Clinical trial results:
REstart or STop Antithrombotics Randomised Trial (RESTART)

Summary

EudraCT number	2012-003190-26
Trial protocol	GB
Global end of trial date	10 February 2021

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021
Summary attachment (see zip file)	RESTART Lancet Main Results (2019_The Lancet_RESTART main results with appendix.pdf) RESTART Lancet Imaging results (2019_Lancet Neurol_RESTART imaging paper with appendix.pdf) Results of final extended follow-up of RESTART (2021_JAMA Neurol_RESTART extended follow-up.pdf)

Trial information

Trial identification

Sponsor protocol code	RESTART13

Additional study identifiers

ISRCTN number	ISRCTN71907627
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Academic and Clinical Central Office for Research and Development (ACCORD)
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Head of Research Governance , Academic and Clinical Central Office for Research and Development (ACCORD), +44 0131 242 3330, enquiries@accord.scot
Scientific contact	Professor Rustam Al-Shahi Salman, University of Edinburgh, +44 0131 242 7014, rustam.al-shahi@ed.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2019
Global end of trial reached?	Yes
Global end of trial date	10 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Research question: For adults surviving 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, does a policy of starting antiplatelet drugs result in a beneficial net reduction of all serious vascular events compared with a policy of avoiding antiplatelet drugs?

Primary objective of the pilot phase: 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.

This entry on EudraCT relates to the main results of the trial, published in 2019. This entry also includes the final results after 2-year extended follow-up, published in 2021, as a summary attachment.

Protection of trial subjects:

RESTART was conducted in accordance with all relevant data protection, ethical and regulatory requirements to ensure the privacy and security of patient information and to ensure the rights, safety and well-being of the patients and the quality of the research data.

We sought support and advice from members of the patient reference group for the Research to Understand Stroke due to Haemorrhage (RUSH) programme for ongoing review of our study materials and on trial progress. We also included a member of this group as part of our Independent Steering Group.

We sought to minimise risk and the burden to the patient without compromising the scientific rigour of the trial. Risk was minimised by excluding patients in whom the risks were likely to be the greatest e.g. patients on anticoagulation. Annual follow-up questionnaires were kept to a minumum to avoid burden and a central helpline was available to support participants, families, general practitioners (GPs) and research staff.

Background therapy:

Any background therapy was determined for participants by the clinical teams at each of our 104 hospital sites.

Evidence for comparator:

The intervention in RESTART was standard care and antiplatelet therapy (any of aspirin, clopidogrel, or dipyridamole); the comparator was standard care without antiplatelet therapy.

The Antithrombotic Trialists' Collaboration meta-analysis of randomised controlled trials found that aspirin use for the secondary prevention of occlusive vascular disease reduces risk of major vascular events, even though it might increase the risk of intracranial haemorrhage (a composite of intracerebral, subarachnoid, or subdural haemorrhages). However, these trials excluded patients with intracerebral haemorrhage, the commonest subtype of intracranial haemorrhage with the worst outcome. We searched the Cochrane Stroke Group Register, the Cochrane Central Register of Controlled Trials, Ovid MEDLINE (from 1948), Ovid Embase (from 1980), online registries of clinical trials, and bibliographies of relevant publications on Jan 28, 2019, for randomised controlled trials of starting versus avoiding antiplatelet therapy after intracerebral haemorrhage, from database inception until Jan 28, 2019, without language restrictions. We found no completed randomised controlled trials. A meta-analysis of observational studies found no difference in the risk of haemorrhagic events and a lower risk of

occlusive vascular events associated with antiplatelet therapy resumption after any type of intracranial haemorrhage.

Actual start date of recruitment	04 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 537
Worldwide total number of subjects	537
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	86
From 65 to 84 years	376
85 years and over	75

Subject disposition

Recruitment

Recruitment details:

Between May 22, 2013, and May 31, 2018, 562 patients were consented and 537 enrolled in 104 of 122 UK hospitals. 25 patients were not enrolled; 6 were ineligible; 7 had deterioration of health condition; in 11 cases the patients, clinician, carer or family member were not uncertain about antiplatelet use and 1 consented after recruitment ended.

