STATISTICAL ANALYSIS PLAN

ISRCTN Number: ISRCTN71907627
EudraCT Number: 2012-003190-26
Funder: British Heart Foundation
Sponsors: The University of Edinburgh and NHS Lothian
Version: 1.7
Date: 25th January 2019
Chief Investigator: Professor Rustam Al-Shahi Salman
Author: Professor Gordon Murray

25/01/2019
Date

25/01/2019
Date

Professor Gordon Murray
(University of Edinburgh)

Professor Rustam Al-Shahi Salman
(University of Edinburgh)
## Document Version History

<table>
<thead>
<tr>
<th>Version Number</th>
<th>Reason for Update</th>
<th>Updated By:</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>Creation of new statistical analysis plan</td>
<td>Gordon Murray</td>
<td>8th October 2015</td>
</tr>
<tr>
<td>1.01</td>
<td>Revised ahead of circulation to TSC for discussion, with initial input from CI</td>
<td>Gordon Murray</td>
<td>14th October 2015</td>
</tr>
<tr>
<td>1.1</td>
<td>Revised following discussion with TSC</td>
<td>Gordon Murray</td>
<td>10th December 2015</td>
</tr>
<tr>
<td>1.2</td>
<td>Revised to reflect Version 7.0 of the protocol and to take account of the funding extension which allows the trial to run until 28th February 2019</td>
<td>Gordon Murray</td>
<td>19th April 2016</td>
</tr>
<tr>
<td>1.3</td>
<td>Revised following discussions with the TSC Chair</td>
<td>Gordon Murray/ Rustam Al-Shahi Salman</td>
<td>26th September 2017</td>
</tr>
<tr>
<td>1.4</td>
<td>Revised following discussions with the TSC</td>
<td>Gordon Murray</td>
<td>16th October 2017</td>
</tr>
<tr>
<td>1.5</td>
<td>Revised to reflect Version 8.0 of the protocol, and to be compliant with published guidelines on the content of Statistical Analysis Plans (JAMA 2017;318(23):2337-2343)</td>
<td>Gordon Murray</td>
<td>29th March 2018</td>
</tr>
<tr>
<td>1.6</td>
<td>Revised to reflect the primary sources of outcome ascertainment that will be used by the trial, analyses that will be included in the primary report of the main trial, and the imaging analyses that will be reported in a separate publication.</td>
<td>Rustam Al-Shahi Salman</td>
<td>18th September 2018</td>
</tr>
<tr>
<td>1.7</td>
<td>Revised the categorisation of time since ICH for analysis of the MRI sub-study in view of the distribution of outcomes in the whole trial dataset and specified the approach to be followed should any of the multivariate analysis models used with the MRI sub-study data fail to converge (before database lock and unblinding to treatment allocation)</td>
<td>Rustam Al-Shahi Salman / Gordon Murray</td>
<td>25th January 2019</td>
</tr>
</tbody>
</table>
1 Table of contents

1 Table of contents ........................................................................................................... 3

2 List of abbreviations .................................................................................................... 5

3 Introduction .................................................................................................................... 6

3.1 Responsibilities ....................................................................................................... 6

3.2 Definitions ................................................................................................................. 6

4 Study design .................................................................................................................. 6

4.1 Brief Description ....................................................................................................... 6

5 Overall statistical principles ....................................................................................... 7

5.1 Handling of missing data ........................................................................................ 7

5.2 Quality control (QC) of summary tables and statistical analysis ....................... 7

5.2.1 QC/Validation - Summary Tables ..................................................................... 7

5.2.2 QC/Validation - Statistical Analysis ................................................................. 8

5.3 Un-blinding procedures ........................................................................................... 8

6 Population for analysis ............................................................................................... 8

6.1 Intention-to-treat population ................................................................................... 8

6.2 Datasets for analysing the main study and the imaging sub-studies . 8

7 List of analyses to be performed .................................................................................. 8

7.1 Recruitment and retention ...................................................................................... 8

7.2 Baseline data: demographics, baseline/clinical characteristics ........................... 8

7.3 Protocol deviations/violations ............................................................................... 9

7.4 Adherence to allocated treatment ........................................................................... 9

7.5 Co-interventions ....................................................................................................... 9

7.6 Analysis of outcomes .............................................................................................. 9

7.7 Primary outcome ..................................................................................................... 9

7.7.1 Sensitivity analyses .......................................................................................... 10

7.8 Secondary outcomes .............................................................................................. 10

7.8.1 All serious haemorrhagic events ..................................................................... 10

7.8.2 All serious vaso-occlusive events (including revascularisation procedures) ................................................................. 10

