

STUDY PROTOCOL

Open Access



# The REstart or STop Antithrombotics Randomised Trial (RESTART) after stroke due to intracerebral haemorrhage: study protocol for a randomised controlled trial

Rustam Al-Shahi Salman<sup>1\*</sup>, Martin S. Dennis<sup>1</sup>, Gordon D. Murray<sup>2</sup>, Karen Innes<sup>1</sup>, Jonathan Drever<sup>1</sup>, Lynn Dinsmore<sup>1</sup>, Carol Williams<sup>1</sup>, Philip M. White<sup>3</sup>, William N. Whiteley<sup>1</sup>, Peter A. G. Sandercock<sup>1</sup>, Cathie L. M. Sudlow<sup>1</sup>, David E. Newby<sup>4</sup>, Nikola Sprigg<sup>5</sup>, David J. Werring<sup>6</sup> and the RESTART collaborators

## Abstract

**Background:** For adults surviving stroke due to spontaneous (non-traumatic) intracerebral haemorrhage (ICH) who had taken an antithrombotic (i.e. anticoagulant or antiplatelet) drug for the prevention of vaso-occlusive disease before the ICH, it is unclear whether starting antiplatelet drugs results in an increase in the risk of recurrent ICH or a beneficial net reduction of all serious vascular events compared to avoiding antiplatelet drugs.

**Methods/design:** The REstart or STop Antithrombotics Randomised Trial (RESTART) is an investigator-led, randomised, open, assessor-blind, parallel-group, randomised trial comparing starting versus avoiding antiplatelet drugs for adults surviving antithrombotic-associated ICH at 122 hospital sites in the United Kingdom. RESTART uses a central, web-based randomisation system using a minimisation algorithm, with 1:1 treatment allocation to which central research staff are masked. Central follow-up includes annual postal or telephone questionnaires to participants and their general (family) practitioners, with local provision of information about adverse events and outcome events. The primary outcome is recurrent symptomatic ICH. The secondary outcomes are: symptomatic haemorrhagic events; symptomatic vaso-occlusive events; symptomatic stroke of uncertain type; other fatal events; modified Rankin Scale score; adherence to antiplatelet drug(s). The magnetic resonance imaging (MRI) sub-study involves the conduct of brain MRI according to a standardised imaging protocol before randomisation to investigate heterogeneity of treatment effect according to the presence of brain microbleeds. Recruitment began on 22 May 2013. The target sample size is at least 720 participants in the main trial (at least 550 in the MRI sub-study).

**Discussion:** Final results of RESTART will be analysed and disseminated in 2019.

**Trial registration:** ISRCTN71907627 ([www.isrctn.com/ISRCTN71907627](http://www.isrctn.com/ISRCTN71907627)). Prospectively registered on 25 April 2013.

**Keywords:** Secondary prevention, Antiplatelet therapy, Stroke, Intracerebral haemorrhage, Randomised controlled trial

\* Correspondence: [Rustam.Al-Shahi@ed.ac.uk](mailto:Rustam.Al-Shahi@ed.ac.uk)

<sup>1</sup>Centre for Clinical Brain Sciences, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK  
Full list of author information is available at the end of the article

## Background

Patients with stroke due to spontaneous intracerebral haemorrhage (ICH) often have past histories of systemic arterial hypertension, smoking, and diabetes mellitus. These risk factors also contribute to the occurrence of other conditions before ICH, such as ischaemic stroke, coronary artery disease, and atrial fibrillation. These risk factors and diseases may also cause vaso-occlusive events after ICH, which – overall – appear to occur with a similar frequency to recurrent ICH [1].

Among individuals at high risk because of a prior vaso-occlusive event, aspirin provides statistically and clinically significant absolute reductions in all serious vascular events from 8.2% to 6.7% per year, in all stroke from 2.5% to 2.1% per year, and in coronary events from 5.3% to 4.3% per year, despite a non-significant increase in the risk of intracranial haemorrhage [2]. Antiplatelet drugs also seem to be beneficial for preventing vaso-occlusive events in patients with atrial fibrillation and no past history of vaso-occlusive events, without a detectable increase in the risk of extracranial or intracranial haemorrhage [3]. However, patients with spontaneous ICH were not included in the randomised controlled trials (RCTs) contributing to these analyses [2, 3], but it is likely that the benefits of secondary prevention with antiplatelet drugs would apply after ICH (although whether they are outweighed by the risk of recurrent ICH is unknown).

There are no published RCTs comparing the effects of starting versus avoiding antiplatelet drugs for the prevention of vaso-occlusive disease in adults after ICH [4]. Four small, non-randomised observational studies have not identified consistently beneficial or harmful outcomes associated with starting or avoiding antiplatelet drugs after ICH [5–8]: one study found that aspirin was associated with a beneficial reduction in the composite endpoint of recurrent ICH, ischaemic stroke or acute coronary syndrome during follow-up in the sub-group of patients with ICH and indications for aspirin [6], whilst another study of 104 survivors of lobar ICH found an increase in the subsequent risk of recurrent ICH associated with aspirin in multivariable analyses [5].

Because the benefits of antiplatelet drugs for the prevention of vaso-occlusive disease are likely to continue to apply after ICH and because the effect of antiplatelet drugs on the risk of recurrent ICH is unknown, it is reasonable to consider starting antiplatelet drugs. However, because the published observational studies have not provided evidence of a substantial increase in the risk of recurrent ICH with antiplatelet drugs in such patients, a RCT is needed to assess the balance of benefits and harms. A similarly designed RCT has proven feasible and acceptable for patients who had been taking low-dose aspirin before peptic ulcer bleeding [9].

Therefore, our aim is to conduct a RCT to determine whether antiplatelet drugs increase the risk of recurrent symptomatic ICH to an extent that might outweigh any beneficial reduction in vaso-occlusive disease. The results of this RCT may indicate whether a subsequent large-scale RCT is needed to determine whether the gains from prevention of vaso-occlusive disease with antiplatelet drugs outweigh the risks of intracranial and extracranial haemorrhage, and hence whether there is net benefit for patients after ICH associated with anti-thrombotic drug use. Here, we report the final version of the trial protocol, compliant with the SPIRIT reporting guideline (Additional file 1).

## Methods/design

### Study setting

At the time of writing, RESTART collaborators are based at 122 hospital sites in the National Health Service in the United Kingdom (see the ‘Acknowledgements’ section below for a list of these sites and collaborators). In view of slow recruitment [10], we conducted the Promoting Recruitment using Information Management Efficiently (PRIME) stepped-wedge, cluster randomised study within a trial (SWAT) at 72 sites to determine whether a complex intervention could boost recruitment [11, 12]. One hundred and four sites are recruiting participants to the sub-study, which involves the conduct of brain magnetic resonance imaging (MRI) before randomisation according to the MRI sequences and parameters specified by an imaging protocol ([www.restarttrial.org/documents/RESTART\\_MRI\\_protocol.pdf](http://www.restarttrial.org/documents/RESTART_MRI_protocol.pdf)).

### Eligibility criteria

Inclusion criteria: patient aged 18 years or older; spontaneous ICH not attributable to preceding head injury and either ‘secondary’ to an underlying structural cause (e.g. aneurysm, tumour, arteriovenous malformation, or intracranial venous thrombosis), or ‘primary’ (if the investigator either does not suspect an underlying structural cause, or it is not detected by further radiographic investigation); patient had taken an antithrombotic (i.e. anticoagulant or antiplatelet) drug for the prevention of vaso-occlusive disease for any length of time before the onset of the qualifying ICH; patient is at least 24 h after ICH symptom onset; patient and their physician are both uncertain about whether to start or avoid antiplatelet drugs; patient is registered with a general (family) practitioner (GP); brain imaging study that first diagnosed the qualifying ICH is available; consent to randomisation; if eligible for the brain MRI sub-study, the MRI must be performed after the ICH but before randomisation. Exclusion criteria: ICH due to head injury or haemorrhagic transformation of an ischaemic stroke,

in the opinion of the investigator; patient is taking an anticoagulant drug following ICH; patient is pregnant, breastfeeding, or of childbearing age and not taking contraception; patient and carer unable to understand spoken or written English (local translator is not available); patients are ineligible for the brain MRI sub-study if they are claustrophobic or they have a contraindication to MRI.