Pre-assignment

Screening details:

RESTART did not require sites to collect information about patients screened for eligibility, however we analysed screening logs at sites that kept them and published the results in Trials 2017;18:162 (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1909-4).

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Staff following up the participants at the trial coordinating centre were masked to treatment allocation. Outcome event adjudicators were masked to participant identity, treatment allocation, and drug use.

Arms

Are arms mutually exclusive?	Yes
Arm title	Start Antiplatelet

Arm description:

The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant.

Arm type	Experimental
Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As instructed by clinician

Investigational medicinal product name	Dipyridamole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As directed by clinician

Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As prescribed by randomising clinician

Arm title	Avoid Antiplatelet

Arm description:

The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Start Antiplatelet	Avoid Antiplatelet
Started	268	269
Completed	268	268
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Start Antiplatelet
Reporting group description:	
The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant.	
Reporting group title	Avoid Antiplatelet
Reporting group description:	
The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation.	

Reporting group values	Start Antiplatelet	Avoid Antiplatelet	Total
Number of subjects	268	269	537
Age categorical			
At baseline, participants in the two treatment groups were on average 76 years old			
Units: Subjects			
<70 years	73	73	146
≥ 70 years	195	196	391
Age continuous			
Age Overall (median)			
Units: years			
median	77.0	76.0	
inter-quartile range (Q1-Q3)	69.0 to 82.0	69.0 to 82.0	-
Gender categorical			
As in many other randomised trials of intracerebral haemorrhage, most participants were male, which might be because of their propensity to be invited or consent rather than differences in incidence or outcome of intracerebral haemorrhage compared with women.			
Units: Subjects			
Female	95	82	177
Male	173	187	360
Ethnicity Units: Subjects			
White	251	242	493
Asian	12	18	30
Black	4	5	9
Other	1	4	5
Probability of good 6-month outcome			
Predicted probability of being alive and independent at 6 months. See Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. Stroke 2002; 33(4):1041-1047			
Units: Subjects			
<0.15	48	51	99
>=0.15	220	218	438
Location of intracerebral haemorrhage Units: Subjects			
Non-Lobar	102	103	205
Lobar	166	166	332
Time since ICH symptom onset to			

randomisation Groups Units: Subjects			
0-6 days	10	11	21
7-30 days	59	59	118
>30 days	199	199	398
Context of enrolment - Location Units: Subjects			
Clinic	181	173	354
Hospital	87	96	183
Context of enrolment - Consent giver Units: Subjects			
Proxy	56	56	112
Patient	212	213	425
History of intracranial or extracranial haemorrhage Units: Subjects			
Yes	22	25	47
No	246	244	490
Indication for antithrombotic therapy before intracerebral haemorrhage			
Full category name; > At least one occlusive vascular disease ----With atrial fibrillation ----Without atrial fibrillation >No occlusive vascular diseases ----With atrial fibrillation ----Without atrial fibrillation			
Units: Subjects			
Occlusive vascular disease (with AF)	42	50	92
Occlusive vascular disease (without AF)	194	189	383
No occlusive vascular disease (with AF)	19	23	42
No occlusive vascular disease (without AF)	13	7	20
Time since ICH symptom onset to randomisation in days (Overall) Units: day			
median	80.0	71.0	
inter-quartile range (Q1-Q3)	29.5 to 148.5	29.0 to 144.0	-

End points

End points reporting groups

Reporting group title	Start Antiplatelet
Reporting group description:	
The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant.	
Reporting group title	Avoid Antiplatelet
Reporting group description:	
The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation.	