7.8.3 Composite of all serious haemorrhagic or vaso-occlusive events ... 10

7.8.4 Sensitivity analysis .......................................................................................... 11

7.8.5 Annual assessment of modified Rankin Scale (mRS) .................................... 11

7.9 Sub-group analyses ............................................................................................... 11

7.10 Serious adverse events ......................................................................................... 11

7.11 Imaging sub-studies .............................................................................................. 11

8 Data Sharing ............................................................................................................... 12

Appendix 1: Outcome measures specified in the protocol ......................................... 13

Primary 13
Secondary ......................................................................................................................... 13

Annual ratings of participant function completed by participant or their carer 13

Appendix 2: Statistical extracts from the protocol ......................................................... 14
Sample size calculation ................................................................. 14
Proposed analyses ................................................................. 14
Primary analysis ................................................................. 15
Secondary analyses ............................................................. 15
Sub-group analyses ............................................................. 15
Brain MRI sub-study ............................................................ 16
# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CONSORT</td>
<td>CONsolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>ECTU</td>
<td>Edinburgh Clinical Trials Unit</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracerebral haemorrhage</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
</tr>
<tr>
<td>n</td>
<td>Number of patients with an observation</td>
</tr>
<tr>
<td>Q1</td>
<td>First (lower) quartile</td>
</tr>
<tr>
<td>Q3</td>
<td>Third (upper) quartile</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RESTART</td>
<td>REstart or STop Antithrombotics Randomised Trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
</tbody>
</table>
3 Introduction

This document details the criteria to be used for the definition of the analysis populations and the statistical methodology for analysis of the Restart or Stop Antithrombotics Randomised Trial (RESTART). This document has been compiled according to Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) “Statistical and Analysis Plans”. This document has been written based on information contained in the final study protocol dated 19th September 2017, Version 8.0.

For ease of reference, two appendices contain extracts from the study protocol. Appendix 1 lists the study outcomes as set out in the protocol and Appendix 2 sets out the statistical aspects, comprising the sample size justification and an outline of the proposed statistical analyses.

3.1 Responsibilities

The statistician at ECTU will be responsible for the production of the following items using ECTU SOPs: summary tables, formal statistical analysis and the statistical report.

3.2 Definitions

Throughout the reporting of the study, the studied interventions will be reported as ‘start antiplatelet drugs’ versus ‘avoid antiplatelet drugs’, and will be collectively referred as the treatment groups.

4 Study design

4.1 Brief Description

RESTART is a randomised controlled trial (RCT) involving two parallel groups, designed to help assess whether patients who survive a stroke due to spontaneous intracerebral haemorrhage (ICH) which developed while the patient was taking antithrombotic drugs for the prevention of vaso-occlusive disease should start antiplatelet drugs for continued secondary prevention of vaso-occlusive disease.

Full inclusion/exclusion criteria are set out in the protocol, but in summary patients are: aged 18 years or older; have suffered a spontaneous ICH not attributable to preceding head injury; have taken an antithrombotic drug for the prevention of vaso-occlusive disease before the onset of the qualifying ICH; and the patient and their physician are both uncertain about whether to start or avoid antiplatelet drugs.

The primary objective of the RCT is to estimate the relative and absolute effects of antiplatelet drugs on the risk of recurrent symptomatic ICH associated with a policy of starting antiplatelet drugs after the acute phase of spontaneous ICH. The aim is to recruit 720 patients (360 per treatment group). Since the primary objective of the trial is to estimate a treatment effect, the trial does not fit into a conventional superiority, equivalence or noninferiority hypothesis testing framework.

RESTART collects all participants’ diagnostic brain imaging (usually computed tomography [CT], but sometimes magnetic resonance imaging [MRI] alone) that diagnosed ICH before randomisation. An imaging sub-study was also conducted involving brain MRI to test for an interaction between the presence of brain microbleeds (which are one of many imaging biomarkers of cerebral small vessel disease) and the effects of antiplatelet drugs. The aim was to recruit at least 550 of the 720 RESTART participants into the MRI sub-study.
RESTART follows participants via: clinic/hospital discharge forms; annual postal/telephone questionnaires to participants and their general practitioners (GPs); and ad hoc reports from GPs, participants, carers, or research staff sites. RESTART will request, obtain and examine linked data on participants held by administrative datasets (death certificates and hospital admissions), but because all of these sources of data are not available in all of the UK countries participating in RESTART, administrative data will not be a primary source of ascertainment of information about outcome events in RESTART.