### Interventions

RESTART randomises participants to policies of starting or avoiding antiplatelet drugs. The intervention is restricted to the use of one or more of aspirin, dipyridamole (to which prior ICH is not a contraindication in the Summary of Product Characteristics (SPC)) or clopidogrel (to which only 'active pathological bleeding' (judged to occur within the first 24 h of ICH symptom onset) is a contraindication). The specific antiplatelet drug(s) and their doses are determined at the discretion of the consultant responsible for the participant and should be prescribed to start within 24 h of randomisation. The comparator is a policy of avoiding antiplatelet drugs; there is no placebo. Participants may discontinue antiplatelet drugs (e.g. if a bleeding outcome event occurs) or if the prescription of a contraindicated medication is required in a participant taking antiplatelet drugs (e.g. if a vaso-occlusive outcome event occurs which requires treatment with an anticoagulant). To increase the likelihood that participants will receive antiplatelet drugs if allocated to a policy of starting them, RESTART: encourages the randomising clinician to emphasise the importance of adhering to the allocated treatment policy; writes to the GP shortly after enrolment to alert them to the participant's inclusion and treatment allocation in the trial; writes to the participant at home (when the hospital/clinic discharge form is received) reminding them of the purpose of RESTART and the importance of adhering to their treatment allocation. RESTART monitors adherence in all participants regardless of treatment allocation by recording antiplatelet and anticoagulant use: after randomisation on the discharge form; on annual participant questionnaires; on annual GP questionnaires; and from *ad hoc* reports by participants or their carers to the trial coordinating centre.

### Outcomes

RESTART uses multiple sources of ascertainment to detect outcome events, including: the hospital/clinic discharge form after randomisation; annual participant questionnaires; annual GP questionnaires; *ad hoc* reports from participants, carers, and GPs.

Primary outcome:

- Fatal or non-fatal radiographically or pathologically proven, recurrent, symptomatic ICH (defined as the abrupt onset of headache, altered level of consciousness, or focal neurological deficit, anatomically referable to a focal collection of blood predominantly located within the brain parenchyma (diagnosed on brain imaging or at autopsy), which was not attributable to prior trauma or haemorrhagic transformation of an ischaemic stroke)

Secondary outcomes:

- Fatal (i.e. followed by death within 30 days) or non-fatal (i.e. not followed by death within 30 days) serious vascular events:
  - Symptomatic haemorrhagic events
    - Symptomatic spontaneous or traumatic extradural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, or intraventricular haemorrhage (not accompanying spontaneous ICH)
    - Symptomatic major extracranial haemorrhage, sub-divided by site (requiring transfusion or endoscopic treatment or surgery, or resulting in death within 30 days)
  - Symptomatic vaso-occlusive events
    - transient ischaemic attack
    - ischaemic stroke
    - acute coronary syndrome
    - peripheral arterial occlusion
    - mesenteric ischaemia
    - retinal arterial occlusion
    - deep vein thrombosis
    - pulmonary embolism
    - revascularisation procedures (carotid, coronary, or peripheral arterial)
    - cardiac death with symptoms suggestive of myocardial ischaemia (type 3), or evidence of arrhythmia
  - Symptomatic stroke of uncertain sub-type
    - Non-fatal stroke, with brain imaging performed too late to distinguish ICH from cerebral infarction
    - Rapidly fatal stroke, but without radiographic or pathological confirmation
- Other fatal events
- Annual ratings of participant function completed by participant or their carer:
  - Simplified modified Rankin Scale postal questionnaire [13, 14]
  - Structured telephone interview with non-responders to the postal questionnaire [15]

**Participant timeline**

Figures 1 and 2 illustrate the schedule of enrolment, randomisation, treatment allocation, and assessments for participants.

**Co-enrolment**

Inclusion in another research study, including another RCT but not including a phase I or first-time-into-human study, does not preclude participation in RESTART as long as: participants are not overburdened; their inclusion would not confound RESTART’s results or complicate attribution of serious adverse events and outcomes; and co-enrolment has been agreed with the chief investigators of all studies involved in co-enrolment. Participants in TICH2 ([www.tich-2.org](http://www.tich-2.org), ISRCTN93732214) may be co-enrolled in RESTART if at least 21 days have elapsed after enrolment in TICH2 and the terms of the co-enrolment agreement are upheld [16].

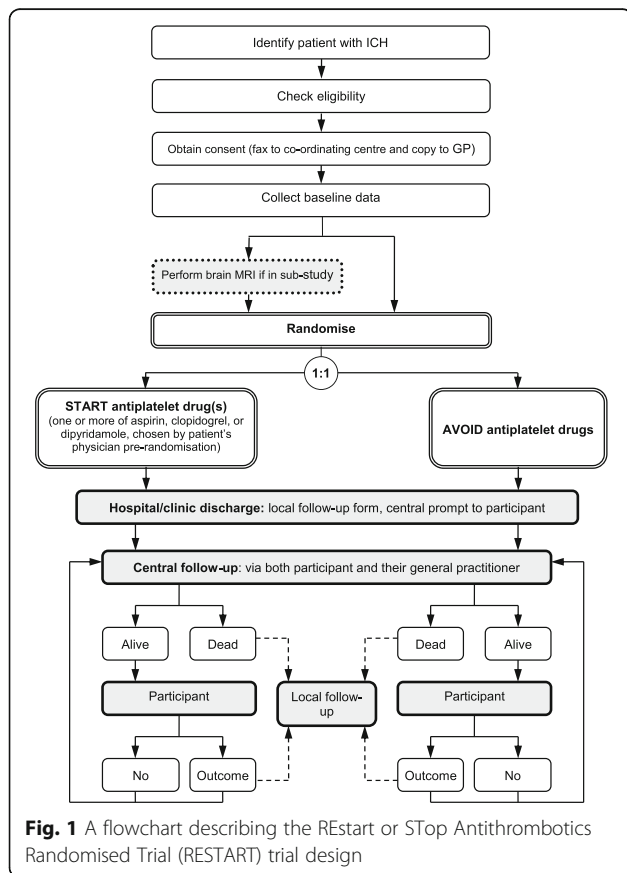
**Sample size**

There is considerable uncertainty about the absolute risks of recurrent symptomatic ICH among survivors who were taking antiplatelet drugs at the time their index event, but a review of the academic literature suggests that the event rate lies in the range of about 1.8 to

7.4% per year [1]. Similarly, information about the relative increase in the risk of recurrent ICH on antiplatelet drugs is scarce, but estimated relative risks from non-randomised studies have ranged from no excess (relative risk (RR) = 1) to a four-fold excess (RR = 4) [5–7]. This study of 720 patients will have excellent power (after all participants have been followed for at least 2 years) to detect a doubling of the rate of ICH if the true rate is 4.5% per annum [2, 5, 7, 17], but there would be 93% power at the 5% significance level to detect a four-fold increase in risk of recurrent ICH if the annual risk is only 1%. In both these scenarios the absolute excess risk of recurrent ICH may be higher than any plausible benefit of treatment, in which case it may be inappropriate to consider a larger trial designed to demonstrate net benefit. The Trial Steering Committee will review the target sample size and adjust this based on accruing data on: the number of primary outcome events, completeness of follow-up, and the enrolment into specific pre-specified sub-groups (e.g. lobar ICH location). Contraindications to MRI, claustrophobia, non-attendances, and scheduling constraints preclude MRI in approximately 25% of patients, so we hope to obtain brain MRI on approximately 550 patients before randomisation.

**Recruitment and retention**

Potentially eligible patients are identified in the everyday clinical practice of research staff, or referred to them for assessment of eligibility having been identified elsewhere (e.g. by clinical staff who are not research staff in secondary or primary care). Collaborators screen new admissions to stroke services and may identify patients looked after by their stroke service for ICH in the past using data extracts from stroke audits that were developed for the PRIME SWAT (e.g. <https://www.strokeaudit.org/Research/Data-requests/Accepted-aggregate-data-requests.aspx>) [11], or their stroke service’s database. Collaborators identify patients at least 24 h after ICH symptom onset and at a time when uncertainty arises about whether to avoid or start antiplatelet drugs. There is no specific time window for identifying participants, so they may be recruited during their hospital admission for the qualifying ICH or at a later stage in an outpatient clinic. The principal investigator or physician with delegated responsibility is responsible for confirming eligibility, ensuring informed consent is obtained and that the informed consent form is completed, signed and dated by all parties and faxed to the RESTART trial office before randomisation. Local research staff follow the laws that govern consent procedures in their jurisdiction, in particular those governing incapacitated adults: if a patient lacks capacity to consent for themselves then a personal/legal/professional representative may provide consent on the patient’s behalf. Consent must also be provided explicitly if the participant is to undergo



