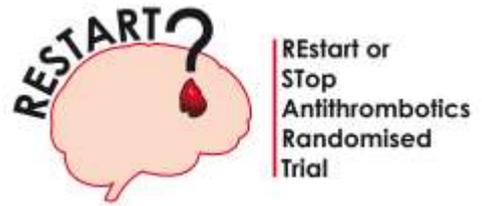


Frequently asked questions (FAQs)



If you still have questions after reading the protocols and other information available at www.restarttrial.org/about.html, please read the FAQs below. If these do not answer your questions, please contact RESTART.trial@ed.ac.uk.

PATIENT ELIGIBILITY

Q: How often might I encounter an eligible patient?

A: Roughly 20% of newly-diagnosed patients with non-traumatic intracerebral haemorrhage (ICH), or roughly **2% of all new strokes**, are eligible. We derived this estimate in NHS Lothian (population ~800,000), where there were 166 patients with newly-diagnosed ICH in one year, 33 of whom (20%) had been on an antithrombotic (i.e. antiplatelet or anticoagulant) drug until the time of their ICH and survived for at least 30 days afterwards.

Q: Is there a minimum time window from the onset of ICH to randomisation?

A: Yes. You should not randomise a patient within the first 24 hours of ICH symptom onset.

Q: Is there a maximum time window from the onset of ICH to randomisation?

A: No. You can randomise an eligible patient **at any time after the ICH**, provided the brain imaging that first diagnosed the ICH is available and they meet the other eligibility criteria. Note that the web portal will alert you if the ICH occurred more than 90 days before you randomise the patient, but this is not a problem it's just intended to minimise data entry errors.

If the patient is an inpatient, randomisation can occur at any time before their discharge from the hospital to which they were admitted (or to which they were repatriated from a hyperacute stroke unit).

If the patient is an outpatient, try to randomise them on the same day as you see them in a TIA/stroke/neurovascular clinic. See the recruitment FAQs below, for top tips on how to do this.

Q: What if my patient's prognosis is poor?

A: It is difficult to give specific guidance about this, which is why it is not in the eligibility criteria. We expect our collaborators to be uncertain about the use of antiplatelet drugs in patients who are likely to survive an ICH and who may benefit from protection against ischaemic events. We will determine the effects of antiplatelet drugs over two years of follow-up, so there should be a reasonable expectation that patients who are recruited will survive that long.

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Q: Is a patient eligible if they have had an ICH and then an ischaemic event before randomisation?

A: Yes. Provided the patient fulfils all of the eligibility criteria, this is permitted. Please describe the ischaemic event that followed the ICH on the Randomisation Form in the, "Other indication for antithrombotic drugs" part of section 5 and/or in Section 9.

Q: Is a patient eligible if they have been given an antiplatelet drug for an ischaemic event occurring after ICH but before randomisation?

A: Yes, if there is uncertainty about whether or not they should be taking an antiplatelet drug. However, we recommend that you wait for **one week** since the last dose of the antiplatelet drug was given before randomising the patient.

Q: Is a patient eligible if they have used an antithrombotic drug for primary prevention before ICH?

A: For patients with **atrial fibrillation (AF)**, antithrombotic drugs, especially anticoagulants, are beneficial for primary prevention of ischaemic events (see below), so these patients are eligible and suitable for RESTART.

For patients in **sinus rhythm**, there is insufficient evidence to support the use of antiplatelet drugs for primary prevention of ischaemic events. We do not expect there to be uncertainty about restarting antiplatelet drugs for most of these patients after an ICH. However, in rare circumstances, investigators and patients may be uncertain, so please mention 'primary prevention' on the Randomisation Form in the, "Other indication for antithrombotic drugs" part of section 5, and describe your reasons for uncertainty in Section 9.

Q: Is a patient eligible if they have purely subarachnoid/subdural/extradural haemorrhage distant from an intracerebral haemorrhage that makes them eligible for RESTART?

