CLINICAL STUDY PROTOCOL

Cervical Artery Dissection in Stroke Study (CADISS)

Feasibility Phase

Sponsor's R&D Registration Number: 04.0287
Sponsor's Details: St George's University of London (SGUL)
EudraCT number: 2006-002827-18
ISTRCTN number: ISRCTN44555237
UK Stroke Research Network UKCRN Study ID: 2181

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Signature Page and Statement

The Chief Investigator (CI) and the JRO have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol except in the case of medical emergency (Section 10.10) or where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the protocol, GCP and UK Regulations for CTIMPs, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005), the Sponsor's SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the Sponsor's procedure outlined in the Standard Operating Procedure (SOP) identified as: JRODOC001 CTIMP Protocol Template V1.0.doc

Chief Investigator
Prof Hugh Markus
Professor of Neurology

St George's, University of London | Signature | Date

Sponsor Representative
Dr Paul Craven
Head of Joint Research Office

St George's University of London | Signature | Date

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1: List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MA	Marketing Authorisation
Main REC	Main Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MS	Member State
MUST	Malnutrition Universal Screening Tool
NHS R&D	National Health Service Research & Development
NIMP	Non- Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event

SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

2: Study personnel

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3: Study synopsis

Full study title:	Cervical Artery Dissection in Stroke Study
Short study title:	CADISS
Study R&D number:	04.0287
Study drug:	Antiplatelets (aspirin, dipyridamole, clopidogrel) vs. Anticoagulants (unfractionated heparin, dalteparin, enoxaparin, tinzaparin, warfarin)
Chief Investigator:	Professor Hugh Markus
Study centres/sites:	Sites listed in "Log of Sites" kept by the CADISS Coordinating centre.
Study duration:	The study will end when the last CADISS patient has had their last assessment.
Clinical phase:	Phase IV
Primary Objective:	To determine the feasibility of a clinical trial comparing antiplatelet therapy with anticoagulation in the acute treatment of patients with cervical artery dissection. Specifically to address whether: (a) There are sufficient clinical endpoints to provide the power to determine treatment effect (b) Adequate numbers of patients can be recruited.
Study population:	Any patient was has suspected or confirmed dissection on imaging, has symptom onset within seven days and is able to provide informed consent or has a relative/carer/witness to provide assent.
Eligibility Criteria:	***Inclusion criteria:*** 1) Extra cranial carotid or vertebral artery dissection with symptom onset within 7 days. This includes: a) Ipsilateral TIA or stroke with known date of onset **OR** b) Ipsilateral Horner's syndrome or neck pain with known date of onset. Patients with TIA or stroke in the last 7 days can be entered even if the history of neck pain is >7 days ago. Patients with a recurrent event can be entered as long as the event falls within the 7 day timeframe **AND** 2) Imaging evidence of definite or probable dissection on MRI/MRA, CTA or ultrasound (patients can be initially randomised on ultrasound alone but subsequent MR or CTA confirmation is needed)

	Exclusion criteria: (i) Intracranial cerebral artery dissection (ii) Symptom onset >7 days (iii) Contraindications to either antiplatelet agents or anticoagulation therapy, including active peptic ulceration or bleeding peptic ulcer within 1 year. (iv) Patient refusal to consent (v) Patients already taking antiplatelets or anticoagulants for other reasons e.g. prosthetic heart valves in whom the treatment cannot be replaced by either antiplatelets or anticoagulants. (vi) Women who are pregnant (vii) Iatrogenic-induced dissection
Study drugs, Dose and Mode of Administration:	
Duration of Treatment:	Patients will be randomised to either antiplatelet agents or anticoagulant agents for three months. The treatment choice is at the discretion of the prescribing physician. After the three month follow-up appointment the patient will receive standard medical treatment and information on treatments at six months and twelve months will be collected by the coordinating centre via telephone.

4: Introduction

4.1 Background

Dissection of the carotid and vertebral arteries is a major cause of stroke in persons <50 years of age, mainly due to embolism from clot sealing the tear. At present physicians treat these patients with anticoagulants or antiplatelet drugs to prevent further stroke, but neither therapy is evidence-based. Anticoagulants may be powerful anti-embolic agents but are also more hazardous than aspirin, and potentially could encourage further dissection. Most published studies are flawed by retrospective data, with no reference to the number of patients in the original study cohort and do not include the critical principles of randomisation and 'blinding' of outcomes.

