, and what training they have received.**
Face to Face Interview	2	30 mins	Visits to assess neurological function, at baseline and day 35.
Telephone Interview	1	30 mins	Telephone call at 90 days to assess function, cognition, quality of life and mood.

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

(•) Yes ( ) No

If Yes, give details of procedures in place to deal with these issues

On entry into the trial, contact details of the patient and a person (relative or friend) not living with the patient are obtained. They are made aware of the follow up required for the trial (as previously specified). This includes a telephone questionnaire at 'day 90' performed by our 'follow−up coordinator'. She is a trained nurse and well practiced (from current involvement in the ENOS trial with similar follow−up) and can deal sensitively with issues involving stroke. Prior to making the phone call, the follow up coordinator will contact the patient's GP to ensure that they are still living at the same address.

The questionnaire is standardised and contains questions that have all been validated in previous research studies. These include questions on current ability (modified Rankin score and the Bartel Index) quality of life (EuroQoL questionnaire), depression (Zung depression scale) and cognition (TICS score).

If the patient is unable to answer the questions due to the disabilities from their stroke, their main care giver will be asked to answer the questions as accurately as possible on the patients behalf.

We use the same measurement scales in the ongoing MRC ENOS trial (www.enos.ac.uk/) where they are administered by telephone. So far, more than 800 patients have had these assessments without any significant problems.

No information on probidity is relevant to the trial.

The Information Sheet should make it clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

90 (±7) days

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non−clinical)?

The main risk of triple antiplatelet therapy is one of causing bleeding. This is monitored very closely with regular visits and blood counts as described.

The patient information sheet contains details on how bleeding might present itself to the patient. This will also be re−iterated verbally during the consent process. It will be stressed to the patient that if they notice anything abnormal they should report it immediately to the medical staff on the ward (if they are an inpatient) or to get in contact with the research team directly (with provided contact details). Appropriate action can then be taken, such as telephone advice or medically reviewing the patient.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

The additional blood tests may cause some pain and minor bruising.

The transcranial doppler scans will require the patient to keep quite still for 1 hour and may cause discomfort as a consequence.

The extra visits (if the patient has been discharged) may cause some patients an inconvenience to their lifestyle in terms of travel and time.

The day−90 follow−up telephone questionnaire will cover issues regarding recovery from their stroke and will need to be dealt with sensitively.

A18. What is the potential for benefit to research participants?

The trial may benefit those on triple antiplatelet therapy by reducing their risk of another stroke and therefore improving their chances of independent living and improved quality of life.

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves? *(if any)*

None

A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

Potential patients will be identified by the Stroke Consultant and members of the clinical care team (which may include trial medics and nurses) via ward rounds and the TIA / stroke clinic. The study will be presented to the potential patients. Following adequate time for consideration and questions about the the trial, patients will be invited to enroll.

If patients are incompetent to consent, e.g. due to dysphasia or confusion, relatives or an independent physician (if no family are available) will be invited to give consent on the patients behalf. At all times, patients and relatives will be invited to ask questions about the trial and answered by trial medics and nurses. Consent will be gained by a doctor knowledgeable about the trial.

A21. Where research participants will be recruited via advertisement, give specific details.

☑ Not Applicable

If applicable, enclose a copy of the advertisement/radio script/website/video for television (with a version number and date).

A22. What are the principal inclusion criteria?*(Please justify)*

Patients at high risk of recurrent stroke need to be included:

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, and/or with an ABCD2 score >5 (stroke rate at 13 weeks>10%)

A23. What are the principal exclusion criteria?*(Please justify)*

1. Age<40; (patients younger than this are likely have an alternative cause of their stroke other than atherosclerosis)
2. Motor weakness lasting <30 minutes (pure sensory, vertigo or dizziness, speech or visual disturbance symptoms without weakness are excluded);
3. Patients with contraindications to, or intolerance of, Aspirin, Clopidogrel or Dipyridamole;
4. Pre−morbid dependency (mRS>3);
5. No enteral access (i.e. they cannot effectively receive the trial drugs within 48 hours of their stroke because they cannot swallow or do not have a feeding tube);
6. Parenchymal haemorrhagic transformation (PH I/II), subarachnoid haemorrhage or other non ischaemic cause for weakness;

7. TIA not fulfilling inclusion criteria
8. Definite need for, or currently on triple antiplatelet therapy or anticoagulation;
9. Indication for, or received (in last week), thrombolysis;
10. Presumed cardioembolic stroke (e.g. AF, recent MI, or other conditions need for anticoagulation);
11. Severe high BP (BP>185/110 mmHg);
12. Bleeding within 1 year (e.g. peptic ulcer, intracerebral haemorrhage); Planned surgery during 3 month follow−up (e.g. carotid endarterectomy).
13. Concomitant acute coronary syndrome;
14. Stroke secondary to a procedure (e.g. carotid or coronary intervention);
15. Planned surgery during first month post stroke (e.g. carotid endarterectomy);
16. Coma (GCS<8)
17. Non−stroke life expectancy<6 months;
18. Dementia
19. Participation in another drug trial concurrently or within 30 days. (Patients may be randomised into observational studies or non−drug trials)
20. Not available for follow−up e.g. no fixed address, overseas visitor
21. Females of childbearing potential, pregnancy or breastfeeding
[Note: Clopidogrel will be stopped around procedures that become necessary after enrolment].