There are no formal planned interim analyses. Accumulating data from the trial are being monitored by an independent Data Monitoring Committee. The stopping guideline is based on the ‘overwhelming evidence’ principle, and hence there is no need to adjust the final significance level of this RCT.

5 Overall statistical principles

The statistician at ECTU will perform the statistical programming and analysis to produce all summary tables and figures using the statistical package SAS (v9.3 or a more recent version).

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, inter quartile points at 25% and 75% (Q1 and Q3) and number of patients with an observation (n).

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level, leading to 95% (2-sided) confidence intervals (CIs), unless otherwise specified.

All analyses will follow the “intention-to-treat” principle.

5.1 Handling of missing data

There will be no imputation for the data with regard to missing values or withdrawals for the statistical summaries and statistical analysis unless otherwise specified.

Some of the covariates specified for the statistical analyses are required to inform the minimisation algorithm, and so there should be no missing data for these baseline covariates. Strenuous efforts are being made to obtain virtually complete outcome data.

Any required/applicable imputation of data will be performed at the discretion of the ECTU statistician. All imputations (if any) will be detailed in the statistical result report.

5.2 Quality control (QC) of summary tables and statistical analysis

Ahead of database lock and un-blinding, a full statistical report will be produced based on dummy randomisation codes, to allow for checking of the data and the proposed summaries/analyses.

Isolated data errors detected in the database as a result of the QC checks that are deemed significant will be submitted for enquiry to the trial manager or designee.

Systematic data errors in the data reporting will be investigated further; the data will be corrected if necessary, and the appropriate table then re-checked.

5.2.1 QC/Validation - Summary Tables

A random selection of unique analysis and summary tables will be QC’d using manual
methods (i.e. comparison of results in the table to results calculated by a calculator, spreadsheet, database output or any alternative summarisation tool).

5.2.2 QC/Validation - Statistical Analysis
QC/Validation of statistical analyses will be performed by peer review of program code, log and output. Additionally, the primary outcomes analysis will be replicated independently by a second statistician.

5.3 Un-blinding procedures
Not applicable

6 Population for analysis
6.1 Intention-to-treat population
The intention-to-treat (ITT) population will comprise all patients who have been randomised into the RESTART study, regardless of whether they were subsequently deemed ineligible after independent review of their diagnostic brain imaging.

6.2 Datasets for analysing the main study and the imaging sub-studies
The main report of the RCT will include the entire ITT population. However, in the brain imaging studies within RESTART, imaging may: not have proceeded despite consent being obtained; my not have been provided; may have been undertaken but may have contravened the required protocol; may have been undertaken, but was degraded by motion artefact; have demonstrated that the patient was ineligible for inclusion in RESTART (which precluded collection of ratings by the RESTART Imaging Panel). Therefore, patients will be included in the CT imaging study and the MRI sub-study datasets if their pre-randomisation brain imaging was readable and confirmed their eligibility for RESTART.

7 List of analyses to be performed
7.1 Recruitment and retention
No formal statistical testing will be performed. A CONSORT flow diagram will be provided. The statistical report will tabulate the number of patients consented, randomised, treated, adherent, and completed follow-up overall and by treatment group. The number of patients discontinued early from the study will be summarised by reason for withdrawal and treatment.

7.2 Baseline data: demographics, baseline/clinical characteristics
No formal statistical testing will be performed. The following will be presented and summarised by treatment group and overall:

- the covariates used in the minimisation algorithm (qualifying ICH location; time since ICH symptom onset; antiplatelet drug(s) that patient’s physician would use if allocated; age; predicted six month outcome)

- sex; ethnicity; diagnostic imaging; MRI sub-study imaging; indicated uncertainty about starting antiplatelet drugs; functional status; modified Rankin Scale score; co-morbidities; antithrombotic drugs taken before ICH; timing of key events – symptom onset to randomisation – symptom onset to earliest imaging study – earliest imaging study to randomisation – symptom onset to sub-study MRI (if applicable) – sub-study MRI to randomisation (if applicable)
7.3 Protocol deviations/violations

Any change, divergence, or departure from the trial design or procedures defined in the protocol or Good Clinical Practice are identified and recorded as a deviation (if it does not significantly affect a participant’s rights, safety, or well-being, or trial outcomes), or a violation (if the deviation may potentially significantly impact the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a patient’s rights, safety, or well-being). All protocol deviations/violations will be listed, but no formal statistical testing will be performed.