The only prospective data available[1] suggests that anticoagulants are more effective than antiplatelet agents in reducing further TIA and stroke after dissection, but the numbers were small and lack reliable statistical confirmation. This study was not a randomised controlled trial and therefore may be open to bias in selection of treatment. In addition, it found that most recurrent events occur within the first month and thereafter the number tails off. A total of about 1800 patients would be required for a two armed trial comparing antiplatelet agents with anticoagulants calculated on these data.

Authors of a previous Cochrane review [2] reviewing available published literature calculated that a total of about 2800 patients (1400 in each treatment arm) are needed for a blinded randomised trial of anticoagulants vs antiplatelet agents. This would need a major, probably international, study involving over 100 centres, and would be an expensive undertaking. Prior to starting such a study it is important to determine whether this would be feasible. This is particularly important for carotid and vertebral dissection which is a diagnosis frequently missed, at least during the acute phase. Limited natural history outcome data suggests the risk of recurrent stroke and TIA following carotid and vertebral dissection is only markedly raised during the first week to month [1, 3] and therefore early identification and recruitment of patients is essential if any treatment effect is to be demonstrated.

For these reasons a feasibility study is essential before any large scale clinical trial. Specifically two things need to be determined; firstly, whether sufficient patients can be recruited sufficiently early from participating centres, and secondly, in view of the limited data on the rate of recurrent TIA and stroke in patients with recent dissection, we need more data to obtain a robust estimate of early risk to inform power calculations for a large scale study.

A preliminary informal survey conducted by Clinical Neurosciences, St George's University of London, in association with the Association of British Neurologists, has indicated that at least 27 neurologists/stroke physicians throughout the UK would be interested in collaborating and enrolling consecutive consenting patients into such a study comparing anticoagulation or antiplatelet therapy.

4.2 Investigational Medicinal Product (IMP)

(a) Antiplatelet therapy: Aspirin, dipyridamole or clopidogrel alone or in dual combination.

(b) Anticoagulation with heparin (either unfractionated heparin or a therapeutic dose of low molecular weight heparin) followed by warfarin aiming for an INR in the range 2-3. Local protocols for heparin therapy can be used.

Treatment will be open-label.

Low dose heparin prophylaxis for prevention of DVT is not a contra-indication, but its use should be recorded. Such prophylaxis may be continued after randomisation in the antiplatelet arm at the discretion of the local clinician.

4.3 Pre-clinical data

All drugs used to treat CADISS patients have a known safety profile and are used as part of routine care.

4.4 Clinical data

All drugs used to treat CADISS patients have a known safety profile and are used as part of routine care.

4.5 Study Rationale and risk/benefit analysis

The CADISS Study is a pragmatic trial comparing two regimes: antiplatelet therapy and anticoagulation. Both regimes fall into low risk categories and do not present a higher risk than patients would expect from normal medical care.

4.6 Management of potential study risks

Not applicable to the CADISS Study.

5: Study objectives

5.1 Primary objective

To determine the feasibility of a clinical trial comparing antiplatelet therapy with anticoagulation in the acute treatment of patients with cervical artery dissection. Specifically to address whether:

(c) There are sufficient clinical endpoints to provide the power to determine treatment effect
(d) Adequate numbers of patients can be recruited.

This study will lead to a fully powered definitive treatment trial assuming the results of the feasibility phase indicate this is realistic, and particularly that sufficient end-points occur and adequate recruitment can be achieved.

5.2 Secondary objectives

This is a feasibility study and no secondary endpoints have been defined.

6: Trial design

6.1 Overall design

This will be a randomised prospective multicentre study comparing antiplatelet therapy with anticoagulation for patients with carotid and vertebral dissection. Recruitment must be within seven days of onset of symptoms. Patients should not be precluded from randomisation if they are currently treated with antiplatelet or anticoagulant drugs.

6.2 Dosage regimen and rationale

At randomisation, patients will be randomised to either antiplatelets or anticoagulants. The treatment the patient receives will be at the discretion of the prescribing physician and will reflect the treatment options outlined in protocol section 3.2. This drug treatment will continue until the three month follow-up appointment unless the medication of choice needs to be stopped for safety reasons. Following the three month period the patient should be continued on whatever treatment the prescribing physician feels is best for the patient in question.

6.3 Concomitant treatment

CADISS patients will continue on any concomitant medications at the discretion of the prescribing physician. Information on the use of antiplatelets, anticoagulants, antihypertensive agents, hypoglycaemic agents, cholesterol lowering drugs and any thrombolysis treatment will be captured on the entry form and all subsequent follow-up forms.