A24. Will the participants be from any of the following groups? *(Tick as appropriate)*

- ☐ Children under 16
- ☐ Adults with learning disabilities
- ☑ Adults who are unconscious or very severely ill
- ☐ Adults who have a terminal illness
- ☐ Adults in emergency situations
- ☐ Adults with mental illness (particularly if detained under Mental Health Legislation)
- ☐ Adults with dementia
- ☐ Prisoners
- ☐ Young Offenders
- ☑ Adults in Scotland who are unable to consent for themselves
- ☐ Healthy Volunteers
- ☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- ☑ Other vulnerable groups

Justify their inclusion.

Patients (including the elderly) with acute stroke may be severely ill or semi−conscious and should not be excluded since they have much to gain from potential efficacious treatments. This is standard practice in stroke trials.

- ☐ No participants from any of the above groups

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

◉ Yes ○ No ○ Not Known

If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?

Patients receiving non−drug related trial interventions e.g. venous compression stockings (MRC−CLOTS trial)may be enrolled. Patients in other drug related trials may not be enrolled.

A26. Will informed consent be obtained from the research participants?

◉ Yes ○ No

If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe any arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.

Patients, relatives or an independent physician (if no relatives are available) may give consent and will be informed of potential risks and benefits, including using an information sheet.
If patients are incompetent to consent, e.g. due to dysphasia or confusion, relatives or an independent physician will be invited to give consent on the patients behalf. At all times, patients and relatives will be invited to ask questions about the trial and answered by trial medics and nurses.

Copies of the written information and all other explanatory material should accompany this application.

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

If Yes, attach a copy of the information sheet to be used, with a version number and date.

A28. How long will the participant have to decide whether to take part in the research?

All patients will be given adequate time to consider participation and will not be rushed into a decision. Patients will be recruited into this trial within 48 hours of onset of their stroke or TIA. Therefore, the patient / relative / independent physician will have time to ask questions and consider involvement. However, the nature of the trial is to assess treatment given to reduce early brain damage and early recurrence, and so patients/carers will have a few hours to decide.

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

Unfortunately, the agreed funding for the trial does not include translation costs. However, we accept the point made by the committee in the meeting on 8/10/08 and the Chief Investigator will cover the costs of translation for Asian populations (a group at greater risk of ischaemic stroke).

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

If new information becomes available about the trial drugs the research staff will tell the patients or relatives about the new information. They will then decide if they want to continue and sign an updated consent form if necessary.

Question(s) 30–1 disabled.

A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit?*(see the guidance notes)*

○ Yes ◉ No

A32a. Will the research participants' General Practitioner (and/or any other health professional responsible for their care) be informed that they are taking part in the study?

(•) Yes ( ) No

If Yes, enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A32b. Will permission be sought from the research participants to inform their GP or other health professional before this is done?

(•) Yes ( ) No

If No to either question, explain why not

It should be made clear in the patient information sheet if the research participant's GP/health professional will be informed.

A33. Will individual research participants receive any payments for taking part in this research?

( ) Yes (•) No

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

(•) Yes ( ) No

If Yes, indicate how much and on what basis this has been decided:

Travel costs for all patients and carers will be provided for each attendance at hospital related to the trial. If appropriate, researchers will visit patients at home to perform assessments.

A35. Insurance/indemnity to meet potential legal liabilities

Note: References in this question to NHS indemnity schemes include equivalent schemes provided by Health and Personal Social Services (HPSS) in Northern Ireland.

A35–1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s)* for harm to participants arising from the *management of the research*?

Note: Where a NHS organisation has agreed to act as the sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, describe the arrangements and provide evidence.

( ) NHS indemnity scheme will apply
(•) Other insurance or indemnity arrangements will apply (give details below)

The University of Nottingham will act as sponsor and has appropriate trials insurance. Evidence of this cover has been provided within the application.

Please enclose a copy of relevant documents.

A35–2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the *sponsor(s) or employer(s)* for harm to participants arising from the *design of the research*?

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), describe the arrangements and provide evidence.

- ○ NHS indemnity scheme will apply to all protocol authors
- ◉ Other insurance or indemnity arrangements will apply (give details below)

The University of Nottingham will act as sponsor and has appropriate trials insurance.

Please enclose a copy of relevant documents.

A35–3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of *investigators/collaborators* and, where applicable, *Site Management Organisations*, arising from harm to participants in the *conduct of the research*?

Note: Where the participants are NHS patients, indemnity is provided through NHS schemes or through professional indemnity. Indicate if this applies to the whole of the study (there is no need to provide documentary evidence). Where non–NHS sites are to be included in the research, including private practices, describe the arrangements which will be made at these sites and provide evidence.