Assessment	Baseline				Follow-up
	Recruit	Randomise	Hospital / clinic discharge	30 days	Annually
<b>Local</b>					
Confirm eligibility	•				
Verify brain imaging that diagnosed qualifying ICH is available	•				
Give PIL to patient and/or carer	•				
Obtain consent	•				
Collect baseline data	•				
Book and obtain MRI prior to randomisation date (if in MRI sub-study)	•				
Fax consent form to trial co-ordinating centre	•				
Randomise		•			
Record study number and allocation		•			
Complete enrolment sticker in notes		•			
Prescribe antiplatelet drugs (if allocated to starting) and inform GP		-----			
Send brain imaging that diagnosed qualifying ICH to the trial co-ordinating centre		•			
Send MRI to trial co-ordinating centre (if in MRI sub-study)		•			
Complete discharge form ASAP after death in hospital or discharge			•		
Adverse events			•		
All medications			•		
Adherence			•		
Updated contact details			•		
Clinical information & imaging for outcomes			•		•
<b>Central</b>					
Email notification of treatment allocation to hospital	•				
Write to GP about participation, treatment allocation, & BP control	•				
Prompt to participants about treatment allocation (on receipt of discharge form)			•		
Confirm receipt of brain imaging ± MRI				•	
Confirm receipt of discharge form				•	
GP postal questionnaire ± reminder					•
Outcome events					•
Latest BP measurement					•
All medications					•
Patient postal questionnaire ± reminder					•
Outcome events					•
Modified Rankin Scale structured questions					•
Adherence					•

**Fig. 2** Schedule of enrolment, interventions, and assessments

brain MRI specifically for RESTART. Annual follow-up is coordinated by the trial coordinating centre, and begins with a postal questionnaire to each participant's GP (followed by a telephone reminder if required) to establish each participant's vital status, the occurrence of primary and secondary outcome events, hospital admissions, a recent blood pressure (BP) measurement, a list of current medications (specifically enquiring about antithrombotic and antihypertensive drugs), and up-to-date contact details for the participant. If the participant is still alive and appropriate for questionnaire follow-up, the participant will be sent a postal questionnaire (followed by a telephone reminder if required) to establish the occurrence of primary and secondary outcome events, hospital admissions, antiplatelet drug use, and their current modified Rankin Scale score [13–15]. If the participant does not have capacity or cannot speak English, their carer will be asked to complete and return the forms. If the follow-up information cannot

be obtained by either postal or telephone questionnaire the local research team is asked to assist. The chief investigator (RA-SS) makes the final attempt to obtain missing GP/participant follow-up. A telephone helpline is available for participants, carers or GPs to report or discuss outcome events. These methods have been reviewed and approved by the patient reference group for the Research to Understand Stroke due to Haemorrhage (RUSH) programme ([www.RUSH.ed.ac.uk](http://www.RUSH.ed.ac.uk)).

**Allocation**

Having obtained consent, the researcher collects the baseline data necessary to complete a randomisation form, enters the participant's baseline data into a computerised central randomisation service by means of a secure round-the-clock web interface or a telephone call to the trial office during office hours (if the web interface is not operational). The web interface checks these baseline data for completeness and consistency. To avoid predictable alternation of treatment allocation (and potential

consequent loss of allocation concealment) a minimisation algorithm randomly allocated the first participant with a probability of 0.5 to one arm of the trial, but the randomisation algorithm for each subsequent participant involves adaptive stratification (i.e. minimisation) and allocates them with a probability of 0.8 to the group which minimises differences between the two arms of the trial with respect to five variables collected by research staff at baseline. The participant is then allocated a unique study identification number and their allocation to starting or avoiding antiplatelet drugs is displayed on the web interface and in an email to all local research staff at the hospital site, having been concealed until that point. If the participant is allocated to starting antiplatelet drugs, they are reminded about the antiplatelet drug that would be prescribed as stated on the randomisation form.

#### **Masking (blinding)**

Treatment allocation in RESTART is not masked, and therefore it is open to participants, the clinicians caring for them in secondary and primary care, and local research staff. Central research staff carrying out follow-up are masked to participants' treatment allocation when obtaining information (questionnaires and the trial database do not reveal treatment allocation to them), as are outcome event adjudicators (they review source documentation of events that might be outcomes with identifiable and treatment information redacted).

#### **Data collection methods**

Research staff at collaborating hospital sites collect all baseline data on demographics, co-morbidities, the qualifying ICH, and treatments from participants or their medical records. The patient's hospital consultant indicates the intended antiplatelet therapy if randomised to starting antiplatelet drugs, which is collected before randomisation. Validation rules embedded within the web interface ensure 100% completeness of baseline data. Images that diagnosed the qualifying ICH and any brain MRI sub-study images that were obtained before randomisation are copied in Digital Imaging and Communications in Medicine (DICOM) format, pseudonymised with the participant ID, and sent to the trial coordinating centre after randomisation. Following receipt, the RESTART imaging manager checks each imaging study to ensure that it relates to the appropriate participant at the appropriate time, that it is the appropriate modality, and that all the required images and sequences have been sent; after quality assurance these images are uploaded to an electronic archive and allocated to one of a panel of consultant neuroradiologists via the in-house, web-based, systematic image review system (<https://www.ed.ac.uk/clinical-sciences/edinburgh-imaging/research/imaging-services-for-research/trial-images-service-smartis>) for confirmation of ICH diagnosis,

ICH location, and other radiographic evidence of small-vessel disease [18–20]. Outcome data are collected using structured postal/telephone questionnaires (available from the corresponding author upon reasonable request). Completeness of follow-up information is maximised by preventing the inclusion of participants who do not have a GP, monitoring completeness of follow-up at fortnightly team meetings, limiting the collection of unnecessary data from investigators and participants, emphasising retention of participants until the end of the trial, and ensuring that participants' contact details are kept up to date. There are no provisions for ancillary and post-trial care given that the intervention being tested is available in standard clinical practice.

#### **Data management**

All records are kept in a secure storage area with limited access, clinical information will not be released without the written permission of the participant, and research staff may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to them for the purpose of the study. All research staff must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and uphold the Act's core principles. Data completeness, range, and consistency checks are performed at randomisation and hospital/clinic discharge, as well as on imaging data collection forms. Incomplete data on follow-up forms are chased by the chief investigator. Documentation about RESTART's data management procedures can be obtained from the corresponding author upon reasonable request.

#### **Statistical methods**

We intend to publish a final Statistical Analysis Plan as an update to this protocol before the database is locked for analysis and the results are known. In order to preserve fully the huge benefit of randomisation, we will include all randomised participants in the analysis (irrespective of whether they adhere to the allocated treatment), all retained in the group to which they were allocated (i.e. 'as-randomised'). This will comprise a Kaplan-Meier survival analysis of time to first outcome event after randomisation. Follow-up will be censored at death (unrelated to an outcome event), last available follow-up, or voluntary withdrawal from the trial. We will compare the survival function in the two trial arms using a Cox proportional hazards regression model, adjusting for all the covariates included in the minimisation algorithm, and presenting the result as an estimated adjusted hazard ratio with its corresponding 95% CI. We will also report the unadjusted estimate of the hazard ratio and its corresponding 95% CI, together with the

result of the log-rank test. We will use available data and not impute missing data. We will analyse heterogeneity of treatment effect using statistical tests of interaction.

#### **Data monitoring**

A Data Monitoring Committee (DMC), which is independent of the sponsor, oversees the safety of participants in the trial, according to the terms of reference in the DMC charter, which is available from the corresponding author on reasonable request. During the period of recruitment into the study, interim analyses of the baseline and follow-up data are supplied, in strict confidence, to the chairman of the DMC, along with any other analyses that the committee may request. In the light of these analyses, the DMC will advise the independent chair of the Trial Steering Committee if, in their view, the randomised comparisons have provided both (1) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (2) evidence that might reasonably be expected to materially influence future patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but the DMC will work on the principle that a difference of at least three standard errors in an interim analysis of a major outcome event (e.g. the primary outcome) may be needed to justify halting, or modifying, a trial before the planned completed recruitment. This criterion has the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed. Unless this happens, however, the Trial Steering Committee, the collaborators and central administrative staff will remain ignorant of the interim results.

#### **Harms**

RESTART is a pragmatic RCT involving antiplatelet drugs which have well-established safety profiles. The trial will routinely collect data on outcomes, serious adverse events (SAEs), and serious unexpected adverse reactions (SUSARs), and these will be reviewed by the independent DMC. The trial procedures are based on routine clinical procedures and include (1) prescription of antiplatelet drugs in routine clinical practice for standard indications, (2) collecting routine clinical information from the medical records, and (3) informed consent. There are no complex procedures or interventions for the participants or research staff in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in this research study is considered to be low in each of these categories. The university has insurance in place (which includes no-fault compensation) for negligent harm caused by poor

protocol design by employees of Edinburgh University. Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

#### **Auditing**

The RESTART internal monitoring procedure to assure appropriate conduct of the trial uses a combination of central data monitoring and remote self-monitoring unless issues are identified that can only be addressed by site monitoring in accordance with the Monitoring Plan agreed by the sponsor. This is regularly reviewed during the course of the trial.