A: Yes. Subarachnoid haemorrhage at a distant site may arise from a separate spontaneous subarachnoid haemorrhage at the same time as the ICH, or circulation of subarachnoid haemorrhage from an ICH that extends to the subarachnoid space. However, under these circumstances, please make sure that both bleeds are not explained by trauma; that would make the patient ineligible. Of course, if the history and imaging indicate that a patient had a spontaneous ICH and then also sustained traumatic haemorrhage as a result of a fall, then they would be eligible.

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Q: What do you mean by antithrombotic, anticoagulant, and antiplatelet drugs?

A: Antithrombotic drugs are a group of drugs including antiplatelet agents (i.e. platelet aggregation inhibitors, such as aspirin, dipyridamole, and clopidogrel), anticoagulant agents (i.e. vitamin K antagonists, heparin, direct thrombin inhibitors and Xa inhibitors) and thrombolytic enzymes. For patients randomised in RESTART, there should be uncertainty about whether to start or avoid **antiplatelet drugs** after ICH.

Q: What if my patient was on anticoagulant drugs until the time of their ICH?

A: If your patient was on anticoagulant drugs prior to their ICH, you do not intend to restart anticoagulant drugs, and you are uncertain about whether or not to start antiplatelet drugs then your patient might be eligible for RESTART.

Q: What if I intend to start my patient on anticoagulant drugs after their ICH?

A: They are not eligible for RESTART.

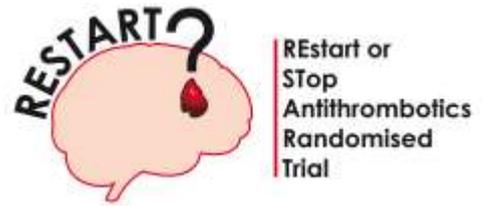
Q: My patient was on an anticoagulant drug before their ICH because of atrial fibrillation. Is it appropriate to recruit them to RESTART?

A: Deciding whether or not to restart antithrombotic drugs in patients with AF after anticoagulant-associated ICH is difficult, because these patients were not included in RCTs that investigated the effects of antithrombotic drugs for patients with AF. The options in this situation, none of which is supported by evidence from RCTs, are: avoid all antithrombotic drugs, restart warfarin, start a novel oral anticoagulant, occlude the left atrial appendage, start an antiplatelet drug, or randomise the patient in RESTART. The CHA₂DS₂-VASc and HAS-BLED prediction scores are useful adjuncts to supporting this decision. However, the effects of antithrombotic drugs on the event rates predicted by these scores (and the overall balance of benefit and harm) in patients who have AF and an anticoagulant-associated ICH are also not known.

The evidence supporting the use of antithrombotic drugs *for patients with AF* is as follows:

- For patients with **no** previous history of stroke or TIA, three RCTs in a Cochrane review found that aspirin significantly reduced the risk of all vascular events in comparison to avoiding antithrombotic drugs (OR 0.71, 95% CI 0.51 to 0.97).¹
- For patients **with** a previous history of stroke or TIA, one small RCT in a Cochrane review found a *non-significant* reduction of all vascular events in comparison to avoiding antithrombotic drugs (OR 0.89, 95% CI 0.64 to 1.24).²
- A larger meta-analysis of RCTs found antiplatelet drugs to reduce the risk of recurrent stroke.³
- Cochrane reviews have shown that oral anticoagulants are superior to antiplatelet drugs for reducing the risk of all vascular events for secondary prevention,⁴ and for

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reducing the risk of stroke (with an increase in the risk of intracranial haemorrhage) for primary prevention.⁵

- Guidelines differ slightly in their recommendations about antiplatelet drugs and AF:
 - The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) guideline (*Eur Heart J* 2010;31:2369–429) for the management of AF recommends, “that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thrombo-embolism and bleeding, and the relative risk and benefit for a given patient.”
 - The AHA/ACC/HRS guideline (*J Am Coll Cardiol* 2014 *in press*) for the management of patients with AF recommends, “Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient’s preferences.”
 - The UK SIGN guideline (129, June 2013) recommended that in AF, “Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined.”
 - The UK NICE guideline (CG180, June 2014) on the management of AF recommended in section 1.5.15, “Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation.” This may be because of the superior efficacy of anticoagulant drugs, but RCTs do support the use of antiplatelet drugs (as above). There is no legal duty to comply with this NICE recommendation, because it is not worded, ‘must’ or ‘must not’.
 - But of course there is no RCT evidence about the effects of antithrombotic drugs for people in AF who have had ICH, so guidelines have not made specific recommendations for this group, and the use of antiplatelet drugs in RESTART may be reasonable on the basis of the information above.