- ◉ All participants will be recruited at NHS sites and NHS indemnity scheme or professional indemnity will apply
- ○ Research includes non–NHS sites (give details of insurance/indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A36. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

If Yes, give details of the compensation policy:

Please enclose a copy of relevant documents.

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☑ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ Written feedback to research participants
- ☐ Presentation to participants or relevant community groups
- ☐ Other/none e.g. Cochrane Review, University Library

A38. How will the results of research be made available to research participants and communities from which they are drawn?

No specific results will be presented to research participants

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- [x] Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- [x] Electronic transfer by magnetic or optical media, e−mail or computer networks
- [x] Sharing of data with other organisations
- [x] Export of data outside the European Union
- [x] Use of personal addresses, postcodes, faxes, e−mails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [ ] Storage of personal data on any of the following:
  - [x] Manual files including X−rays
  - [x] NHS computers
  - [x] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [x] Laptop computers

Further details:

Computers will be password protected and have appropriate anti−virus software.

Anonymous electronic transfer of images will occur for transferring CT scan data.

This will be a large trial assessing antiplatelet agents in stroke and there are other trials of similar drugs ongoing. Therefore, data may potentially be shared with larger academic collaborations such as the anti−thrombotic collaboration or the Cochrane Collaboration who combine data sets of all trials assessing similar questions in order to provide more scientifically robust answers. Data sharing normally comprises summary/group data where individuals cannot be identified. However, individual patients data may also be shared − this is always done anonymised with identifiers removed thereby preventing identification of individuals.

When the trial expands into the main phase, countries outside of the EU are likely to be involved.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:

All patient data will kept in a secure location (a locked filing cabinet in the research office) and on password protected computers.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

Analysis will be performed within the Division of Stroke Medicine by our departmental statistician and trial medics.

A42. Who will have control of and act as the custodian for the data generated by the study?

Chief Investigator Prof Philip Bath

A43. Who will have access to research participants' or potential research participants' health records or other personal information? *Where access is by individuals outside the normal clinical team, justify and say whether consent will be sought.*

Chief Investigator Prof Philip Bath and members of his research team. All hold honorary contracts with the NHS.

A44. For how long will data from the study be stored?

7 Years **00** Months

Give details of where they will be stored, who will have access and the custodial arrangements for the data:

The data will be stored in locked filing cabinets. Following the study's completion it will be archived in a secure location, by arrangement with Professor Bath. Exact location to be arranged.

A45–1. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi–centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

A45–2. How have the statistical aspects of the research been reviewed? *(Tick as appropriate)*

- [x] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi–centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise

In all cases give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title:	Forename/Initials:	Surname:
Dr	Laura	Gray

Department: Division of Stroke Medicine
Institution: University of Nottingham

Work Address:	Division of Stroke Medicine, City Hospital Campus Nottingham
Postcode:	NG5 1PB
Telephone:	01158231772
Fax:	01158231767
Mobile:	
E−mail:	lg48@le.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

Question(s) 46−47 disabled.

A48. What is the primary outcome measure for the study?

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. The start−up phase will also assess ordinal bleeding (fatal/major/minor/none) at 35 days (end of treatment) as adjudicated by an independent blinded panel.

A49. What are the secondary outcome measures?*(if any)*

Secondary outcomes at 35 and 90 days: Binary stroke; ordinal stroke (fatal stroke/non−fatal stroke/no stroke); binary myocardial infarction; ordinal myocardial infarction (fatal MI/non−fatal MI/no MI); binary composite vascular outcome (non fatal MI & stroke, vascular death); ordinal composite vascular outcome; composite stroke, TIA, acute coronary syndromes and all cause death.

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

Tolerability: Proportion of patients completing 28 days of randomised treatment.

Feasibility: Recruitment rate per week.

Safety measures at 35 and 90 days: Death; binary major bleeding (fatal, symptomatic bleed causing fall in haemoglobin of >2g/l, or leading to transfusion of >2 units of blood/red cells); 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); full blood count (at 35 days); thrombotic thrombocytopenic purpura; granulocytopenia.

Data from two substudies will power substudies within the main phase of the trial:

(i) Transcranial Doppler: TCD recordings will be performed from the middle cerebral artery (MCA) at baseline and day 2 using identical Nicolet/EME TCD systems Pioneer digital systems using a 2MHz transducer. One hour recordings will be stored digitally and transferred on DVD to London for analysis (by Hugh Markus, London St George's Hospital) with blinding to patient and treatment identity. We will use similar recording protocols to those successfully used in the CARESS study (of which Hugh Markus was the Chief Investigator).

(ii) Platelet Function − 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 5, fixed (to allow batching of samples), posted by Royal Mail to Nottingham, and P−selectin measured using a standardised assay 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 Cardiovascular Medicine at QMC. 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. Several blood biomarkers are surrogate markers of outcome, such as S-100. 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.

A50. How many participants will be recruited?
If there is more than one group, state how many participants will be recruited in each group. For international studies, say how many participants will be recruited in the UK and in total.

Start-up phase 350, and then upto 5000 for the main phase.

A51. How was the number of participants decided upon?