7.4 Adherence to allocated treatment

No formal statistical testing will be performed. Adherence will be reported descriptively per treatment group at discharge and at each annual follow-up.

7.5 Co-interventions

Use of anticoagulant drugs will be reported descriptively per treatment group at discharge and at each annual follow-up. Because blood pressure (BP) control is the other main confounder of the frequency of the primary outcome, the use of BP-lowering drugs at discharge after randomisation and at each annual follow-up will be reported (along with a summary of the available BPs of participants by treatment group).

7.6 Analysis of outcomes

The trial will be analysed on an intention-to-treat basis, incorporating all patients who were randomised and for whom outcome data are available, with patients analysed according to their allocated intervention, irrespective of whether the patient’s actual management complied with the allocated intervention.

The survival function per treatment group will be estimated using a Kaplan-Meier survival analysis of time to first outcome event during follow-up from 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 (Qualifying ICH location of lobar versus non-lobar; Time since ICH symptom onset of 0-6 days versus 7-30 days versus over 30 days; Antiplatelet drug(s) that the patient’s clinician would start if allocated to aspirin alone versus any other regimen; Participant’s age at randomisation of less than 70 years versus 70 years or older; Predicted probability of a good six month outcome of less than 0.15 versus 0.15 or greater), 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 logrank test. The absolute difference in event rates at one, two, three and four years will be estimated from the Kaplan-Meier analysis.

The proportional hazards assumption will be assessed graphically, and if there is strong evidence of violation of the assumption the impact on the analysis will be assessed by comparing the results of the pre-specified analysis with the results obtained using the restricted survival time approach.*

7.7 Primary outcome

The primary outcome event is the first fatal or non-fatal radiographically- or pathologically-proven recurrent symptomatic ICH.

* Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Statistics in Medicine 2011;30(19):2409-21
7.7.1 Sensitivity analyses
We will conduct two exploratory sensitivity analyses of our primary analysis, by
adding the following secondary outcomes to the primary outcome in the following
order, to account for the possibility that some fatalities and non-fatal neurological
events without adequate investigation may be recurrent ICH:

- Fatal or non-fatal symptomatic stroke consistent with the clinical manifestations
  of ICH, but without radiographic or pathological confirmation (or with brain
  imaging performed too late to distinguish ICH from ischaemic stroke).
- Deaths without a clear cause and without further investigation.

7.8 Secondary outcomes
The two key secondary outcomes are a composite of all serious haemorrhagic events
and a composite of all serious vaso-occlusive events (including revascularisation
procedures). These composites are defined specifically as:

7.8.1 All serious haemorrhagic events
This composite outcome includes all fatal or non-fatal symptomatic events (that are
'serious' because of their usual need for hospitalisation and influence on outcome and
antithrombotic treatment):

- Radiographically- or pathologically-proven recurrent symptomatic ICH (the
  primary outcome)
- Other forms of symptomatic spontaneous or traumatic intracranial haemorrhage
  - Radiographically- or pathologically-proven spontaneous or traumatic
    extradural haemorrhage, subdural haemorrhage, subarachnoid
    haemorrhage, or intraventricular haemorrhage (not accompanying
    spontaneous ICH).
- Extracranial haemorrhage at any site requiring transfusion / endoscopic
treatment / surgery, or resulting in death

7.8.2 All serious vaso-occlusive events (including revascularisation
procedures)
This composite outcome includes fatal or non-fatal symptomatic events (that are
'serious' because of their usual need for hospitalisation and influence on outcome and
antithrombotic treatment) or revascularisation procedures (we will not include transient
ischaemic attack or retinal artery occlusion):

- Fatal or non-fatal vaso-occlusive events
  - Ischaemic stroke, acute coronary syndrome (unstable angina or
    myocardial infarction), mesenteric ischaemia or peripheral arterial
    occlusion.
  - Symptomatic deep vein thrombosis, pulmonary embolism.
- Carotid, coronary, or peripheral arterial revascularisation procedures.

7.8.3 Composite of all serious haemorrhagic or vaso-occlusive events
A further secondary analysis will be performed on the composite event which combines
the two composites defined above, i.e. the composite of any serious haemorrhagic or
vaso-occlusive event.

For completeness, the corresponding analysis will also be performed for each
composite outcome event proposed in the trial protocol.

The interpretation of the trial findings will respect this prespecified hierarchy of primary
outcome, key secondary outcomes and other secondary outcomes, and no formal
adjustment will be made to significance levels to allow for multiplicity.