PATIENT RECRUITMENT

Q: When is the best time to recruit a participant?

A: To date, our collaborators have randomised participants in RESTART at a median average of 57 days after ICH symptom onset. Many patients are being randomised in outpatients, and we would like all of our collaborators to use this approach as much as possible, especially to bring suitable, eligible patients back. So your options are to:

- Identify potentially eligible patients whilst they are inpatients.
- Perform sub-study MRI and randomise suitable eligible inpatients whilst in hospital.
- If inpatients are not ready to be randomised by discharge, then confirm eligibility and obtain consent before discharge. Flag them for recruitment at an outpatient appointment.
- It may be appropriate to confirm eligibility and obtain consent whilst an inpatient, and arrange an outpatient MRI after which recruitment and randomisation can occur in outpatients.

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IMAGING QUESTIONS

Q: Can I use a 'phantom' scan for the test scan?

A: No, the test scans must be of a person, as we need to review the image quality.

Q: Do I need to consent the patient whose imaging is used for the test scan?

A: Since you should only send anonymised imaging that does not contain personal data, this does not require consent according to the Data Protection Act. MRI sequences and parameters vary from patient to patient according to the protocol determined by radiologists in everyday practice, so changing your local MRI sequences and parameters for the RESTART test MRI is no different from what is done in routine clinical practice without explicit patient consent. The RESTART MRI protocol should not take longer than your usual MRI 'stroke protocol', and its sequences and parameters are thought to be optimal for the investigation of stroke so we hope your radiologist may decide to adopt it anyway! If you still have concerns about this, we recommend you seek the advice of your local Caldicott Guardian.

Q: Must I encrypt the CD that I use to send the imaging?

A: Ideally if you have encryption software then yes, however you may send an unencrypted CD so long as it is anonymised correctly and there are no patient identifiable data on it.

Q: Who can upload the scans via the RESTART website?

A: Any member of your team who has completed the RESTART training, has a current GCP certificate and is named on the delegation log can upload the imaging. This will usually be the trial co-ordinator but may also be a research radiographer at your hospital.

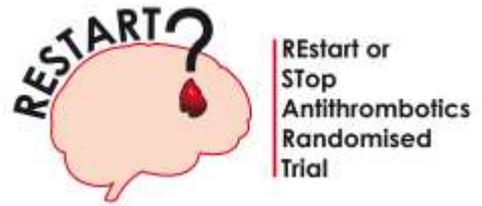
Q: Does an image transfer form have to be completed when sending a CD?

A: Yes, you must complete an image transfer form on the web site, print a copy and enclose it in the parcel with the CD. Full instructions for doing this are in the Imaging Guidelines.

Q: Does my hospital have to be able to participate in the brain MRI sub-study to become a RESTART site?

A: No, it's not compulsory. If a patient has had brain computed tomography (CT) and isn't suitable for MRI for one reason or another, randomise them anyway. However, we do want as many of the patients as possible to have MRI before randomisation. So, we will start the site initiation process at hospitals that can participate in the MRI sub-study.

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Q: Does my hospital have to have a research MRI scanner to be in the MRI sub-study?

A: No, provided your NHS MRI scanner can be set up with a specific sequences and related parameters specified in the RESTART MRI protocol (www.restarttrial.org/about.html). If your site is participating in CROMIS-2, the same MRI protocol is suitable for RESTART. Please try and **perform the gradient echo sequence first**, before the other sequences.

Q: My patient's ICH was diagnosed using MRI. Can I use that MRI for the MRI sub-study?