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).

If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

The start-up phase is sized to assess safety, i.e. where the addition of clopidogrel might be hazardous when added to aspirin and dipyridamole; the key concern for antiplatelet agents relates to bleeding. The sample size calculation uses assumptions
based on data from our recent pilot trial. Assuming bleeding rates for control (aspirin and dipyridamole) is 15% and active (aspirin. dipyridamole and clopidogrel) 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; 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 ~5,000.]

A52. Will participants be allocated to groups at random?

(•) Yes ( ) No

If yes, give details of the intended method of randomisation:

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.

A53. Describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

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 (including by age, sex, indication (stroke/TIA). Safety analyses will be performed 6 monthly during the start-up phase by the independent Data Monitoring Committee.

A54. Where will the research take place? *(Tick as appropriate)*

- [x] UK
- [x] Other states in European Union
- [x] Other countries in European Economic Area
- [x] Other

If Other, give details:

The start up phase will be in the UK only. The main phase will be expanded overseas.

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?

(●) Yes ( ) No

If Yes give details of each rejected application including:

Name of Research Ethics Committee or regulatory authority:	South East Research Ethics Committee
Decision and date taken:	Rejected 8/10/2008
Research ethics committee reference number:	08/H1102/92

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

	Number of organisations
[x] Acute teaching NHS Trusts	5
[x] Acute NHS Trusts	15
[ ] NHS Primary Care Trusts or Local Health Boards in Wales	
[ ] NHS Trusts providing mental healthcare	
[ ] NHS Health Boards in Scotland	
[ ] HPSS Trusts in Northern Ireland	
[ ] GP Practices	
[ ] NHS Care Trusts	
[ ] Social care organisations	
[ ] Prisons	
[ ] Independent hospitals	
[ ] Educational establishments	
[ ] Independent research units	
[x] Other (give details)	

Other:

20 sites have initially agreed for the start–up phase of the trial (within the Trent LRN and South–East LRN). Further sites will be identified when moving into the main phase of the trial.

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

The independent Data Monitoring Committee (DMC) will assess the data in full knowledge of what the patients have received, i.e. they will review unblinded data. This will be done after each 50 patients have been enrolled for the first 350 patients. They will deem whether it is safe or not to continue with the trial. The DMC will determine the frequency of monitoring in the main phase (not less than twice yearly).

A Trial Steering Committee (independent chair, grant applicants and lay person) will oversee the study, meeting annually. The Trial Management Committee will run the trial on a day−to−day basis and meet twice per month (with support by the trial statistician). Neither the TSC nor TMC have access to unblinded data.

A57a. Will a data monitoring committee be convened?

(•) Yes ( ) No

If Yes, details of membership of the data monitoring committee (DMC), its standard operating procedures and summaries of reports of interim analyses to the DMC must be forwarded to the NHS Research Ethics Committee which gives a favourable opinion of the study.

What are the criteria for electively stopping the trial or other research prematurely?

We will use the same Data Monitoring Committee charter that is agreed for MRC ENOS trial which states:

"During the period of recruitment into the study, the trial statistician will perform interim analyses on major outcome events (including serious adverse events believed to be due to treatment) 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 light of these analyses, the Data Monitoring Committee will advise the Chairman of the Steering Committee and Principal Investigator if, in their view, the randomised comparisons in ENOS 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 in terms of the primary outcome measure, 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. The Steering Committee can then decide whether to modify intake to the study (or to seek extra data). Unless this happens, however, the Steering Committee, the collaborators, and the central administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results.
Collaborators, and all others associated with the study, may write through the ENOS office, Nottingham to the Chairman of the Data Monitoring Committee, drawing attention to any worries they may have about the possibility of particular side−effects, or about particular categories of patient requiring special consideration, or about any other matters that may be relevant.
* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a common view is that a difference of at least 3 standard deviations in an interim analysis of a major outcome event may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.
Committee discussions: The committee will convene mainly via telephone conferences which should take place as soon as reasonably possible after the committee members have received data from the trial statistician; they must include all four members. Minutes of any telephone conference or meeting will be agreed by the committee and kept by the Chairman. The DMC Chairman will report to the Chairman of the Trial Steering Committee and the Principal Investigator."

In practice, the committee will look at the balance between benefit (reduction in death, dependency and TIA) and hazard (increase in significant bleeding). The Data Monitoring Committee would expect to inform the Trial Steering Committee if hazard exceeded benefit by a statistically significant margin (the so−called 3 standard deviation rule which is commonly used in clinical trials).

A58. Has external funding for the research been secured?