6.4 Schematic of trial design

Recruitment

1. Review inclusion/exclusion criteria
2. Give patient the Patient Information Sheet or patient's relative/carer the relative/carer information sheet.
3. Obtain Informed Consent (1 original for CRF; 1 copy for patient notes; 1 copy for patient)

Randomisation

1. Telephone Aberdeen randomisation service:
   0800 387 4444 (*Service requires: 4 digit centre ID code and initials)*
2. PI or Sub-I to complete Entry Form and Drug Prescription Form for pharmacy
3. Insert prescription forms into drug chart
4. Fax consent form, entry form and patient contact information sheet to CADISS Office within 24 – 48h
5. Send GP letter

3 Month Follow-Up

1. PI or Sub-I to complete 3 month Follow-Up Form
2. Download all 3 month follow-up images onto CD and send to CADISS Office.
3. Inform patient that at 6 months and 1 year telephone follow-up will be undertaken by coordinating centre (St. George's.)

SAE/SAR/SUSAR

1. PI or Sub-I to complete SAE Reporting Form within 24 h of being notified of event
2. Refer to SAE Reporting SOP
3. Fax initial SAE Report to CADISS Office.
4. CADISS Office, C.I. and Sponsor review SAE Form to classify as either SAE or SUSAR.
5. Complete Follow-Up report within seven days of reporting initial report.
6. All SAEs and SUSARs will need to be followed up until resolution.

Primary or Secondary Clinical Endpoints

1. PI or Sub-I to complete Major Event Form or Drop Out Form.
2. Provide as much clinical information as possible about the clinical event.
3. Fax form and send images (if applicable) to CADISS Office.

7: Eligibility criteria

7.1 Inclusion criteria

(i) Extra cranial carotid or vertebral artery dissection with symptom onset within the last 7 days

This includes: (a) Ipsilateral TIA or stroke with known date of onset

OR (b) Ipsilateral Horner's syndrome or neck pain with known date of onset

Patients with stroke or TIA within the last 7 days can be entered even if the history of neck pain is > 7 days ago.

Patients with a recurrent event can be entered as long as the event falls within the 7 day timeframe.

and

(ii) Imaging evidence of definite or probable dissection on MRI/MRA, CTA or ultrasound (patients can be initially randomised on ultrasound alone but subsequent MR or CTA confirmation is needed)

7.2 Exclusion criteria

(i) Intracranial cerebral artery dissection

(ii) Symptom onset > 7 days

(iii) Contraindications to either antiplatelet agents or anticoagulation therapy, including active peptic ulceration or bleeding peptic ulcer within 1 year.

(iv) Patient refusal to consent

(v) Patients already taking antiplatelets or anticoagulants for other reasons e.g. prosthetic heart valves in whom the treatment cannot be replaced by either antiplatelets or anticoagulants.

(vi) Women who are pregnant

(vii) Iatrogenic-induced dissection.

8: Subject/Patient Recruitment process

Patient recruitment at a site will only commence once the trial team has ensured that the following approval/essential documents are in place:

1. The main REC, and Clinical Trial Authorization (CTA) approval,
2. Final sponsorship and host site approval,
3. Sponsor has conducted the trial initiation procedure.

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA),
2. Host site (R&D approval)
3. Signed Delegation of Duties and Responsibilities Log.

All subjects who wish to enter the study will be fully screened and consented by the Principle Investigator, or one of the qualified clinicians involved in the study such as Sub-investigator.

9: Study procedures

9.1 Informed consent

Informed consent will be obtained by the Principal Investigator and/or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log. Only those members of the study team who have clinical responsibility for the care of patients under the care of the general medical service will be permitted to undertake informed consent. All individuals taking informed consent will have received training in Good Clinical Practice (GCP).

Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, usually up to 24 hours.

Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group.

Likewise, periods longer than 24 hours will be permitted should the patient request this. The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one field in the TMF). A copy of the consent form will also be given to the patient.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

A witnessed consent form can be used in cases where the patient has understood the study and its relative risks but is unable to provide written consent *i.e.* dysphasia.

In cases where potential participants are deemed incompetent to make a decision during the acute phase following their stroke, advice will be sought from a relative or carer. The relative or carer will be provided with the information sheet for relatives and carers outlining their role and also the requirements of the participant in the study. The relative or carer will be encouraged to ask questions and to discuss the decision with family members, friends and medical professionals. In such cases, the patient's relative or carer may act as the patient's representative and provide assent to the study procedures.

In both cases, the patient will be given the opportunity to discuss and confirm consent or opt out of the study when they are able to independently consent as assessed by the local doctor.