#### **Dissemination policy**

This report of the protocol complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 reporting guideline [21, 22]. On completion of the trial, the data will be analysed and tabulated, a clinical study report will be prepared in accordance with Good Clinical Practice (GCP) guidelines, and a manuscript for publication will be prepared in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. Active collaborators included in the delegation logs at sites that have recruited participants will be included in any listing of collaborators. The primary trial publication will be drafted by a writing committee whose membership has been approved by the Trial Steering Committee, who will approve the manuscript before submission for publication. Results will be disseminated to participants who have opted in to receive them at the time of providing informed consent, and via social media channels (<https://twitter.com/BleedingStroke> and <https://www.facebook.com/bleedingstroke>).

#### **Data sharing**

Ownership of the data arising from this study resides with the Trial Steering Committee. Consistent with recent guidance [23], access to the datasets generated and/or analysed during RESTART will be available on reasonable request after the publication of the main results. Access will be controlled by the chief investigator, with the approval of the Trial Steering Committee. Trial participants or their proxies are provided with assurances about the maintenance of privacy and confidentiality in the information leaflet and they are asked to consent to the statement, 'I agree that information about me and my brain scans may be used in other ethically approved research studies in the future as long as all the information (including the images) is anonymised'.

## Discussion

Since RESTART began in 2013, recruitment has been challenging. We have learned that one in 12 eligible patients is actually randomised, mostly because morbidity and mortality after ICH and physician certainty are impediments to recruitment [10]. We have tried to boost recruitment with a variety of promotional activities, including: patient-orientated information on our website (<http://www.restarttrial.org/patient.html>), monthly collaborator newsletters, annual collaborator meetings, a complex recruitment intervention which has been rolled out to all sites after the PRIME SWAT was completed [11], and one-to-one engagement with site investigators by the chief investigator by telephone and in person.

Other similar RCTs are underway in France (<https://clinicaltrials.gov/ct2/show/NCT02966119>) and Scandinavia (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-002636-13/SE>) [4]. The chief investigators of these studies have formed a Collaboration Of Controlled Randomised trials of Oral Antithrombotic drugs after intraCranial Haemorrhage (COCROACH), with the intent of performing a prospectively planned, individual-patient, data meta-analysis of these RCTs to maximise power to detect the effects of antithrombotic drugs in these patients overall, and in sub-groups of interest ([www.ed.ac.uk/clinical-brain-sciences/research/so-start/for-collaborators](http://www.ed.ac.uk/clinical-brain-sciences/research/so-start/for-collaborators)).

## Trial status

The first participant was randomised on 22 May 2013. Recruitment is on-going and will end on 31 May 2018. The current protocol is version 7.0, created on 23 December 2015 (all protocol updates since version 3.0, created 1 February 2013, which was implemented before randomisation began, have been approved by the sponsor and Research Ethics Committee and also communicated to investigators and trial registries).

## Additional file

**Additional file 1:** RESTART protocol SPIRIT Checklist. (DOCX 50 kb)

## Abbreviations

DMC: Data Monitoring Committee; GP: General (family) practitioner; ICH: Intracerebral haemorrhage; MRI: Magnetic resonance imaging; PRIME: Promoting Recruitment using Information Management Efficiently; RCT: Randomised controlled trial; RESTART: REstart or STop Antithrombotics Randomised Trial; SWAT: Study within a trial

## Acknowledgements

We are grateful to the independent members of the Trial Steering Committee: Professor Daniel S Lasserson (Institute of Applied Health Research, University of Birmingham, Birmingham, UK), Professor Colin Baigent (MRC Population Health Research Unit, University of Oxford, Oxford, UK), and Dr. Johanna Carrie. The RESTART collaborators are:

**Western General Hospital, Edinburgh:** Professor Martin Dennis, Professor Cathie Sudlow, Dr. William Whiteley, Mrs. Christine Lerpiniere; **Edinburgh Royal Infirmary, Edinburgh:** Mrs. Katrina McCormick, Mr. Jack Perry, Professor Rustam Al-Shahi Salman, Dr. Ruwan Parakramawansa, Dr. Neil Hunter, Dr.

Fergus Doubal, Ms. Ruth Paulton, Dr. Richard O'Brien, Mrs. Christine Lerpiniere, Mrs. Seona Burgess, Professor Gillian Mead, Ms. Pat Taylor; **Aberdeen Royal Infirmary, Aberdeen:** Dr. Mary-Joan MacLeod, Mrs. Beverly MacLennan, Dr. Rebecca Clarke, Mrs. Vicky Taylor, Mrs. Katrina Klaasen, Mrs. Nichola Crouch, Mrs. Baljit Jagpal, Dr. Jacqueline Furnace, Mrs. Janice Irvine, Mrs. Heather Gow, Mrs. Anu Joyson, Miss Sandra Nelson, Dr. Sarah Ross; **Arrowe Park Hospital, Wirral:** Dr. Ruth Davies, Ms. Deepa Jose, Miss Naomi Robinson, Ms. Laura Codd, Mrs. Angela Dodd, Ms. Helen Moroney, Mrs. Pauline Weir, Mrs. Victoria Little, Dr. Valerie Gott, Dr. Graeme Sangster, Ms. Paula Owings, Ms. Suja Cherian, Ms. Susan Downham; **Barnet Hospital, Barnet:** Dr. Daniel Epstein, Dr. Adam Webber, Dr. Sammie Qureshi, Mr. Paul Nicholas, Mr. Vinodh Krishnamurthy, Ms. Avani Shukla, Mr. Ifan Jones; **Barnsley Hospital NHS Foundation Trust, Barnsley:** Dr. Ashraf Ahmed, Mrs. Mishell Cunningham, Dr. Tajammal Zahoor, Mrs. Sharon Johnson, Mrs. Carol Dennis, Dr. Mo Albazzaz; **Bradford Royal Infirmary, Bradford:** Dr. Hawraman Ramadan, Dr. Stuart Maguire, Chris, Patterson, Mrs. Ruth Bellfield, Mrs. Brigid Hairsine, Mrs. Outi Quinn, Mrs. Michaela Hooley; **Calderdale Royal Hospital, Halifax:** Dr. Anand Nair, Mr. Mohammad ifan alam, Mrs. Jill Greig, Dr. Pratap Rana, Mr. Matthew Robinson; **Chesterfield Royal Hospital, Chesterfield:** Dr. Mahmud Sajid, Mrs. Margaret Ball, Mrs. Rachel Gascoyne, Dr. George Ghaly; **City Hospital, Nottingham:** Dr. Senthil Raghunathan, Mrs. Judith Clarke, Miss Gwendoline Wilkes, Dr. Zhe Law, Dr. Jason Appleton, Mr. Oliver Matias, Mr. Benjamin Jackson, Miss Rekha Keshvara, Miss Katherine Whittamore, Miss Carla Jordan, Ms. Saima Sheikh, Mr. Jack Roffe, Miss Nicola Gilzeane, Dr. Kailash Krishnan, Miss Amanda Buck, Mrs. Diane Havard, Mrs. Amanda Hedstrom, Miss Faye Shelton, Dr. Nikola Sprigg, Mrs. Margi Godfrey; **Countess of Chester NHS Foundation Trust, Chester:** Dr. Timothy Webster, Dr. Syed Haider, Mrs. Samantha Seagrave, Ms. Sandra Leason, Dr. Arumugam Nallasivan, Dr. Kausic Chatterjee, Ms. Charlotte Perkins; **Deriford Hospital, Plymouth:** Dr. Azlisham Mohd Nor, Ms. Nicola Persad, Ms. Charlotte Eglinton, Mrs. Claire Brown, Mrs. Marie Weinling, Dr. Alex Shah, Dr. John Baker, Mr. Benjamin Hyams; **Doncaster Royal Infirmary, Doncaster:** Dr. Manohar Kini, Mrs. Rosanna Fong, Dr. Dinesh Chadha, Mrs. Deborah Walstow; **Dorset County Hospital NHS Foundation Trust, Dorchester:** Dr. Harald Proeschel, Mr. Simon Sharpe, Mrs. Sarah Horton, Mrs. Stephanie Jones; **Forth Valley Royal Hospital, Larbert:** Dr. Anthony Byrne, Mrs. Caroline McGhee, Ms. Amanda Smart, Dr. Claire Copeland; **Gloucestershire Royal Hospital, Gloucester:** Dr. Dipankar Dutta, Mrs. Rehana Bakawala, Mrs. Susan O'Connell, Miss Chloe Hughes, Ms. Pauline Brown, Dr. Fiona Davis, Miss Kayleigh Collins, Ms. Deborah Ward, Ms. Jennifer Turfrey; **Guys and St Thomas, London:** Professor Tony Rudd, Ms. Katherine Marks, Miss Sagal Kullane, Dr. Birns Jonathan, Dr. Ajay Bhalla; **Hairmyres Hospital, East Kilbride:** Dr. Brigitte Yip, Mrs. Murdina Bell, Dr. Brian MacInnes, Mrs. Linda MacIver, Mr. Derek Esson; **Heartlands Hospital, Birmingham:** Dr. Rajendra Yadava, Mrs. Samantha Stafford, Mrs. Julie Reddan, Mrs. Mirriam Sangombe, Dr. Khalid Azhar; **Hereford County Hospital, Hereford:** Dr. Colin Jenkins, Dr. Fiona Price, Miss Claire Hughes, Ms. Lily Mercer; **Hillingdon Hospital, Uxbridge:** Dr. Evangelos Vasileiadis, Mrs. Cathy Mason, Dr. Basaam Aweid, Mrs. Melinda Holden, Dr. Anthea Parry, Mrs. Geraldine Landers; **James Cook University Hospital, Middlesbrough:** Dr. David Broughton, Mrs. Kath Chapman, Mr. Andrew Sigsworth, Dr. Dinesh Tryambake, Mr. Andrew Young, Ms. Lynn Dixon, Dr. Adrian Bergin; **Monklands Hospital, Airdrie:** Dr. Mark Barber, Mr. Derek Esson, Dr. Fiona Brodie; **Morrison Hospital, Swansea:** Dr. Talat Anjum, Ms. Lynda Connor, Mrs. Susan Tucker, Mr. Sarah Thomas, Mrs. Caroline Davies, Dr. Peter Slade, Ms. Shelley Treadwell, Dr. Mushtaq Wani, Ms. Teresa Beaty, Dr. Manju Krishnan, Mrs. Lynne Dacey, Miss Jayne Spencer, Miss Leanne Quinn, Dr. Srikanth Chenna, Ms. Sharon Storton, Mr. Terry Jones, Miss Helen Thompson Jones; **Musgrove Park Hospital, Taunton:** Dr. Malik Hussain, Mrs. Jane Homan, Miss Eliza Foster, Miss Lucy Brotherton, Mrs. Helen Durman, Mr. Nicholas Hunt, Mrs. Jayne Foot, Mrs. Alison Whitcher, Miss Corinne Pawley, Dr. Mohammad Khan, Dr. Robert Whiting, Dr. Miriam Harvey, Mrs. Sarah Brown, Miss Leanne Foote; **Nevill Hall Hospital, Abergavenny:** Dr. Bella Richard, Mrs. Claire Triscott, Ms. Mandy Edwards, Mrs. Heidi Lawson, Mrs. Rebecca Wallace, Mrs. Claire Nott, Sally Moseley, Mr. Steve Buckle, Miss Procter Sarah, Miss Jessica Whiteman; **New Cross Hospital, Wolverhampton:** Dr. Ken Fotherby, Ms. Donna Butler, Ms. Angela Willberry, Dr. Nasar Ahmad, Mrs. Karla Jennings-Preece, Dr. Farrukh Baig, Mrs. Debbie Morgan, Mrs. Angela Stevens;