(•) Yes ( ) No

If Yes, give details of funding organisation(s) and amount secured and duration:

Organisation:	The British Heart Foundation
Address:	14 Fitzhardinge St London
Post Code:	W1H 6DH
UK contact:	
Telephone:	020 7487 9408
Fax:	020 7725 0497
Mobile:	
E–mail:	research@bhf.org.uk
Amount (£):	£233,283 Duration: 36 Months

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

○ Yes ◉ No

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

◉ Yes ○ No

Lead sponsor *(must be completed in all cases)*

Name of organisation which will act as the lead sponsor for the research:

University of Nottingham

Status:

○ NHS or HPSS care organisation ◉ Academic ○ Pharmaceutical industry ○ Medical device industry ○ Other

If Other, please specify:

Address:	University Park University Boulevard Nottingham
Post Code:	NG7 2DR
Telephone:	0115 9515679
Fax:	
Mobile:	
E–mail:	paul.cartledge@nottingham.ac.uk

Sponsor's UK contact point for correspondence with the main REC *(must be completed in all cases)*

Title: Mr Forename/Initials: Paul Surname: Cartledge

Work Address: Research Innovation Services, University of Nottingham
Kings Meadow Campus, Lenton Lane
Nottingham
Post Code: NG7 2NR
Telephone: 01159515679
Fax: 01159513633
Mobile:
E−mail: paul.cartledge@nottingham.ac.uk

Co−sponsors

Are there any co−sponsors for this research?

○ Yes ◉ No

Legal representative* of the sponsor in the EU for the purpose of this trial *(if applicable)*

Title: Forename/Initials: Surname:

Work Address:

Post Code:
Telephone:
Fax:
Mobile:
E−mail:

** A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.*

A60. Has any responsibility for the research been delegated to a subcontractor?

○ Yes ◉ No

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

○ Yes ◉ No

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

○ Yes ◉ No

A64. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share−holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

(•) Yes ( ) No

If yes, give details including the amount of any monetary payment or the basis on which this will be calculated:

The Chief Investigator works for the University of Nottingham (the sponsor for the trial)

A65. Research reference numbers: *(give any relevant references for your study):*

Applicant's/organisation's own reference number, e.g. R&D (if available):	
Sponsor's/protocol number:	31350
Funder's reference number:	PG/08/083/25779
International Standard Randomised Controlled Trial Number (ISRCTN):	
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	2007−006749−42
Project website: http://www.tardistrial.org	

A66. Other key investigators/collaborators *(all grant co−applicants or protocol co−authors should be listed)*

Title: Professor Forename/Initials: Thompson Surname: Robinson

Post:	Professor of Stroke Medicine
Qualifications:	MBBS MD FRCP
Organisation:	University of Leicester
Work Address:	Department of Cardiovascular Sciences University Hospitals of Leicester Gwendolen Road, Leicester
Postcode:	LE5 4PW
Telephone:	0116 258 4081
Fax:	
Mobile:	
E−mail:	tgr2@le.ac.uk

Title: Professor Forename/Initials: Graham Stuart Surname: Venables

Post:	Consultant Neurologist & Honorary Professor of Vascular Neurology
Qualifications:	BA, MA, BM BCh, DM, FRCP, FRCOphth
Organisation:	Sheffield University
Work Address:	Neurology Department Royal Hallamshire Hospital Sheffield
Postcode:	S10 2JF
Telephone:	0114 271 2197
Fax:	
Mobile:	
E−mail:	graham.Venables@sth.nhs.uk

Title: Professor Forename/Initials: Stanley Surname: Heptinstall

Post: Professor of Thrombosis and Haemostasis
Qualifications: BSc, PhD
Organisation: University of Nottingham
Work Address: Cardiovascular Medicine
Queens Medical Centre
Nottingham
Postcode: NG7 2UH
Telephone: 0115 8231013
Fax:
Mobile:
E–mail: heptinstall@nottingham.ac.uk

Title: Professor Forename/Initials: Hugh Surname: Markus

Post: Professor of Neurology
Qualifications: BA, BMBcH, MRCP, DM, FRCP,
Organisation: St George's University of London
Work Address: Clinical Neuroscience
St George's University of London
Cranmer Terrace, London
Postcode: SW17 ORE
Telephone: 02087252735
Fax:
Mobile:
E–mail: hmarkus@sgul.ac.uk

Title: Mrs Forename/Initials: Margaret Surname: Adrian

Post: Trial Coordinator
Qualifications: Diploma in Adult Nursing
Organisation: University of Nottingham
Work Address: Division of Stroke Medicine
CSB, City Hospital Campus,
Hucknall Rd, Nottingham
Postcode: NG5 1PB
Telephone: 0115 8230210
Fax:
Mobile:
E–mail: margaret.adrian@nottingham.ac.uk

Title: Dr Forename/Initials: Tim Surname: England

Post: Clinical Research Fellow
Qualifications: MBChB MRCP
Organisation: University of Nottingham
Work Address: Division of Stroke Medicine
CSB, City Hospital Campus,

	Hucknall Rd, Nottingham
Postcode:	NG5 1PB
Telephone:	0115 823010
Fax:	
Mobile:	
E−mail:	timothy.england@nottingham.ac.uk

A67. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

The trial treatment is intended for the subacute treatment of stroke (for the 1st month) and continued provision is not required once the trial has ended.