9.2 Randomisation procedure

Randomisation will be via an automated 24 hour randomisation service provided by the University of Aberdeen Health Services Research Unit. The local investigator or delegated person will personally contact this service on 0800 387 4444 along with the trial ID code specific for each centre, known only to the randomisation centre and local investigator. During the call you will also be required to enter the patient's initials. Once this information has been submitted you will receive a randomisation code and a treatment allocation stating either "anticoagulants" or "antiplatelets." Once randomised into the study, all patients will be included in an "intention to treat" analysis.

In the unlikely event of a system failure where you are unable to contact the automated randomisation service you should call the back-up number 01224 554 673 or perform a manual randomisation by flipping a coin. Please assign a treatment arm to each side of the coin and ask an independent person to flip the coin. Please retain accurate records regarding the event. If you perform a manual randomisation please contact the trial coordinator as soon as possible so that the randomisation details can be passed on to the University of Aberdeen who will update the system retrospectively.

9.3 Emergency unblinding

Not applicable to the CADISS Study.

10: Study Assessments

10.1 Screening assessments

When assessing the patient against the eligibility criteria please carry out the following:

- Review patient's medical history to establish the signs and symptoms associated with suspected dissection. Ensure any relevant signs and symptoms have an onset within seven days.
- Arrange for imaging to confirm dissection.
- Once imaging has been performed review imaging with neuroradiologist to confirm that the dissection does not extend intracranially.
- Ensure patients entered into the study do not have a contraindication to either anticoagulants or antiplatelets. If the patient is already taking anticoagulants or antiplatelets review the indication for which the drug is being taken.
- Discuss the likelihood of pregnancy with any female patients.
- Check for the likelihood of an iatrogenic induced dissection.

10.2 Baseline assessments

When a patient has been randomised, please collect the following information:

- Current cholesterol
- Blood pressure
- Modified Rankin on admission

10.3 Treatment procedure

Patients will be randomised to either antiplatelet or anticoagulation therapy initially for at least 3 months, and thereafter at the discretion of the attending physician.

(a) Antiplatelet therapy: Aspirin, dipyridamole or clopidogrel alone or in dual combination.

(b) Anticoagulation with heparin (either unfractionated heparin or a therapeutic dose of low molecular weight heparin) followed by warfarin aiming for an INR in the range 2-3.

The dose and frequency of IMP should reflect local policy and NICE guidelines.

10.4 Subsequent assessments

This section is not applicable to the CADISS Study.

10.4.1 Follow up assessments

Patients will be seen for follow-up at 3 months post randomisation. Data on outcome and occurrence of recurrent stroke and TIA will be recorded. Repeat imaging with MRA, CTA or intra-arterial angiography should be performed at follow-up to assess vessel recanalisation whenever possible.

In addition, patients will be contacted via telephone at 6 months and 1 year post-randomisation by the central study co-ordinating office at St George's University of London.

To help prevent the loss of participants to follow-up and accurately measure study outcomes, the NHS Information Centre Medical Research Information Service will carry out long-term follow up of study participants. This will include providing relevant information to the Chief Investigator when the following occur during follow up:

- A participant dies
- A participants Primary Care Trust (PCT) changes

Where contact with a subject has been lost and a notification of PCT change has been received, the Chief Investigator will contact the PCT to request details of the participants new General Practitioner (GP). Subsequently the Chief Investigator will then contact the identified GP to request the contact details of the participant or that his contact details are passed onto the participant.

10.5 Summary flow chart of study assessments

Study Procedures	Screening	Following Randomisation: Treatment Initiation	Follow up (*3 mnths*)	Follow up (*6 mnths*)	Follow up (*12 mnths*)
Informed consent	X				
Inclusion/exclusion criteria	X				
Medical history	X				
Demographies	X				
Baseline	X				
Screening	X				
Biochemistry	X Cholesterol Only				
Imaging: MRI dissection views, MRA. CTA, or intra-arterial angiography	X		X		
Telephone call				X	X
Dispensing/Administration of IMP		X			
Concomitant Medication	X		X	X	X

10.6 Methods

10.6.1 Laboratory procedures

Please obtain a cholesterol reading as part of the screening process and document on entry CRF.

10.6.2 Imaging Requirements for study entry

The diagnosis of dissection is based on different modalities in different centres. Centres should use their usual imaging protocol to diagnose dissection. Diagnoses on the basis of MRI with cross-sectional imaging through the artery wall, MRA, CT angiography or intra-arterial angiography are all acceptable. Randomisation on the basis of ultrasound imaging alone is allowable, but in such cases confirmatory imaging by MRI, MRA, CTA or intra-arterial angiography must be performed after study entry.