**Norfolk and Norwich University Hospital, Norwich:** Dr. Kneale Metcalf, Mrs. Susan McDonald, Mr. Garth Ravenhill, Dr. Ajmal Anversha, Dr. Naval Shinh, Ms. Rebekah Perfitt, Mr. Richard Greenwood, Dr. Janak Saada, Mrs. Kelly Waterfield, Mr. Patrick Sutton, Ms. Jenny Jagger, Mrs. Alison Wiltshire;

**North Middlesex University Hospital, London:** Dr. Robert Luder, Mrs. Venetia Vettimootal Johnson, Miss Hayley Bridger, Dr. Maneesh Bhargava, Ms. Jill Gallagher, Dr. Tolu Adesina, Miss Chloe van Someren;

**Pinderfields Hospital, Wakefield:** Dr. Michael Carpenter, Ms. Marion Walker, Dr. Andrew Stanners, Ms. Julie Ball, Ms. Linda Jackson, Dr. Prabal Datta, Mr. Gavin Bateman, Dr. Razik Fathima, Dr. Richard Davey, Mrs. Ann Needle;

**Queen Alexandra Hospital, Portsmouth:** Dr. Prasad Siddegowda, Dr. Suheil Ponnambath, Mrs. Anne Suttlng, Miss Yasmin Harrington-Davies, Miss Rebecca Butler, Miss Claire James, Miss Stacey Valentine, Mrs. Tracey Dobson, Dr. Peter Howard, Dr. Jane Tandy, Mrs. Lisa Hyatt, Dr. David Jarrett, Dr. Afaq Saulat;

**Queen Elizabeth Hospital, Birmingham:** Dr. Don Sims, Dr. Mark Willmot, Mrs. Carole Green, Mrs. Rachael Jones, Mr. James Cunningham, Mrs. Susan Maiden, Dr. Claire Sutton, Mrs. Jennifer Hurley, Dr. Edward Littleton;

**Queen Elizabeth Hospital, Kings Lynn:** Dr. Raj Shekhar, Mrs. Rachel Crown, Dr. Iman Ahmed, Sister Tracy Fuller, Mrs. Ellie Gilham, Mrs. Kelly Waterfield;

**Queens Hospital, Romford:** Dr. Sreeman Andole, Dr. Naveen Gadapa, Miss Karen Dunne, Dr. Magdalin Krommyda, Miss Evelyn Burssens, Mr. Sam King;

**Royal Blackburn Hospital, Blackburn:** Dr. Neetish Goorah, Mrs. Angela Bell, Mrs. Farzana Patel, Dr. Benjamin Tomlinson, Mr. Stephen Duberley, Dr. Arun Singh, Mrs. Christine Kelly, Miss Jamie Walford;

**Royal Cornwall Hospital, Truro:** Dr. Frances Harrington, Dr. Christine Schofield, Mrs. Linda Lucas, Ms. Sam Ellis, Mrs. Kirsty Bond, Dr. Abhijit Mate, Dr. Katja Adie, Mrs. Ali James, Ms. Bev Maund, Mrs. Gillian Courtauld;

**Royal Devon and Exeter Hospital, Exeter:** Dr. Paul Mudd, Dr. Anthony Hemsley, Mr. Kevin Thorpe, Ms. Karin Gupwell, Dr. Anita Goff, Dr. Jane Sword, Ms. Caroline Roughan, Dr. David Strain, Ms. Julie Cageao, Ms. Angela Bowring, Ms. Samantha Keenan, Dr. Martin James, Ms. Hayley Kingwell, Dr. Keniesha Miller;

**Royal Hallamshire Hospital, Sheffield:** Dr. Kirsty Harkness, Ms. Clare Doyle, Professor Arshad Majis, Mrs. Kathy Stocks, Dr. Ahmad Maatouk, Mr. Luke Barron, Mrs. Katy Dakin, Dr. Ralf Lindert, Miss Christine Kamara, Mrs. Pauline Bayliss, Dr. Jessica Redgrave, Mrs. Faith Kibutu, Dr. Catrin Blank, Dr. Ali Ali, Mrs. Olesia Balitska, Mrs. Kathryn Birchall, Mrs. Emma Richards, Miss Jo Howe;

**Royal Hampshire County Hospital, Winchester:** Dr. Elio Giallombardo, Mrs. Charlotte Eglinton, Dr. Lucy Sykes, Mrs. Jenny Wilson;

**Royal Infirmary, Glasgow:** Professor Peter Langhorne, Dr. Christine McAlpine, Mrs. Louise Humphreys, Dr. Mohammad Shahzad Iqbal, Ms. Ruth Graham, Dr. Gillian Kerr, Dr. Fiona Wright;

**Royal Lancaster Infirmary, Lancaster:** Dr. Pradeep Kumar, Dr. Philip Thomas, Mrs. Charlotte Culmsee, Dr. Isabel Huggett, Miss Linda Dunn, Dr. James Barker;