7.8.4 Sensitivity analysis
A sensitivity analysis will be performed to reflect the cumulative incidence of serious haemorrhagic or vaso-occlusive events. This analysis will use re-randomisation tests, as described by Ford et al.†

7.8.5 Annual assessment of modified Rankin Scale (mRS)
A separate analysis will be performed for each annual assessment. The analysis at year ‘x’ will be restricted to those recruits who were randomised at least ‘x’ years prior to study close, to avoid including early deaths in the relevant follow-up year when the corresponding surviving recruits would not have had the potential to be assessed. The analysis will comprise a tabulation of mRS by randomisation group, with the formal analysis being based on a Mann-Whitney test. Participants’ type of domicile will be described as categorised on the discharge form and each annual participant questionnaire.

7.9 Sub-group analyses
A priori sub-groups for the primary analysis will be explored as follows:
- The five covariates used in the minimisation algorithm
- Pre-ICH antithrombotic drug regimen (antiplatelet versus anticoagulant)

We will also perform sub-group analyses according to whether a history of atrial fibrillation was documented as a co-morbidity at randomisation.

These sub-group analyses will be applied to the primary outcome and the key secondary outcomes: (i) all serious haemorrhagic events, (ii) all serious vaso-occlusive events (including revascularisation procedures), and (iii) the composite of all serious haemorrhagic or vaso-occlusive events.

These analyses will be performed by including an interaction term between treatment group and the relevant covariate in the Cox proportional hazards regression model described in Section 7.6 above. For the subgroup analysis relating to time since ICH symptom onset, two subgroups will be defined based on the time from onset being above or below the median time observed in the trial.

7.10 Serious adverse events
Serious adverse events (SAEs) are reported in RESTART if they not outcome events or expected complications of stroke. SAEs will be grouped by body system and for each event and each grouped set of events the number of events and the number of individuals experiencing at least one such event will be tabulated per randomised group.

7.11 Imaging sub-studies
The analysis of the imaging sub-studies will be largely exploratory. The MRI sub-study will test hypotheses about microbleeds and explore hypotheses about other modifiers of the effect of antiplatelet drugs. The diagnostic CT imaging study will explore hypotheses about modifiers of the effect of antiplatelet drugs.

The RESTART Imaging Panel’s report of MRI sub-study imaging will describe the baseline characteristics of the participants’ brains (e.g. brain microbleed

presence/location and burden; old infarcts or haemorrhages; superficial siderosis; white matter hyperintensities; enlarged perivascular spaces; and atrophy) and ICH (e.g. location, intraventricular extension; subarachnoid extension; and ICH volume).  
In the MRI sub-study, the focus of our hypothesis will be on testing whether the presence, number, or location of brain microbleeds modifies the effect of antiplatelet drugs on the primary outcome, adjusted for the same covariates used in the primary analysis of the entire RCT (although time since ICH will be grouped into 0-30 versus >30 days in view of the distribution of outcomes in the whole trial dataset. Should any of these adjusted regression models fail to converge then the corresponding unadjusted analysis will be reported instead. [before database lock and un-blinding to treatment allocation]). For dichotomous analysis the number of brain microbleeds will be split as 0 or 1 versus 2 or more and for categorical analysis the split will be 0 or 1 versus 2 to 4 versus 5 or more. Brain microbleed location will be grouped as strictly lobar versus other.

The RESTART Imaging Panel's report of diagnostic imaging will describe the baseline characteristics of the trial population’s brains (e.g. old vascular lesions, periventricular lucencies, and atrophy) and ICH (e.g. location, intraventricular extension, subarachnoid extension, ICH volume, and finger-like projections‡).

8 Data Sharing

A set of files, containing the final data will be prepared, along with their corresponding data dictionary. These will be made available to the Chief Investigator at the end of the analysis phase.

Ownership of the data arising from this study resides with the Trial Steering Committee. 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.

Appendix 1: Outcome measures specified in the protocol

Primary
- Fatal or non-fatal radiographically- or pathologically-proven recurrent symptomatic ICH.