Patients can be randomised if the local stroke/neurology team agrees that the diagnosis is probable or definite based on clinical features and imaging as above. Hard copies of imaging must be recorded for central reading. The primary analysis will include only those patients judged to have probable or definite dissection on central reading of MRI, MRA, CTA or intra-arterial angiography hard copies by the study neuroradiologist.

MRI, MRA, CTA or intra-arterial angiography should be performed at 3 months to assess vessel recanalisation. These images will also be reviewed centrally.

10.6.3 Transcranial Doppler (TCD) Sub-Study

Centres that have the appropriate equipment can also perform TCD recordings on patients recruited to CADISS in order to ascertain whether treatment with anticoagulation, or with antiplatelet therapy, is more effective at reducing asymptomatic embolisation. For patients recruited to CADISS who also consent to the TCD sub-study the following additional investigations will be performed.

Transcranial Doppler recordings for embolic signals will be performed from the ipsilateral middle cerebral artery (MCA; for carotid dissection) and from the ipsilateral posterior cerebral artery (PCA; for vertebral dissection) for a period of one hour immediately after randomisation but prior to commencement of study treatment. Recordings will be repeated on day 7 (at the same time of day as the initial recording +/- two hours). The MCA and PCA should be identified via the transtemporal window, and the transducer fixed in position using a headset.

All recordings will be made onto digital audio tape or other suitable digital media. Recordings will then be analysed at St George's for the presence of embolic signals by an experienced investigator. Standard criteria will be used to identify embolic signals[(4)]. Embolic signals ≥7dB will be identified as these have been shown to associate with increased risk of recurrent stroke in previous studies.

Single channel transcranial Doppler recordings will be performed. Transcranial Doppler equipment can only be used if the output can be analysed by the central reading station at St George's. Suitable equipment includes the following:

1. Nicolet/EME Pioneer TCD systems with analogue signal being recorded onto digital audio tape.
2. DWL systems with analogue output being recorded onto digital audio tape.
3. Digital Nicolet/EME systems with digital output being recorded onto CD.

Digital systems other than the EME system cannot be used as the data cannot be read centrally. Analogue systems other than DWL and TCD should not be used until similarity of the Doppler to the systems being used in the study have been determined.

Patients will be treated as their own control and the primary endpoint will be the reduction in embolic signals. Secondary endpoint will be the abolition of embolic signals (i.e. a negative recording).

10.7 Definition of the End of Trial

The trial end will be when the last CADISS patient (number 250) has had their last visit.

10.8 Discontinuation/withdrawal of participants and stopping rules

10.8.1 Withdrawal procedure, treatment suspension and 'stopping rule(s)'

Patients will only be withdrawn from the study if consent is withdrawn. In this circumstance no follow-up data will be collected.

If a patient is randomised and later imaging shows that there is no dissection, the patient should still have all follow-up visits and calls as this is an intention to treat study.

11: IMPs and non-IMPs used in the trial

11.1 Name and description of each IMP

The CADISS Study is comparing two well known therapies: antiplatelet treatment and anticoagulation. The drugs used will include:

(a) Antiplatelet IMPs: Aspirin, dipyridamole or clopidogrel alone or in dual combination.

(b) Anticoagulation IMPS: Heparin (either unfractionated heparin or a therapeutic dose of low molecular weight heparin namely dalteparin, enoxparin and tinzaparin) followed by warfarin aiming for an INR in the range 2-3.

11.2 Source of IMPs including placebo

All IMPs will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy'.

11.3 Accountability procedures for the IMP(s)

IMP labelling will not be applied to any antiplatelet or anticoagulant as their use falls under the remit of Regulation 46(2) of the Medicines for Human Use (Clinical Trials) Regulations, for the following reasons:

1) The IMPs are marketed products, used broadly within their authorisations (Ischemic stroke and TIA.)

2) The IMPs will be dispensed to subjects in accordance with a prescription given by an authorised health care professional.

3) The IMPs will be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 that apply in relation to dispensed relevant medicinal products.

A member of the study team should always try, where possible, to document the batch number of the medication given to any CADISS patient. This is to allow transparency when SUSARs are reported to the CADISS coordinating centres.

11.4 Route of administration, dosage, dosage regimen, and treatment period(s) of the IMPs

The dose and frequency of IMP should reflect local policy and NICE guidelines.

CADISS patients should be given IMP from the time of randomisation until their three month follow-up appointment. After this time, the treatment choice is at the discretion of the prescribing physician and the patient should begin taking non-IMP.