**Royal Liverpool and Broadgreen University Hospital, Liverpool:** Dr. Aravind Manoj, Dr. Paul Fitzsimmons, Miss Paula Lopez, Dr. Nikhil Sharma, Mrs. Penelope Cox, Mr. Glyn Fletcher, Mr. Mark Wilkinson;

**Royal Preston Hospital, Preston:** Dr. Hedley Emsley, Ms. Sonia Raj, Ms. Donna Doyle, Ms. Bindu Gregory, Dr. Shuja Punekar, Dr. Sulaiman Sultan, Mrs. Alison McLoughlin;

**Royal Surrey County Hospital, Guildford:** Dr. Kath Pasco, Miss Olga Balazikova, Dr. Ashraf Nasim, Miss Cassilda Peixoto;

**Royal Sussex County Hospital, Brighton:** Dr. Ingrid Kane, Dr. Alexandra Pitt-Ford, Dr. Simon Hervey, Dr. Philip Thompson, Miss Laura Latter, Mrs. Emma Barbon, Mrs. Joanna Breeds, Professor Chakravarthi Rajkumar, Dr. Nicola Gainsborough, Mrs. Jane Gaylard;

**Royal United Hospital, Bath:** Dr. James Choulerton, Dr. Louise Shaw, Mrs. Barbara Madigan, Ms. Deborah Howcroft, Ms. Suzanne Lucas, Dr. Andrew Stone, Miss Joanne Avis, Dr. Lukuman Gbadamoshi, Mrs. Denise Button, Ms. McCann Stephanie, Dr. Lindsey Dow;

**Royal Victoria Infirmary, Newcastle upon Tyne:** Dr. Michelle Davis, Mrs. Teresa Thompson, Mrs. Valerie Hogg, Mrs. Carole Hays, Mrs. Michelle Fawcett, Ms. Natalie Atkinson, Mrs. Helen Guy, Mr. Stephen Woodward;

**Salford Royal Foundation Trust, Manchester:** Dr. Adrian Parry-Jones, Mrs. Sally Marshall, Mr. Rowilson Jarapa, Ms. Stephanie Lee, Mrs. Louise Harrison, Miss Mary Johnes, Miss Victoria Ouloughlin, Miss Edith Wood, Mrs. Jane Perez, Mrs. Zin Naing, Mr. Jordi Morell, Ms. Tracy Marsden, Miss Andrea Ingham, Dr. Ilse Burger, Miss Kelly Marie Shaw, Miss Andrea Hall, Dr. Martin Punter;

**Southampton General Hospital, Southampton:** Dr. Nic Weir, Dr. Sue Evans, Miss Ashleigh Walters, Miss Imogen Gartrell, Miss Fiona Smith, Miss Chloe Cox, Charge Nurse Simon Smith, Miss Shuna Egerton, Miss Robyn Creeden,

Dr. James Richard Marigold, Mr. Alex Blades, Dr. Pam Crawford, Dr. Lucy Sykes, Dr. Emma Battersby-Wood, Ms. Vanessa Pressly, Mr. Christopher Allen, Ms. Gabriella Howard;

**South Glasgow University Hospital, Glasgow:** Professor Keith Muir, Dr. Dheeraj Kalladka, Mrs. Wilma Smith, Ms. Nicola Day, Dr. Fiona Moreton, Dr. Bharath Kumar Cheripelli, Dr. Xuya Huang, Mrs. Angela Welch, Dr. Salwa El Tawil, Dr. Sankaranarayanan Ramachandran, Ms. Caroline Crosbie, Dr. Jennifer Elliot;

**St George's Healthcare NHS Trust, London:** Ms. Gillian Cluckie, Dr. Brian Clarke, Mrs. Nilofar Dayal, Mr. Chukwuka Orefo, Mrs. Temi Adedoyin, Mrs. Rita Ghatala, Ms. Natasha Clarke, Dr. Val Jones, Dr. Adrian Blight, Dr. Caroline Lovelock, Mrs. Neha Chopra, Dr. Barry Moynihan, Ms. Kate Kennedy, Ms. Rebecca Williams, Miss Lourda Kerin, Miss Naomi Jeyaraj, Dr. Lillian Choy, Mr. Fran Watson, Ms. Sarah Trippier, Ms. Joanna O'Reill;

**St Mary's Hospital, Newport Isle of Wight:** Dr. Mohammad Haque, Mr. Stuart Symonds, Dr. Mehran Maanoosi, Mrs. Jane Herman;

**Stepping Hill Hospital, Stockport:** Dr. Joseph Vassallo, Dr. Shrivakumar Krishnamoorthy, Mrs. Helen Cochrane, Mrs. Deborah Walter;

**Sunderland Royal Hospital, Sunderland:** Dr. Janice O'Connell, Ms. Charlotte Fox, Dr. Ramesh Krishnamurthy, Ms. Emily Osborne, Mr. Andrew Smith, Ms. Betty Mokoena, Mrs. Diane Gulliver, Mrs. Helen Brew, Dr. Min Myint, Dr. Nikhil Majmudar, Dr. George Bunea, Dr. Naweed Sattar;

**The Princess Royal Hospital, Telford:** Dr. Meena Srinivasan, Dr. Indranil Mukherjee, Mrs. Nichola Motherwell, Mrs. Denise Donaldson, Dr. Robert Campbell, Mrs. Frances Hurford;

**The Royal Bourne-mouth Hospital, Bourne-mouth:** Dr. Kamy Thavanesan, Dr. Owen David, Dr. Divya Tiwari, Mrs. Gail Hann, Mrs. Barbara Longland, Mrs. Jo Bell, Miss Emily Rogers, Miss Caroline Bagnall, Miss Arshi Iqbal, Mrs. Marketa Keltos, Dr. Becky Jupp, Mr. Josh Roberts, Mrs. Chantel Cox, Miss Catherine Ovington;

**Torbay District General Hospital, Torquay:** Dr. Biju Bhaskaran, Mrs. Joanne Garfield-Smith, Mrs. Jean Buxton, Mrs. Kathleen Horan, Dr. Afaq Saulat, Mrs. Georgina Ayres, Mrs. Helen Bearne, Mrs. Dawn Tomlin, Mrs. Susan Szabo, Dr. Debs Kelly, Dr. Isam Salih, Dr. Harbens Bhakri, Mrs. Pauline Fitzell;

**Ulster Hospital, Belfast:** Dr. David Wilson, Ms. Belinda Wroath, Dr. Kevin Dynan, Dr. Michael Power, Ms. Susan Thompson;

**Ayr Hospital, Ayr:** Dr. Sandip Ghosh, Mrs. Margo Henry, Ms. Danielle Gilmour, Mrs. Elizabeth Barrie;

**University Hospitals Coventry and Warwickshire, Coventry:** Dr. Antony Kenton, Miss Sheila Nyabadza, Miss Irene Martin, Dr. Benjamin Hunt, Hardi Hassan, Dr. Bander Dallo;

**University Hospitals of North Midlands NHS Trust, Stoke-on-Trent:** Dr. Girish Muddegowda, Miss Joanne Hiden, Ms. Holly Maguire, Ms. Jeanette Grocott, Mrs. Kay Finney, Mr. Adrian Barry, Professor Christine Roffe, Mrs. Sue Lyjko, Dr. Ranjan Sanyal, Mrs. Alda Remegoso, Dr. Phillip Ferdinand, Mr. Adrian Butler, Ms. Nenette Abano, Miss Chelsea Causley, Ms. Hayley Denic, Mrs. Racquel Carpio, Miss Stephanie Stevens, Mr. Andrew Moores, Mrs. Resti Varquez;

**University Hospital North Durham, Durham:** Dr. Yogish Pai, Dr. David Bruce, Dr. Sofia Dima, Dr. Vidya Baliga, Dr. Muhammad Naeem, Ms. Gill Rogers, Mrs. Ellen Brown, Mrs. Rachel Hayman, Dr. Mark Garside, Dr. Mahesh Dhakal, Dr. Gemma Marie Smith, Mrs. Susan Clayton;

**West Cumberland Hospital, Whitehaven:** Dr. Enoch Orugun, Mrs. Una Poultney, Ms. Rachel Glover, Ms. Hannah Crowther, Miss Sarah Thornthwaite;

**William Harvey Hospital, Ashford:** Dr. Tom Webb, Dr. Eva Beranova, Ms. Susannah Walker, Mrs. Tracey Cosier, Mrs. Hannah Rudenko, Ms. Linda Cowie, Ms. Anna Verrion, Miss Audrey Thomson;

**Wythenshawe Hospital, Manchester:** Dr. Ed Gamble, Bethan Charles, Dr. Rebecca Grue, Mrs. Sujata Blane, Dr. Adam Hague;