A: Yes, provided your MRI scanner has performed the MRI in accordance with the specific sequences and related parameters described in the RESTART MRI protocol (www.restarttrial.org/about.html). We will reimburse you £350 for a per-protocol MRI whether or not it was performed in routine clinical practice, or specifically for RESTART.

Q: How long after the sub-study MRI can I randomise my patient?

A: There is no fixed time limit on this, but we expect RESTART sites to randomise patients within the week after a specific sub-study MRI is performed.

Q: What if my patient's baseline MRI shows lots of brain microbleeds?

A: We do not know whether brain microbleeds affect the risk of recurrent ICH for patients who take antiplatelet drugs after ICH. There have been no randomised controlled trials addressing this issue (until RESTART). There have been very few observational studies, none of which showed a dramatic effect. Therefore, you can randomise patients with any number of microbleeds if you feel uncertain about the risks and benefits of antiplatelet drugs.

Q: Will RESTART issue a clinical report on brain MRIs obtained for the trial?

A: No, clinical reports are the responsibility of the local radiology department.

TREATMENT ALLOCATION

Q: If a participant is randomised to 'start antiplatelet drugs', which drugs may I prescribe?

A: You may prescribe one or more of aspirin, clopidogrel, or dipyridamole, as pre-specified by the patient's clinician at the time of randomisation. ICH is not a contraindication to the use of aspirin or dipyridamole. Active bleeding is a contraindication to the use of clopidogrel, which is why patients cannot be randomised within 24 hours of ICH symptom onset.

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TREATMENT DURING FOLLOW-UP

Q: What if an ischaemic event occurs during follow-up and my patient was randomised to a policy of avoiding antiplatelet drugs?

A: Ischaemic events during follow-up should be managed as they normally would and at the discretion of the treating clinician.

Q: Can patients randomised to a policy of avoiding antiplatelet drugs use aspirin for pain relief?

A: If an alternative analgesic could be used instead of aspirin, please use it for patients allocated to a policy of avoiding antiplatelet drugs.

OUTCOME EVENTS DURING FOLLOW-UP

Q: What if I become aware of an outcome event during follow-up?

A: Please help us detect all outcome events by recording and reporting the occurrence of a primary outcome (recurrent ICH) or secondary outcome using the 'New Event Report form' which is available via the > Documents > Downloads section of the RESTART web portal. This brief form should be faxed to 0131 242 7995 or emailed to Rustam.Al-Shahi@nhs.net.

FUNDING

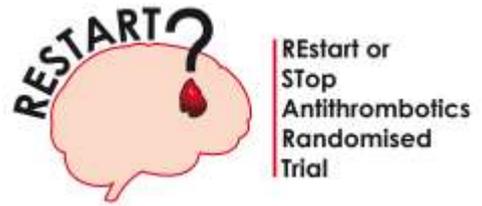
Q: What funding is available?

A: The reimbursement is £50 for a copy of the diagnostic CT and baseline data, and £350 for both MRI and associated copying/transferring/administrative costs.

Q: Are patients' travel costs funded?

A: Because follow-up is done centrally, it would be exceptional for a patient to need to return to hospital for RESTART, so there is no reimbursement of transport costs.

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RELATIONSHIP TO OTHER STUDIES AND TRIALS IN THE UK

Q: Can I co-enrol a patient into another randomised controlled trial (RCT)?

A: Participants in TICH2 (www.tich-2.org) 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. 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. Arrangements for co-enrolment with another CTIMP will be bound by a written agreement between the RESTART Chief Investigator and Co-Sponsors and the Chief Investigator and Sponsor(s) of the other CTIMP(s). This agreement will include: safety reporting measures if required; a minimum wash-out period between last dose in one study and first dose in another; a statement to indicate that the chairs of the TSC/DMC from each study that they have no objections to the proposals for co-enrolment; and a statement that arrangements for attribution of liability for co-enrolled participants have been put in place. Research staff should obtain permission to enrol patients who are participants in other CTIMPs from the RESTART Chief Investigator via the TCC or by email and a record of co-enrolled participants should be maintained.

Q: What should I do if my patient is eligible for both RESTART as well as FOCUS?