11.5 Dosage modifications

Any dose modifications (for example in the case of an SAE) are at the discretion of the prescribing physician. Any modifications should be documented in the patient's medical notes.

11.6 Assessment of compliance

Compliance will not be assessed as part of the CADISS Trial.

11.7 Post-trial IMP arrangements

Following study completion, all patient prescriptions will be at the discretion of the usual care provider.

11.8 Name and description of each non-IMP (NIMP)

There will be no NIMPs in this trial. Concomitant medication or therapy will be allowed.

Subjects may continue with any medication as prescribed by their own General Practitioner (GP); (see exclusion criteria) and these prescribed drugs will be recorded as part of their medical history. GP's will be informed about subject's trial participation with a GP letter.

The administration of all concomitant medication must be recorded in the appropriate sections of the Case Report Form (CRF).

12: Pharmacovigilance

12.1 Definitions

Adverse Event (AE)—any untoward medical occurrence in a patient or clinical trial subject who is administered an IMP and which does not necessarily have a causal relationship with this treatment. (i.e. any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom an IMP has been administered, including occurrences unrelated to that product)

Adverse Reaction (AR)—any untoward and unintended responses to an IMP related to any dose administered. (i.e. any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom an IMP has been administered and related to any dose administered)

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)—any Adverse Event or Reaction in a trial subject that:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the IMP regardless of time of diagnosis).

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR)—an Adverse Reaction which is classed in nature as both serious and unexpected.

An Unexpected Adverse Reaction is an Adverse Reaction, when both the nature and severity of the event is not consistent with the information about the medicinal product in question, as set out below:

(a) in the case of a product with a marketing authorization, in the Summary of Product Characteristics (SmPC) for that product,
(b) in the case of any other IMP, in the Investigator's Brochure relating to the trial in question.

12.2 Recording Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes. This information will not be collected centrally as CADISS is a Phase IV trial of licensed medications with well established safety profiles and all drugs are being used within their licensed dose and indication.

12.3 Procedures for recording and reporting SAEs

For the purposes of the CADISS Study we will only be collecting information on the following:

- **SAEs of interest:** TIA, Stroke, any major bleeding, presence of residual stenosis at 3 months (>50%) and any patient deaths.

- **Any SUSAR.** Please ensure you refer to the IMP reference documents including the SmPC used locally and the BNF website (www.bnf.orh.uk) to assess the expectedness of the SAE in relation to the IMP.

The following descriptions will be used to record SAEs:

Clinical symptoms—a simple and brief description.

Severity will be described using the following categories:

Mild—the adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort.
Moderate—the adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.
Severe—the adverse event results in alteration, discomfort or disability which is clearly damaging to health.

Relationship to treatment—the assessment of relationship of AEs to the administration of IMP is a clinical decision based on all available information at the time of the completion of the CRF. The following categories will be used:

Definitely—there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably—there is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Possibly—there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (i.e. the patient's clinical condition, other concomitant events).
Unlikely—there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related—there is no evidence of any causal relationship.
Not Assessable

Expectedness will be described using following categories:

Expected—an AE that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC) **or clearly defined in this protocol.**

Unexpected—an AE that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC).

All SAEs will be recorded in the hospital notes and the CRF, and the Sponsor's SAE Recording Log. The SAE Log will be sent to Sponsor on request and every 2 months.

- All SAEs, SARs and SUSARs should be recorded on the SAE reporting form. Within **24 hours** of learning of a **SAE, SAE or SUSAR**, it should be reported to the CADISS Trial Office using the following fax number: **0208 725 2950** or email address: **cadiss@sgul.ac.uk**.

- All SAEs will be reported to the Sponsor via the JRO on an SAE form unless otherwise stated in the protocol. The Chief or Principal Investigator will complete the Sponsor's SAE form and the form will be faxed to the JRO on 020 8725 0794 or E-mailed to adversevents@sgul.ac.uk, within 24hrs of the Investigator becoming aware of the event.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

All SUSARs will be notified to the Sponsor immediately or at least within 24hrs of the Investigator becoming aware of the event.

12.4 Notification of deaths

Any patient deaths should be recorded on the CADISS SAE reporting form and the patient event form and reported to the CADISS Trial Office using the fax number: **0208 725 2950** or the email address: **cadiss@sgul.ac.uk** within 24 hours.

All deaths will be reported to the Sponsor via the JRO on an SAE form.

12.5 The type and duration of the follow-up of subjects after AEs

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution. He/She must immediately inform the CADISS Trial Office of any secondary worsening, who will then inform Sponsor. Any changes in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported by following the procedure previously mentioned.