**Yeovil District Hospital, Yeovil:** Dr. Khalid Rashed, Mrs. Carinna Vickers, Mrs. Diane Wood, Mrs. Janne Board, Miss Clare Buckley, Mrs. Joanna Allison, Mrs. Sarah Board, Mrs. Barbara William-Yesson, Mrs. Linda Balian, Mrs. Elizabeth Keeling;

**Charing Cross Hospital, London:** Dr. Arindam Kar, Dr. Omid Halse, Miss Vinh Nguyen, Miss Kirsten Harvey, Miss Léjeune Gardener, Miss Sheila Mashate, Ms. Victoria Tilly, Mr. Peter Wilding, Dr. Olivia Geraghty, Ms. Beth Hazel;

**The Royal London Hospital, London:** Dr. Thomas Harrison, Ms. Larissa Cuenod, Miss Grace Auld, Ms. Esther Erumere, Miss Ozlem Redjep, Miss Gemma Grimwood, Miss Laura Howanec, Miss Dionne Hove, Dr. Afraim Salek-Haddadi, Dr. Kari Saastamoinen, Dr. Lucia Argandona;

**Royal Victoria Hospital, Belfast:** Dr. Ivan Wiggam, Ms. Aine Wallace, Mrs. Sarah Cuddy, Mrs. Suzanne Tauro, Mrs. Annemarie Hunter, Dr. Enda Kerr, Dr. Ailsa Fulton;

**Epsom General Hospital, Epsom:** Dr. Janet Putterill, Dr. Puneet Kakar, Dr. Ratneshwari Jha, Rachel Gallifent;

**Lister Hospital, Stevenage:** Dr. Aparna Pusalkar, Miss Kelly Chan, Dr. Puneet Dangri, Mrs. Karen Crabtree, Mrs. Hannah Beadle, Mrs. Angela Cook;

**Salisbury District Hospital, Salisbury:** Dr. Toby Black, Mrs. Julie Cronin, Mrs. Ruth Fennelly, Mrs. Michele Tribbeck, Mrs. Caroline Clarke, Mrs. Skelton Miriam, Mrs. Alpha Anthony, Mrs. Denise Mead;

**Queen Elizabeth Hospital, Gateshead:** Dr. Bernard Esi, Ms. Maria Bokhari, Dr. Tim Cassidy, Mrs. Beverley McClelland;

**Kings Mill Hospital, Mansfield:** Dr. Martin Cooper, Mrs. Inez Wynter, Dr. Anoja Rajapakse, Dr. Mohammad Nasar;

**University Hospital of North Tees, Stockton:** Dr. Ijaz Anwar, Ms. Lynn Dixon, Mrs. Alex Ramshaw, Dr. Arunkumar Annamalai, Mrs. Susan Crawford, Ms. Tarn Nozedar, Dr. Helen Skinner, Dr. Balakrishna Kumar, Mr. Damian McArdle;

**Bristol Royal Infirmary, Bristol:** Dr. Clare Holmes, Miss Emily Dodd, Mrs. Samantha Clarke, Dr. Sarah Caine, Mrs. Pauline Baker, Dr. Peter Murphy, Mrs. Mairead Osborn, Miss Lucy Belle Guthrie, Mrs. Amy Steele, Dr. Nicola Devitt;

**Pilgrim Hospital, Boston:** Dr. David Mangion, Mrs. Jo Fletcher, Mrs. Anne Hardwick, Mrs. Carmen Constantin, Dr. Skarlet Markova, Mrs. Tara Lawrence;

**Peterborough City Hospital, Peterborough:** Dr. Santhosh Subramonian, Miss Natalie Temple, Dr. Peter Owusu-Agyei, Mrs. Nicola Butterworth-Cowin;

**University College London Hospital, London:** Professor David Werring, Miss Caroline Hogan, Mrs. Maria Brestziski, Miss Emma Elliott, Mrs. Nina Francia, Miss Amy Ashton, Dr. Isabel Hostettler, Miss Nnebuife Oji, Miss Azra Banaras, Miss Krishna Patel, Ms. Luci Crook, Miss Caroline Watchurst, Dr. Duncan Wilson, Mr. Ifan Jones, Mrs. Renuka Erande;

**Luton and Dunstable NHSFT University Hospital, Luton:** Dr. Lakshmanan Sekaran, Dr. Niaz Mohammed, Ms. Meena Chauhan, Dr. Sakthivel Sethuraman, Mr. Rohan Simon, Mrs. Kiranjit Bharaj, Mrs. Margaret Tate, Mrs. Frances Justin, Dr. Duke Phiri;

**Ystrad Mynach Hospital, Ystrad Mynach, Newport:** Dr. Jonathan Hewitt, Mrs. Claire Nott, Mrs. Jane Gray, Mrs. Rebecca Wallace, Ms. Rina Mardania, Mrs. Claire Triscott, Miss Sarah Procter, Mr. Steve Buckle, Miss Jessica Whiteman;

**Solihull Hospital, Solihull:** Dr. Khaled Elfandi, Mrs. Julie Reddan, Dr. Uzma Khan, Mrs. Samantha Stafford;

**Poole Hospital, Poole:** Dr. Suzanne Ragab, Mrs. Kerstin Knops, Miss Emma Jinks, Mrs. Christine Dickson, Mrs. Laura Gleave, Mrs. Jacqui Leggett, Miss Judith Dube, Dr. Tatiana Garcia;

**Victoria Hospital, Blackpool:** Dr. James McIlmoyle, Dr. Sajjad Anwar, Dr. Saikat Dhar, Mrs. Kirsty Jones, Mrs. Carol Jeffs, Mrs. Christina Dickinson, Ms. Joanne Howard;

**Derby Royal Hospital, Derby:** Dr. Timothy England, Professor Richard Donnelly, Mrs. Amanda Hedstrom, Dr. Mohana Maddula;

**Leeds General Infirmary, Leeds:** Dr. Ahamad Hassan, Mrs. Emelda Veraque, Miss Mary Kambafwile, Mrs. Linetty Makawa, Dr. Marc Randall, Dr. Vasileios Papavasileiou, Mr. Dean Waugh;

**Sandwell General Hospital, Birmingham:** Dr. Sissy Ispoglou, Mrs. Anne Hayes, Dr. Sandeep Ankolekar, Miss Rachel Evans;

**Bedford Hospital, Bedford:** Dr. Hlaing Ni, Miss Carol Graham, Mrs. Josin Jose, Mrs. Josette Milligan, Dr. Bithi Rahman;

**Raigmore Hospital, Inverness:** Dr. Paul Findlay, Dr. Ashish Macaden, Mr. Ian Shread;

**South West Acute Hospital, Enniskillen:** Dr. Breffni Keegan, Ms. Caroline Blair, Dr. Jim Kelly, Ms. Mandy Doherty;

**Prince Charles Hospital, Merthyr Tydfil:** Dr. Richard Dewar, Dr. James White, Ms. Kelly Thomas;

**Northwick Park Hospital, Harrow:** Dr. David Cohen, Mrs. Anette David, Miss Emmanuelle Owoyele, Dr. Kelechi Njoku, Mr. Philip Poku, Miss Varthi Sukdeo, Miss Aberami Chandrakumar, Mrs. Angela Chamberlain, Dr. Mudhar Abdulsahab, Ms. Fenglin Guo, Miss Anne Oshodi, Dr. Radim Licenik, Dr. Joseph Devine, Dr. Silvie Davies, Dr. Nabeela Nisar, Dr. Rangah Niranchanan, Dr. Tatjana Roganova, Ms. Mushiya Mpelembue, Miss Laura Burgess, Dr. Rajaram Bathula, Dr. Mmua Ngwako;

**Leicester Royal Infirmary, Leicester:** Dr. David Eveson, Dr. Amit Mistri, Miss Claire Stephens, Dr. Kashif Musarrat, Ms. Man Yee Lam, Mrs. Saira Sattar, Mrs. Shagufta Khan, Dr. Mohammed Moqsiith, Dr. Lisa Manning, Mrs. Champa Patel;

**John Radcliffe Hospital, Oxford:** Dr. Ursula Schulz, Dr. James Kennedy, Professor Gary Ford, Dr. George Harston, Mrs. Rachel Teal, Dr. Philip Mathieson, Miss Giulia Lenti, Dr. Ian Reckless;

**University Hospital Aintree, Liverpool:** Dr. Claire Cullen, Mrs. Sarah Stevenson, Mrs. Melanie Harrison, Mr. Jordan Ewing, Mrs. Daniela Shackcloth, Dr. Ramesh Durairaj, Ms. Mellor Zoe, Ms. Tanya Ingram, Dr. Hlaing Thant, Ms. Jenny Peters, Mrs. Victoria Sutton;