Secondary
In addition to the primary outcome defined above these additional outcome events will be captured for individual analysis and/or the derivation of composite endpoints:-
- 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
  - Deaths without a clear cause and without further investigation
  - Deaths from any other cause

Annual ratings of participant function completed by participant or their carer
- Simplified modified Rankin Scale postal questionnaire
- Structured telephone interview with non-responders to the postal questionnaire
Appendix 2: Statistical extracts from the protocol

Sample size calculation

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 literature suggests that the event rate lies in the range of about 1.8 to 7.4% per annum. 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 (RR=1) to a 4-fold excess (RR=4). This pilot study of 720 patients will have excellent power (after all participants have been followed for at least two years) to detect a doubling of the rate of ICH if the true rate is 4.5% per annum, but there would be 93% power at the 5% significance level to detect a 4-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. Previous meta-analyses of RCTs of antiplatelet drugs have provided reliable information on the relative effects of antiplatelet regimens in the sorts of people with vaso-occlusive disease who will have been recruited into RESTART, so information about the overall rates of serious vascular events (for both arms combined) will be used together with reasonable assumptions about the effects of antiplatelet drugs on such events in order to assess the plausibility of a net benefit emerging in a larger main study.

The TSC 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 subgroups (e.g. lobar ICH location).

Contraindications to MRI, claustrophobia, non-attendances, and scheduling constraints lead to an attrition of ~25% of patients, so we would hope to obtain brain MRI on ~550 patients before randomisation. To maximise our chances of recruiting the target number of patients with brain MRI, we will target the set-up of sites where brain MRI is available in the first 3-6 months of the start-up phase of RESTART.

Proposed analyses

Our provisional analysis plan is described below, but we intend to publish a final Statistical Analysis Plan 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 logrank test.
Primary analysis

This will be restricted to the primary outcome of first fatal or non-fatal radiographically- or pathologically-proven recurrent symptomatic ICH.

Secondary analyses

Other possible manifestations of recurrent spontaneous ICH

We will conduct two exploratory sensitivity analyses of our primary analysis, by adding the following secondary outcomes to the primary outcome in the following order, to account for the possibility that some fatalities and non-fatal neurological events without adequate investigation may be recurrent ICH:

- Fatal or non-fatal symptomatic stroke consistent with the clinical manifestations of ICH, but without radiographic or pathological confirmation (or with brain imaging performed too late to distinguish ICH from ischaemic stroke).
- Deaths without a clear cause and without further investigation.

Other potential composite outcomes

Other forms of symptomatic spontaneous or traumatic intracranial haemorrhage

- Fatal or non-fatal radiographically- or pathologically-proven spontaneous or traumatic extradural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, or intraventricular haemorrhage (not accompanying spontaneous ICH).

Fatal or non-fatal extracranial haemorrhage

- At any site (but this will mainly be upper or lower gastrointestinal bleeding), requiring transfusion / endoscopic treatment / surgery, or resulting in death.

Fatal or non-fatal vaso-occlusive events

- Transient ischaemic attack, ischaemic stroke, unstable angina, myocardial infarction, peripheral arterial occlusion, or retinal arterial occlusion.
- Symptomatic deep vein thrombosis, pulmonary embolism.
- Carotid, coronary, or peripheral arterial revascularisation procedures.

Composite outcome of serious vascular events

- Non-fatal myocardial infarction.
- Non-fatal stroke.
- Death from a vascular cause (including sudden death, pulmonary embolism, haemorrhage, and death from an unknown cause).

Sub-group analyses

We will perform the following sub-group analyses of the primary outcome, and test for sub-group interactions if appropriate:
- Qualifying ICH location (lobar versus non-lobar, based on local investigator's interpretation of scan)
- Time since ICH symptom onset (0-6 days, 7-30 days, > 30 days)
- Antiplatelet drug(s) that the patient's physician would start if allocated (aspirin alone versus other antiplatelet regimen [including combination treatment])
- Participant age at randomisation (<70 years versus 70 years or older)
- Predicted six month outcome (predicted probability of good outcome <0.15 versus ≥0.15)
- Pre-ICH antithrombotic drug regimen (antiplatelet versus anticoagulant)

**Brain MRI sub-study**

Brain microbleeds on MRI appear to be a biomarker of bleeding-prone microangiopathies (such as arteriolosclerosis and cerebral amyloid angiopathy), they predict recurrent ICH, and lobar microbleeds also appeared to modify the effect of aspirin on recurrent ICH risk in one observational study. Furthermore, a collaborative meta-analysis of case-case comparisons has found a preponderance of brain microbleeds amongst patients who had an ICH whilst taking antiplatelet drugs compared to those who were not on any antithrombotics when they had an ICH. So we intend to perform a brain MRI sub-study in ~550 of the 720 participants to better understand these microangiopathies by exploring whether the presence, number, or location of brain microbleeds modifies the effect of antiplatelet drugs on the primary outcome."