Any trial subjects suffering from an adverse drug reaction should be followed up every two weeks until the SAE is resolved and the follow-up should be clearly documented in the patient's medical notes.

Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

12.6 Annual Safety Reports (ASRs)

The CI or a delegated PI will prepare the ASR, using the Sponsor's ASR template and in accordance with the Sponsor's ASR SOP. It will be reviewed by the Sponsor and when necessary be referred to an independent committee (i.e. Research Governance Safety Committee). The JRO will provide the main REC and the MHRA with an ASR.

12.7 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR. It will be reviewed by the JRO and sent to the main REC within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, and annually until the trial is declared ended.

12.8 Pregnancy

Any pregnancies in clinical trial subjects should be reported to the CADISS coordinating centre as soon as possible. Pregnancies should be reported using the CADISS pregnancy reporting form.

12.9 Reporting Urgent Safety Measures

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 states "the Sponsor and the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. If measures are taken, the Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures."

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore the CI/PI must report any urgent safety measures to the MHRA directly, and in parallel to the Sponsor.

Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

12.10 Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations, Potential Serious Breaches and Urgent Safety Measures will be recorded using the Sponsor's Log issued during the Sponsor's Trial/Site Initiation meeting/visit.

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol:

(1) The Sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(a) The conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The Sponsor's SOP on the Protocol Violation/Deviations and Serious Breaches will be followed.

13: Data management and quality assurance

13.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, Date of Birth (DOB) and trial Identification Number (ID), will be used for identification.

13.2 Data collection tool

Case Report Forms will be designed by the CI and the final version will be approved by the Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database.

All data will be recorded in the patient's medical notes in the first instance and then transcribed into the CRF. The patient's medical notes will then act as source data and the clinical trials monitor will perform site visits to verify the data recorded in the CRFs.

13.3 Data handling and analysis

All data will be entered into a central, password protected Filemaker Database. This information will be audited by independent persons to ensure all data fields have been completed and that information from the paper CRFs has been accurately transcribed into the Filemaker system. The Filemaker system automatically saves all data that is entered and the St. George's IT department perform a back up of all files once a day.

Data entry is performed by the CADISS clinical trials coordinator. Data analysis is performed by the studies statistician, Sally Kerry.

14: Archiving arrangements

The trial documents (including the Trial Master File (TMF), Case Report Forms (CRFs), Informed Consent Forms along with the trial database) will be kept for a minimum of five years. They will be stored in locked offices within the St George's, University of London site. The Chief Investigator is responsible for the secure archiving of trial document. The trial database will also be kept electronically on the St George's, University of London computer network, for a minimum of five years.

15: Statistical design

15.1 Statistical input in trial design

The data will be analysed by intention to treat using standard statistical tests by the trial statistician. The analyses will compare the treatment groups with respect to the length of time before treatment failure (i.e. occurrence of an outcome event) by means of the Mantel-Haenszel chi-squared test and Kaplan-Meier survival curves. Subgroup analyses will examine risk factors for major outcome events.

15.2 Endpoints

15.2.1 Primary endpoints

Ipsilateral stroke or death (any cause) within 3 months from randomisation

15.2.2 Secondary endpoints

(a) Ipsilateral TIA (including amaurosis fugax), stroke or death (any cause) within 3 months from randomisation

(b) Ipsilateral stroke or death or major bleeding

(c) Any stroke or death

(d) Any stroke or death or major bleeding

(e) Any stroke

(f) Any TIA (including amaurosis fugax) and stroke

(g) Major bleeding

(h) Presence of residual stenosis at 3 months (>50%).

(i) Mortality

Major bleeding will be defined using the International Society on Thrombosis and Haemostasis definition[5] as:

1. Fatal bleeding and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin level of 1.24mmol/L or more, or leading to transfusion of two or more units of whole blood or red cells.

An adjudication committee will assess all primary end points (stroke) and secondary end points.

15.3 Sample size and recruitment

15.3.1 Sample size calculation

It has been estimated that a definitive trial of antiplatelet agents versus anticoagulants would require a total sample size of the order of 2000. The feasibility phase of CADISS will enter 250 patients after which a decision will be taken whether to continue recruitment into a definitive trial with the endpoint of stroke and death, continue the feasibility phase, or stop the study. The information from the feasibility phase, particularly the proportion of patients suffering endpoints during the three month follow-up period will be crucial in determining accurate sample size calculations for a definitive study.

15.3.2 Planned recruitment rate

This is a feasibility study with one of the primary objectives being to look at the recruitment rate of patients. Dissection is a rare indication so it is important to ascertain how likely it is that we will be able to recruit a sufficient number of patients to answer the studies objective.