Primary: Recurrent symptomatic spontaneous intracerebral haemorrhage

End point title	Recurrent symptomatic spontaneous intracerebral haemorrhage
End point description:	
End point type	Primary
End point timeframe:	
First event after randomisation and before death or most recent follow up.	

End point values	Start Antiplatelet	Avoid Antiplatelet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	268		
Units: Events	12	23		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards regression
Comparison groups	Start Antiplatelet v Avoid Antiplatelet
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.06
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.03

Notes:

[1] - Adjusted for minimisation variables: 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.

Secondary: All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage)

End point title	All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage)

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start Antiplatelet	Avoid Antiplatelet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	268		
Units: Events	18	25		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards regression
Comparison groups	Start Antiplatelet v Avoid Antiplatelet
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.27
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.3

Notes:

[2] - Adjusted for minimisation variables: 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.

Secondary: All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial

revascularisation procedures)	
End point title	All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial revascularisation procedures)

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start Antiplatelet	Avoid Antiplatelet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	268		
Units: Events	39	38		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards regression
Comparison groups	Avoid Antiplatelet v Start Antiplatelet
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.92
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.6

Notes:

[3] - Adjusted for minimisation variables: 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.

Secondary: All major haemorrhagic or occlusive vascular events	
End point title	All major haemorrhagic or occlusive vascular events

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start Antiplatelet	Avoid Antiplatelet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	268		
Units: Events	54	61		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards regression
Comparison groups	Start Antiplatelet v Avoid Antiplatelet
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.43
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.24

Notes:

[4] - Adjusted for minimisation variables: 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.

Secondary: Major occlusive vascular events

End point title	Major occlusive vascular events

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start Antiplatelet	Avoid Antiplatelet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	268		
Units: Events	45	52		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards regression
Comparison groups	Start Antiplatelet v Avoid Antiplatelet
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.39
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.25

Secondary: Major vascular events (as defined by the Antithrombotic Trialists' Collaboration)

End point title	Major vascular events (as defined by the Antithrombotic Trialists' Collaboration)

End point description:

End point type	Secondary

End point timeframe:

First event after randomisation and before death or most recent follow up.

End point values	Start Antiplatelet	Avoid Antiplatelet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	268		
Units: Events	45	65		

Statistical analyses

Statistical analysis title	Adjusted Cox proportional hazards regression

Statistical analysis description:

Adjusted for minimisation variables: 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.

Comparison groups	Start Antiplatelet v Avoid Antiplatelet
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.95

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events in the RESTART trial were collected for all participants from the period between randomisation and the end of the trial (unless they withdrew).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Start Antiplatelet

Reporting group description:

The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant.

Reporting group title	Avoid Antiplatelet

Reporting group description:

The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Section 12.5 of the protocol states, "...safety assessments in RESTART are focussed on detecting: primary and secondary outcomes (all of which relate to the safety of antiplatelet drugs in this patient group) and any SAEs and SUSARs... PIs need not report to the TCC or sponsor any non-fatal AEs that are neither primary/secondary trial
outcomes nor SAEs nor SUSARs, and which are expected complications of ICH."