PART A: Summary of Ethical Issues

A68. Overview of the research

To provide all the information required by the REC, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A68−1. Lay summary. *Please provide a brief summary of the research (maximum 300 words) in lay language. This summary will be published on the website of the National Research Ethics Service following the ethical review.*

The risk of recurrent stroke is highest immediately after a stroke or mini−stroke, and may be reduced, but not abolished, with blood−thinning drugs (antiplatelet drugs). We know that taking two drugs is more effective than one and, therefore, taking three could be better than two. Recently, we published that it is feasible to give three drugs (clopidogrel, aspirin and dipyridamole) after a stroke in a randomised controlled trial. The TARDIS randomised trial will assess the effectiveness and safety of three versus two drugs (taken for 1 month) in patients with acute stroke/mini−stroke.

The major risk of taking an extra antiplatelet drug is one of causing extra bleeding, such as bruising on the skin, losing blood into the gut, or bleeding into the brain.

We hypothesise that the potential benefit (reduced chance of having another stroke) will outweigh the risk of bleeding. 350 patients will be recruited from UK Stroke Research Network centres in the first phase (3 years) which will expand into a larger main international trial of up to 5000 patients over the following 5 years

A68−2. Summary of main issues. *Please summarise the main ethical and design issues arising from the study and say how you have addressed them.*

1. Recruitment of patients who may be incompetent to give meaningful, informed, written consent.
Upto 50% of all stroke admissions will not be able to give consent because of dysphasia or confusion. It is important to include these stroke patients in the trial since they are the target group who are potentially most likely to benefit from an effective intervention. In this case, relatives can provide consent, a standard procedure in stroke clinical trials. We would also like to use 3rd party consent by an experienced independent clinician in the event that no relatives are available.

2. The risk of bleeding, as discussed in our reply letter (see response to question (a)).
The patient information sheet contains details on how bleeding might present to the patient. This will also be re−iterated verbally during the consent process. It will be stressed to the patient that if they notice anything abnormal they should report it immediately to the medical staff on the ward (if they are an inpatient) or to get in

contact with the research team directly (contact details will be provided) or their GP/NHS Direct. Appropriate action can then be taken, such as telephone advice or medical review of the patient.

Question(s) 69–71 disabled.

PART B: Section 1 – List of proposed research sites

List below all research sites you plan to include in this study. The name of the site is normally the name of the acute NHS Trust, GP practice or other organisation responsible for the care of research participants. In some cases it may be an individual unit, private practice or a consortium – see the guidance notes.

Principal Investigators at other sites should apply to the relevant local Research Ethics Committee for site–specific assessment (SSA) using the Site–Specific Information Form. Applications for SSA may be made in parallel with the main application for ethical review (once the main REC has validated the application), or following issue of a favourable ethical opinion. Approval for each site will be issued to you by the main REC following SSA.

1. Name of the research site:

Nottingham University Hospitals NHS Trust

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: Philip Surname: Bath

Post: Professor of Stroke Medicine
Work Address: Clinical Sciences Building, City Hospital
Hucknall Road
Nottingham
Postcode: NG5 1PB

2. Name of the research site:

University Hospitals of Leicester

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: Tom Surname: Robinson

Post: Professor of Stroke Medicine
Work Address: Dept of Cardiovascular Medicine
University of Leicester, UHL NHS Trust,
Gwendolen Rd, Leicester
Postcode: LE5 4PW

3. Name of the research site:

Derby Hospitals NHS Foundation Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Khuhood Surname: Muhiddin

Post: Consultant Physician
Work Address: Derby Hospitals NHS Foundation Trust,
Uttoxeter Road,
Derby
Postcode: DE22 3NE

4. Name of the research site:

Kings Mill Hospital (Mansfield)

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Jagdish Surname: Sharma

Post: Consultant Physician
Work Address: Medicine for the Elderly,
Mansfield Rd, Sutton–in –Ashfield,
Nottinghamshire
Postcode: NG17 4JL

5. Name of the research site:

Sheffield Teaching Hospitals

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: Graham Surname: Venables

Post: Consultant Neurologist and Honorary Professor of Vascular Neurology
Work Address: Neurology Dept,
Royal Hampshire Hospital,
Sheffield
Postcode: S10 2JF

6. Name of the research site:

Barnsley Hospital NHS Foundation Trust

Principal Investigator for the study at this site:

Title: D Forename/Initials: Mohammad Surname: Albazzaz

Post: Consultant Physician
Work Address: Barnsley Hospital NHS Foundation Trust
Gawber Road
Barnsley
Postcode: S75 2EP

7. Name of the research site:

Kettering General Hospital NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Khalid Surname: Ayes

Post: Consultant Physician
Work Address: Kettering General Hospital NHS Trust
Rothwell Rd

Kettering, Nothants
Postcode: NN16 8UZ

8. Name of the research site:

Northampton General Hospital NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Melanie Surname: Blake

Post: Consultant Physician
Work Address: Northampton General Hospital NHS Trust
Cliftonville
Northampton
Postcode: NN1 5BD

9. Name of the research site:

Doncaster and Bassetlaw Hospitals NHS Foundation Trust.