**St Richard's Hospital, Chichester:** Dr. Simone Ivatts, Ms. Isobel Amey, Mrs. Lisa Clayton- Evans, Mrs. Yolanda Baird, Mrs. Moore Sally, Miss Sophie Newton;

**Southend University Hospital NHS Foundation Trust, Westcliff on Sea:** Dr. Paul Guylar, Dr. Kheng Xiong Ng, Mrs. Rajalakshmi Orath Prabakaran, Dr. David Ngo, Dr. Sindhu Rashmi, Dr. Lucy Coward, Dr. Nisha Menon, Dr. Shyam Kelavkar, Mrs. Swapna Kunhunnu, Dr. Devesh Sinha, Dr. Anwer Siddiqui, Dr. Amber Siddiqui, Dr. Thayalini Loganathan, Mrs. Sharon Tysoe, Dr. Sweni Shah;

**Leighton Hospital, Crewe:** Dr. Latheef Kalathil, Mrs. Nikki Gautam, Mrs. Julie Meir, Mr. Duncan Bailey, Dr. Maqsud Salehin, Mr. Richard Miller, Miss Amor Kelly;

**Hull Royal Infirmary, Hull:** Dr. Rayessa Rayessa, Miss Alicia Rodgers, Mrs. Lisa Wilson, Miss Charde Naylor, Miss Sarah Wilson, Miss Emma Clarkson;

**Altnagelvin Hospital, Derry/Londonderry:** Dr. Mark McCarron, Dr. Fergal McVerry, Ms. Caroline Blair, Sister Jacqueline McKee, Ms. Mandy Doherty;

**Victoria Hospital, Kirkcaldy:** Dr. Vera Cvor, Dr. Khalil Ullah, Dr. Nicola Chapman, Ms. Mandy Couser, Mrs. Katrina McCormick, Dr. Sean McAuley, Dr. Susan Pound;

**West Suffolk Hospital, Bury St Edmonds:** Dr. Anne Nicolson, Dr. Javed Imam, Mrs. Julie White, Mrs. Lisa Wood;

**Addenbrookes Hospital, Cambridge:** Dr. Eoin O'Brien, Dr. Niamh Hannon, Mrs. Sarah Finlay, Ms. Helen Hayhoe, Mr. Dominic Handley, Dr. Siobhan Kelly, Mrs. Joanne Mcgee, Mrs. Jennifer Mitchell, Mrs. Elaine Amis, Ms. Juliana Sesay, Dr. Sarah Crisp, Mr. Jobbin Francis.

#### Roles and responsibilities

RESTART is sponsored by the Academic and Clinical Central Office for Research and Development (ACCORD), Research & Development Management Suite, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh. EH16 4TJ.

#### Funding

The British Heart Foundation funded RESTART via a special project grant (SP/12/2/29422) and a travel fellowship (FS/13/72/30531) paid to the University of Edinburgh. The British Heart Foundation funded PRIME via a project grant (PG/14/50/30891) paid to the University of Edinburgh.

#### Availability of data and materials

Access to the datasets generated and/or analysed during RESTART will be available on reasonable request after the publication of the main results. Access will be controlled by the chief investigator, with the approval of the Trial Steering Committee.

#### Authors' contributions

RA-SS and MSD conceived the idea. RA-SS, MSD, GDM, DEN, PAGS, CLMS, PMW, WNW, and DJW obtained funding. RA-SS, MSD, KI, JD, LD, and CW designed and implemented the study. GDM performed the statistical analyses. RA-SS wrote the first draft of the manuscript. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

The Scotland A Research Ethics Committee approved RESTART before recruitment began (reference 12/SS/0138). Collaborators who have received GCP and RESTART-specific training and are included in a delegation log obtain written informed consent from participants or their legal representative or nearest relative.

#### Consent for publication

Not applicable

#### Competing interests

The authors declare that they have no competing interests.

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

#### Author details

<sup>1</sup>Centre for Clinical Brain Sciences, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK. <sup>2</sup>Usher Institute of Population Health Sciences and Informatics, University of Edinburgh,

Edinburgh, UK. <sup>3</sup>Institute of Neuroscience and Newcastle University Institute for Ageing, Newcastle-upon-Tyne, UK. <sup>4</sup>Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK. <sup>5</sup>Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK. <sup>6</sup>Institute of Neurology, University College London, London, UK.

Received: 23 October 2017 Accepted: 12 February 2018

Published online: 05 March 2018

## References

- Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014;85(6):660–7.
- Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849–60.
- Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2005;4:CD001925.
- Perry LA, Berge E, Bowditch J, Forfang E, Ronning OM, Hankey GJ, Villanueva E, Al-Shahi Salman R. Antithrombotic treatment after stroke due to intracerebral haemorrhage. *Cochrane Database Syst Rev*. 2017;5:CD012144.
- Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, Smith EE, Greenberg MS, Rosand J, Viswanathan A. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2010;75(8):693–8.
- Chong BH, Chan KH, Pong V, Lau KK, Chan YH, Zuo ML, Lui WM, Leung GK, Lau CP, Tse HF, et al. Use of aspirin in Chinese after recovery from primary intracranial haemorrhage. *Thromb Haemost*. 2012;107(2):241–7.
- Flynn RW, MacDonald TM, Murray GD, MacWalter RS, Doney AS. Prescribing antiplatelet medicine and subsequent events after intracerebral hemorrhage. *Stroke*. 2010;41(11):2606–11.
- Teo KC, Lau GK, Mak RH, Leung HY, Chang RS, Tse MY, Lee R, Leung GK, Siu DC, Cheung RT, et al. Antiplatelet resumption after antiplatelet-related intracerebral hemorrhage: a retrospective hospital-based study. *World Neurosurg*. 2017;106:85–91.
- Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, Leung VK, Wong WW, Chan FK. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med*. 2010;152(1):1–9.
- Maxwell AE, MacLeod MJ, Joyson A, Johnson S, Ramadan H, Bellfield R, Byrne A, McGhee C, Rudd A, Price F, et al. Reasons for non-recruitment of eligible patients to a randomised controlled trial of secondary prevention after intracerebral haemorrhage: observational study. *Trials*. 2017;18(1):162.
- Maxwell AE, Dennis M, Rudd A, Weir CJ, Parker RA, Al-Shahi Salman R. Promoting Recruitment using Information Management Efficiently (PRIME): study protocol for a stepped-wedge cluster randomised controlled trial within the REstart or STop Antithrombotics Randomised Trial (RESTART). *Trials*. 2017;18(1):22.
- Parker RA, Weir CJ, Maxwell AE, Al-Shahi Salman R. Promoting Recruitment using Information Management Efficiently (PRIME): statistical analysis plan for a stepped wedge cluster randomised trial within the REstart or STop Antithrombotics Randomised Trial (RESTART). *Trials*. 2017;18(1):94.
- Bruno A, Shah N, Lin C, Close B, Hess DC, Davis K, Baute V, Switzer JA, Waller JL, Nichols FT. Improving modified Rankin Scale assessment with a simplified questionnaire. *Stroke*. 2010;41(5):1048–50.
- Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal and telephone questionnaires. *Stroke*. 2012;43(3):851–3.
- Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V, Aryal T, Brooks D, Hess DC, Switzer JA, et al. Simplified modified Rankin Scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke*. 2011;42(8):2276–9.
- Sprigg N, Robson K, Bath P, Dineen R, Roberts I, Robinson T, Roffe C, Werring D, Al-Shahi Salman R, Pocock S, et al. Intravenous tranexamic acid for hyperacute primary intracerebral hemorrhage: protocol for a randomized, placebo-controlled trial. *Int J Stroke*. 2016;11(6):683–94.
- McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med*. 2006;119(8):624–38.
- Cordonnier C, Potter GM, Jackson CA, Doubal F, Keir S, Sudlow CL, Wardlaw JM, Al-Shahi Salman R. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). *Stroke*. 2009;40(1):94–9.
- Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jager HR, Werring DJ. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology*. 2009;73(21):1759–66.
- Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822–38.
- Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, Hrobjartsson A, Mann H, Dickersin K, Berlin JA, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200–7.
- Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hrobjartsson A, Schulz KF, Parulekar WR, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
- Tudur Smith C, Hopkins C, Sydes MR, Woolfall K, Clarke M, Murray G, Williamson P. How should individual participant data (IPD) from publicly funded clinical trials be shared? *BMC Med*. 2015;13:298.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