Serious adverse events	Start Antiplatelet	Avoid Antiplatelet	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 268 (1.87%)	5 / 269 (1.86%)	
number of deaths (all causes)	54	50	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer	Additional description: Admitted with vomiting, meleana and haematuria. Investigations highly suggestive of metastic prostate carcinoma.		
subjects affected / exposed	0 / 268 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Colitis	Additional description: admitted following flexisigmoidoscopy with severe colitis and pain		
subjects affected / exposed	0 / 268 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac failure congestive	Additional description: Patient admitted with with shortness of breath - suspected mild pulmonary oedema and small pleural effusions. Diagnosed with congested cardiac failure .		
subjects affected / exposed	1 / 268 (0.37%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder	Additional description: syncopal episode after bowel prep for colonoscopy for change in bowel habit. Needed Mg replacement		
subjects affected / exposed	1 / 268 (0.37%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Strangulated hernia repair	Additional description: admitted for repair of strangulated paraumbilical hernia		
subjects affected / exposed	1 / 268 (0.37%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Postictal paralysis	Additional description: Admitted with right arm shaking,slurred speech was being treated as ischaemic stroke initially and started on Aspirin 300mg,MR scan later ruled out ischaemic stroke and is now thought to be Todds Paresis		
subjects affected / exposed	0 / 268 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hydrocholecystis	Additional description: cholecystis		
subjects affected / exposed	0 / 268 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pelvic fracture	Additional description: fractured pubic rami		
subjects affected / exposed	0 / 268 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture	Additional description: Fractured L neck of femur following fall . Patient has had L dynamic hip screw		
subjects affected / exposed	1 / 268 (0.37%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Start Antiplatelet	Avoid Antiplatelet	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 268 (0.00%)	0 / 269 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2013	AM01 Updated documents; - Protocol v2.0 - Participant Consent form v2.0 - GPIL Letter v2.0 - Participant Annual Questionnaire v2.0 - Participant Prompt v2.0 - Participant Information Sheet v2.0 - Participant Legal Representative Consent form v2.0 - Regained Capacity Participant Information Sheet v2.0 - RIL Participant Information Sheet v2.0
22 April 2013	AM04 New sites
03 July 2013	AM07 New sites Changes PI
11 July 2013	AM05 New sites
23 July 2013	AM06 Updated documents; - GP event form v2.1 - GPIL Letter v4.0 - Participant Annual Questionnaire v4.0 - Participant consent form V3.0 - GP follow up letter and questionnaire V3.0 - Patient Information Leaflet V3.0 - Participant annual questionnaire V4.0 - PLR consent form V3.0 - Protocol V4.0 - RIL V3.0 - Recovered PIL
31 January 2014	AM10 New sites Changes PI
11 March 2014	AM11 New sites Changes PI
23 April 2014	AM13 Updated documents; - GP follow-up letter and questionnaire V4 - Participant annual questionnaire V5 - Protocol V5
18 July 2014	AM15 New sites Changes PI

06 December 2014	AM09 New sites Changes PI
14 January 2015	AM16 Changes PI
16 April 2015	AM18 Updated documents; - RESTART consultant invitation letter to patient V1.2 - RESTART GP invitation letter to patient V1.2 - Protocol V6
19 June 2015	AM19 Changes PI
23 October 2015	AM20 Changes PI
28 January 2016	AM23 Changes PI
05 February 2016	AM21 Updated documents; - Participant consent form V4.0 - Participant consent form [Participant Consent Form] V4.0 - Participant consent form [Personal Legal Representative] V4.0 - Participant information sheet [PIS] V4.0 - Participant information sheet [Relative IF] V4.0 - Participant information sheet [Recovered] V4.0
27 June 2016	AM25 Changes PI
07 October 2016	AM26 Changes of PI
11 January 2017	AM27 Changes of PI's
05 April 2017	AM28 (REC reference AM29) New site Change of PI
28 June 2017	AM29 (REC reference AM30) Change of PI
05 September 2017	AM30 (REC reference AM32) Change of PI
13 October 2017	AM31 (REC reference AM31) Updated documents - Summary of Characteristics booklet v1.0 - Protocol Version v8.0
24 April 2019	AM34 Change to SmPCs for Dipyridamole and Clopidogrel

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitation of the trial was that it did not achieve its intended sample size.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29282142

http://www.ncbi.nlm.nih.gov/pubmed/31129065

http://www.ncbi.nlm.nih.gov/pubmed/28381307

http://www.ncbi.nlm.nih.gov/pubmed/28253897

http://www.ncbi.nlm.nih.gov/pubmed/28245843

http://www.ncbi.nlm.nih.gov/pubmed/30909946

http://www.ncbi.nlm.nih.gov/pubmed/31128924

http://www.ncbi.nlm.nih.gov/pubmed/29506580