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Dinesh Surname: Chadha

Post: Consultant Physician
Work Address: Doncaster Royal Infirmary
Armthorpe Rd
Doncaster
Postcode: DN2 5LT

10. Name of the research site:

United Lincolnshire Hospitals NHS Trust (Lincoln County Hospital)

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Simon Surname: Leach

Post: Consultant Physician
Work Address: Lincoln County Hospital
Greetwell Road
Lincoln
Postcode: LN2 5QY

11. Name of the research site:

United Lincolnshire Hospitals NHS Trust (Pilgrim Hospital, Boston)

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: David Surname: Mangion

Post: Consultant Physician
Work Address: Pilgrim Hospital
Sibsey Rd
Boston
Postcode: PE21 9QS

12. Name of the research site:

The Rotherham NHS Foundation Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: James Surname: Okwera

Post: Consultant Physician
Work Address: Rotherham General Hospital, Moorgate Road,
Oakwood, Rotherham
South Yorkshire
Postcode: S60 2UD

13. Name of the research site:

Chesterfield Royal Hospital NHS Foundation Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Sunil Surname: Punnoose

Post: Consultant Physician
Work Address: Chesterfield Royal Hospital NHS Foundation Trust
Calow, Chesterfield
Derbyshire
Postcode: S44 5BL

14. Name of the research site:

East Sussex Hospitals NHS Trust (Eastbourne DGH)

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Conran Surname: Athulathmudali

Post: Consultant Physician
Work Address: Eastbourne District General Hospital
King's Drive, Eastbourne

East Sussex,
Postcode: BN21 2UD

15. Name of the research site:

Royal Surrey County Hospital NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Adrian Surname: Blight

Post: Consultant Physician
Work Address: Royal Surrey County Hospital
Guildford
Surrey
Postcode: GU2 7XX

16. Name of the research site:

East Kent Hospitals University NHS Trust (Queen Elizabeth The Queen Mother Hospital)

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Gunaratnam Surname: Gunathilagan

Post: Consultant Physician
Work Address: Queen Elizabeth The Queen Mother Hospital
St Peter's Rd
Margate, Kent
Postcode: CT9 4NA

17. Name of the research site:

Ashford and St. Peter’s Hospitals NHS Trust (Ashford Hospital)

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: David Surname: Hargroves

Post: Consultant Physician
Work Address: London Road,
Ashford,
Middlesex
Postcode: TW15 3AA

18. Name of the research site:

St George's Healthcare NHS Trust

Principal Investigator for the study at this site:

Title: Prof Forename/Initials: Hugh Surname: Markus

Post: Consultant Physician
Work Address: Blackshaw Road
Tooting
London
Postcode: SW17 0QT

19. Name of the research site:

Frimley Park Hospital NHS Foundation Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Keith Surname: Mundy

Post: Consultant Physician
Work Address: Frimley Park Hospital NHS Foundation Trust,
Portsmouth Road, Frimley,
Surrey
Postcode: GU16 7UJ

20. Name of the research site:

The Lewisham Hospital NHS Trust

Principal Investigator for the study at this site:

Title: Dr Forename/Initials: Mehool Surname: Patel

Post: Consultant Physician
Work Address: The Lewisham Hospital NHS Trust
Lewisham High Street
London
Postcode: SE13 6LH

PART B: Section 5 – Use of newly obtained human biological materials

1. What types of human tissue or other biological material will be included in the study?

Blood

2. Who will collect the samples?

Trial medics or trial nurses.

3. Will the samples be: *(Tick as appropriate)*

- [x] Obtained primarily for research purposes?
- [ ] Surplus (i.e. left over from tissue taken in the course of normal clinical care for diagnostic or therapeutic purposes)?

4. Will informed consent be obtained from donors for use of the samples:

In this research?

(•) Yes ( ) No

In future research?

(•) Yes ( ) No

5. Will the samples be stored:

In fully anonymised form? *(link to donor broken)*

( ) Yes (•) No

In linked anonymised form? *(linked to donor but donor not identifiable to researchers)*

(•) Yes ( ) No

If Yes, say who will have access to the code and personal information about the donor.

Professor Philip Bath, the Chief Investigator.

In a form in which the donor could be identifiable to researchers?

( ) Yes (•) No

If Yes, please justify:

6. What types of test or analysis will be carried out on the samples?

A full blood count (FBC) will be taken at baseline, day 7±1 and day 35±3 to assess haemoglobin, white cell and platelet levels. These will be performed in the NHS laboratories. These bloods are mandatory for each centre for safety assessments.

Platelet expression of P−selectin will be used to monitor platelet effects in patients. In selected centres, blood will be taken from patients at baseline & day 7±1, fixed (to allow batching of samples), posted by Royal Mail to Nottingham, and P−selectin measured using a standardised assay 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 Cardiovascular Medicine at QMC. All measurements are performed by flow cytometry and are subject to strict quality control.

The following samples will also be taken in centres who have the storage capacity and centrifugation facilities:
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

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. Several blood biomarkers are surrogate markers of outcome, such as S−100. 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.

The separate consent form 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.