15.4 Randomisation

Patients will be randomised using a simple randomisation strategy whereby patients will be assigned to one of two groups in a one to one ratio: anticoagulants and antiplatelets.

15.5 Interim analysis

The results of any interim data analysis will remain confidential to the trial statistician and Data Monitoring Committee until after completion or early discontinuation of the trial. Investigators and the Steering Committee will remain blind until such point.

16: Trial Management and Committees in involved in the trial

The study will be co-ordinated on behalf of the collaborators from the CADISS Trial Office based in Clinical Neuroscience at St Georges, University of London. The office will be responsible for protocol design, data collection and management, and analysis of the results in consultation with the Steering and Data Monitoring Committees, but will consult with the investigators regularly via a regular newsletter, the trial website, and meetings. The principal investigator is Professor Hugh Markus. The principal neuroradiological investigator, responsible for assessment of hard copies of imaging, is Dr Andrew Clifton. The relevant committee membership is shown in the appendix.

Trial Steering Committee (TSC) members:

Hugh S Markus, St George's University of London (Chief Investigator)
John W Norris, St George's University of London, London
Peter M Rothwell, University of Oxford
Graham S Venables, Royal Hallamshire Hospital, Sheffield
Sally Kerry, St George's, London (Trial Statistician)

Data Safety Monitoring Committee (DMC)
Gary A Ford, University of Newcastle (Chair)
Philip M W Bath, University of Nottingham
Chris Weir, University of Glasgow

Adjudication Committee
Prof Lalit Kalra, Stroke Physician, Kings College London (chair)
Dr Denis Briley, Neurologist, Stoke Mandeville Hospital
Dr Andrew Clifton, Neuroradiologist, St George's NHS Healthcare Trust, London
Dr David Bevan, Consultant Haematologist, St George's University of London, London

Study neuroradiologist: Dr Andrew Clifton, St George's NHS Heathcare Trust, London
Trial co-ordinator: Cara Hicks, St George's University of London

17: Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

18: Ethics and regulatory requirements

The Sponsor will ensure that the trial protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the MHRA and a main Research Ethics Committee (REC), prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before site(s) can enrol patients into the trial, the Principal Investigator must apply for Site Specific Assessment from the Trust Research & Development (R&D) and be granted written NHS R&D approval. It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 12 for details of reporting procedures/requirements).

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply a summary report of the clinical trial to the MHRA and main REC within one year after the end of the trial.

19: Monitoring plan for the trial

The trial will be monitored according to the monitoring plan agreed and written by the Sponsor, based on the internal risk assessment procedure. All CADISS monitoring visits will be conducted by the CADISS clinical trials coordinator. It is the responsibility of the JRO to determine the monitoring risk assessment and explain the rationale.

The PI at each site will also be required to complete this self-monitoring template and return the form at the same frequency, to the JRO in parallel for review. It is the JRO's responsibility to ensure that any findings identified in a PI's monitoring report are actioned in a timely manner and any violations of GCP or the protocol reported to the JRO immediately.

Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

The CI will be provided with a copy of the study monitoring report during the Trial Initiation monitoring visit.

20: Finance

The feasibility phase of CADISS has been funded by the Stroke Association of the UK.

21: Insurance and indemnity

St George's University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that St George's has been negligent. This clinical trial is conducted in hospital and the hospital continues to have a duty of care to the participant of the clinical trial. St George's University of London will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees regardless of the hospital being NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of St George's University of London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to St George's University of London, upon request.

22: Publication policy

The results of CADISS, whatever the outcome, will be published in a peer reviewed journal. The primary publication of the results will be prepared by the Central Office and Steering Committee and circulated to participating centres for comment prior to submission of the manuscript for publication on behalf of all the CADISS collaborators. The Data Monitoring Committee (DMC) will review the primary paper prior to submission.

Data ownership rights will lie with the institution.

23: Statement of compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards and UK Clinical Trials Regulation. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

24: References

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3. Biousse V, D'Anglejan-Chatillon J, Touboul PJ, Amarenco P, Bousser MG. Timecourse of Symptoms in Extracranial Carotid Artery Dissections. A Series of 80 patients. Stroke 1995; 26:235-9

4. Ringelstein, E.B., Droste, D.W., Babikian, V.L., Evans, D.H., Grosset, D.G., Kaps, M., Markus, H.S., Russell, D., Siebler, M. Consensus on Microembolus Detection by TCD. *Stroke.* 1998;29:725-729

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