A: If you are running both trials at your hospital, if your patient is eligible for both trials, and if they are willing to be randomised in either trial, we recommend that you randomise the patient in RESTART.

Q: Can I co-enrol my patient in an observational study such as CROMIS-2?

A: Yes, you can. CROMIS-2 (ICH) includes patients with ICH, but provided these patients are eligible for RESTART they can be randomised in RESTART.

ADMINISTRATIVE ISSUES

Q: Is this study adopted onto the UKCRN Portfolio?

A: Yes

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Q: Is RESTART subject to the NIHR High Level Objective of recruiting the first patient within 30 days of NHS permission being granted?

A: RESTART is led from Scotland, so this NIHR High Level Objective does not apply to this trial. Furthermore, non-commercial studies with an overall target of 12 or fewer patients per year are excluded from being measured against the requirement to recruit the first participant within 30 days of NHS permission being granted (High Level Objective 5); given that participants eligible for RESTART constitute ~2% of all new strokes, it is unlikely that a site will recruit more than one patient per month.

Q: What is the duration of the trial and what is the time window for recruitment?

A: Recruitment began in May 2013. Following approval from the BHF in March 2016 the study has been extended by 1 year. The Study end date is now 28th February 2019. The end date for recruitment is now 31st May 2018 and patients will be followed up for a minimum of 6 months.

Q: What are my START and STOP dates on the Delegation Log?

A: Your Start date corresponds to the date you were delegated responsibility for involvement with the trial at your centre. Your STOP date is the day your involvement with the trial ended.

Q: What is the CSP number for RESTART?

A: It is 113625. Our Host for CSP is Sheffield and all the regulatory documents you require are there. RESTART is not a legacy study.

Q: Can you send me the word documents for consent and the patient information leaflet for us to input the trust logo for local review?

A: As part of the trial set up we have asked you to provide us with your trust logo. When we release the SSI to your site we will send you copies of the current versions of all those forms with your trust logo as part of that process. We will not send the SSI or documents to you until we have all the documents that we require.

Q: My Trust only requires the PI to have GCP training every 3 years, will you accept that?

A: No, sorry. The protocol and sponsor require a PI and those working on RESTART to have a current GCP certificate. The definition of current is in the past 24 months. You can do a GCP update session on line or contact your local network to see when the next course local to you is running.

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TECHNICAL PROBLEMS

Q: What happens if I forget my password for the RESTART website?

A: To recover your password please follow these steps:

- Log in to the RESTART web portal via www.RESTARTtrial.org >Login, or type this URL in your browser: <http://dcnapp1.dcn.ed.ac.uk/restart/default.htm>
- Click login at the left hand side
- Beneath the Username and Password boxes is a note to 'click here' if you have forgotten your details. Please click this
- Enter your email address (this is also your username)
- Press the "Submit" button
- Your password will be sent to your email address
- You can now use this to log on
- If this does not work please email restart.itsupport@ed.ac.uk

Q: How do I add new users to the RESTART website?

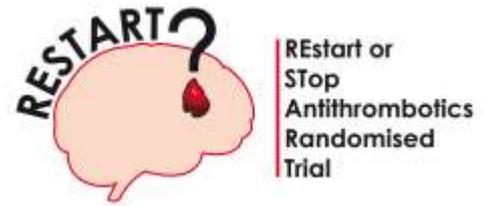
A: Only the Principal Investigator and Centre Coordinator can add new users to the RESTART website. Here's how to add a user:

- Log on to the RESTART web portal
- Look at the 'Management' section on the menu to the left
- Click on the 'Centres' link in the menu to the left
- Click on the centre name or number that you wish to add a member of staff to
- Click the 'Add a new User' link
- Complete the form as required and assign the necessary rights to the user
- The user should then receive a message to the email address you registered them with, including instructions that they need to follow

Q: What happens if I have problems with the website?

A: This problem can be caused if you are using an old web browser. Please try updating your web browser. If this does not work please email restart.itsupport@ed.ac.uk.

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References

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- ³ Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–867
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- ⁵ Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD006186. DOI: 10.1002/14651858.CD006186.pub2