7. Will the research involve the analysis of human DNA in the samples?

(●) Yes ( ) No

8. Is it possible that the research could produce findings of clinical significance for individuals? *(May include relatives as well as donors)*

(●) Yes ( ) No

9. If so, will arrangements be made to notify the individuals concerned?

(●) Yes ( ) No ( ) Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

The main potential clinical finding from the full blood counts is that of anaemia, thrombocytopenia or leucopenia. If this is discovered, then the patient will be contacted by the trial medic or nurse and action taken, which may include clinical assessment or cessation of the trial drugs. Appropriate treatment will be undertaken on the basis of these assessments.

10. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Frozen blood samples will be stored locally and then collected via courier delivery throughout the course of the trial to the TARDIS coordinating centre in Nottingham. The Chief Investigator Philip Bath and his research team will have access to the samples for analysis.

11. What will happen to the samples at the end of the research?

(•) Destruction

( ) Transfer to research tissue bank
(If the bank is in England, Wales or Northern Ireland a licence from the Human Tissue Authority will be required to store the tissue for possible further research.)

( ) Storage by research team pending ethical approval for use in another project
(Unless the researcher holds a licence from the Human Tissue Authority, a further application for ethical review should be submitted before the end of this project.)

( ) Storage by research team as part of a new research tissue bank
(The bank will require a licence from the Human Tissue Authority. A separate application for ethical review of the tissue bank may also be submitted.)

( ) Not yet known

Please give further details of the proposed arrangements:

PART B: Section 7 – Adults unable to consent for themselves

A. Clinical trials of investigational medicinal products – adults unable to consent for themselves

A1. What impairing condition(s) will the participants have?

Patients affected by stroke can be confused or dysphasic which will have a variable degree of recovery often depending on the size of the stroke and their previous co–morbidities

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

○ Yes ◉ No

A3. How will the capacity of potential participants to consent to the research be assessed? Who in the research team will make the assessment and what knowledge of the participant or relevant training/experience will they have to enable them to undertake it?

The trial medics are well trained in Stroke Medicine and are able to make good clinical judgements on a patient's capacity based on whether they can:
- understand the information conveyed
- retain this information
- weigh the risks against the benefits and come to an informed decision

The trial medics will gain the the above from their own history and examination and also information from the multi–disciplinary team (nurses, physiotherapists, occupational therapists and speach and language therapiats) looking after the patient.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? *You may refer back to your answer to Question A18.*

The trial may benefit those on triple antiplatelet therapy by reducing their risk of another stroke and therefore improving their chances of independent living and improved quality of life.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

◉ Yes ○ No

If Yes, please give an assessment below. You may refer back to your answer to Questions A16 and A17. Highlight any risk, burden or discomfort specific to these participants. Justify in relation to the potential benefits.

The main risk of triple antiplatelet therapy is one of causing bleeding as previously described. This is monitored very closely with regular visits and blood counts.
The risk to those from whom we gain relative (or independent physician) consent will be no greater compared to those who have capacity to consent themselves.

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

Permission will be sought from the patient's family or next of kin. They will be provided with an information sheet and given adequate time to ask questions and give consideration. If no family are available (despite best efforts to contact them) then an independent physician (consultant) can be given the an information sheet to decide on the patients' behalf.

A7. Is it possible that a participant might need to be treated urgently as part of the trial before it is possible to identify and seek consent from a legal representative?

○ Yes ◉ No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from a legal representative as soon as practicable thereafter.

A8. What steps will you take to provide information about the trial to participants, according to their capacity of understanding, and to consider the explicit wishes of participants capable of forming an opinion?

Verbal explanation and information sheets will be provided. After sufficient time, there will opportunities for the patients and relatives to ask further question before consent is gained.

A9. What will be the criteria for withdrawal of participants?

The trial is voluntary and the participants may withdraw at any time without giving reason.
If new information becomes available to suggest that the trial is unsafe or there are better alternative treatments then this information will be conveyed to the patient and withdrawal from the trial will be considered.

PART B: Section 8 – Declarations

Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.
4. I undertake to seek an ethical opinion from the main REC before implementing substantial amendments to the protocol or to the terms of the full application of which the main REC has given a favourable opinion.
5. I undertake to submit annual progress reports setting out the progress of the research.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.
7. I understand that research records/data may be subject to inspection for audit purposes if required in future.
8. I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application:

   – Will be held by the main REC until at least 3 years after the end of the study.

   – May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.

   – May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.

   – Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. I understand that the lay summary of this study will be published on the website of the National Research Ethics Service (NRES) as it appears in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Optional – please tick as appropriate:

☑ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name: P BATH

Date: (dd/mm/yyyy)
22/10/2008

Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the sponsor nominated to take the lead for the REC application.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*
3. Any necessary indemnity or insurance arrangements, as described in question A35, will be in place before this research starts.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**
7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.
8. I understand that the lay summary of this study will be published on the website of the National Research Ethics Service (NRES) as it appears in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Signature: .....

Print Name: Paul Carnegie

Post: Head of Research Grants & Contracts

Organisation: Research Innovation Services
The University of Nottingham

Date: (dd/mm/yyyy)
22/10/08