PROTOCOL

RESTART tICrH

A Randomised Trial of Timing to Restart Direct Oral Anticoagulants after Traumatic Intracranial Haemorrhage

V5.0, 10/09/2025

Trial Sponsor:
The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
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ClinicalTrials.gov number: NCT06322953

ISRCTN Reference Number: ISRCTN63161604

CTA Reference number: 21322/0007/001-0001

Research Ethics Ref: 24/SC/0298

Sponsor Ref: RG442-21

Funder Ref: NIHR152506

PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical trial protocol:

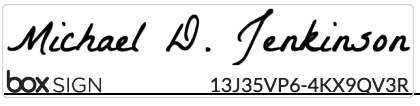
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Signature: 

Date: 11 Sep 2025

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Signature: 

Date: 11 Sep 2025

Michael Jenkinson

Chair of Surgical Trials and Professor of Neurosurgery

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Signature: 

Date: Sep 11, 2025

Rhys Davies

Director of Research and Development

Authorised by the Lead Statistician:

Signature: 

Date: 11 Sep 2025

Ashley Jones, Head of Statistics, signing on behalf of:

Michaela Brown

Speciality Lead Statistician

General Information

This document describes the RESTART tICrH trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the Liverpool Clinical Trials Centre (LCTC) to confirm they have the most up to date version.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority (HRA) guidance.

The Liverpool Clinical Trials Centre brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration Clinical Trials Unit (UKCRC CTU) network since its establishment in 2007 (www.ukcrc.org).

Randomisation: web access – please see randomisation user guidance document

If there are any problems with the randomisation systems contact

LCTC via email on restart.trial@liverpool.ac.uk

(Note that the LCTC is open from 0900 – 1700, Monday – Friday, excluding public holidays and University of Liverpool closed days)

Clinical Queries

Clinical queries relating to this trial should be referred to the Chief Investigators, Catherine McMahon and Michael Jenkinson, via the LCTC restart.trial@liverpool.ac.uk

SAE Reporting

Where the adverse event meets one of the serious categories, an electronic SAE form should be completed by the responsible investigator within 24 hours of becoming aware of the event.

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Additional Contacts:

The contact details for the trial oversight committee members and participating sites are detailed in documents supplementary to the protocol and stored in the Trial Master File.

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2 GLOSSARY

AE	Adverse Event
ALC	Adult Lacking Capacity
BP	Blood pressure
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
CT	Computerised Tomography
CTU	Clinical Trials Unit
DOAC	Direct-acting oral anticoagulants
DPA	Data Protection Act
DVT	Deep Vein Thrombosis
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HES	Hospital Episode Statistics
HR	Heart Rate
HRA	Health Research Authority
ICO	Information Commissioner's Office
IDSMC	Independent Data and Safety and Monitoring Committee
IPD	Individual Participant Data
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
medDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Health Care Products Regulatory Agency
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
OAC	Oral Anticoagulants (includes all DOACs and Warfarin)
PBPP	Public Benefit & Privacy Panel for Health & Social Care
PE	Pulmonary Embolism
PI	Principal Investigator
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RESTART-tICrH	A Randomised Trial of Timing to Restart Direct Oral Anticoagulants after Traumatic Intracranial Haemorrhage
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
RUAE	Related Unexpected Adverse Event

RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TIA	Transient Ischaemic Attacks
tICrH	Traumatic Intracranial Haemorrhage
TMF	Trial Master File
TMG	Trial Management Group
TPN	Total Parenteral Nutrition
TSC	Trial Steering Committee
USM	Urgent Safety Measure
WOCBP	Women of Child Bearing Potential

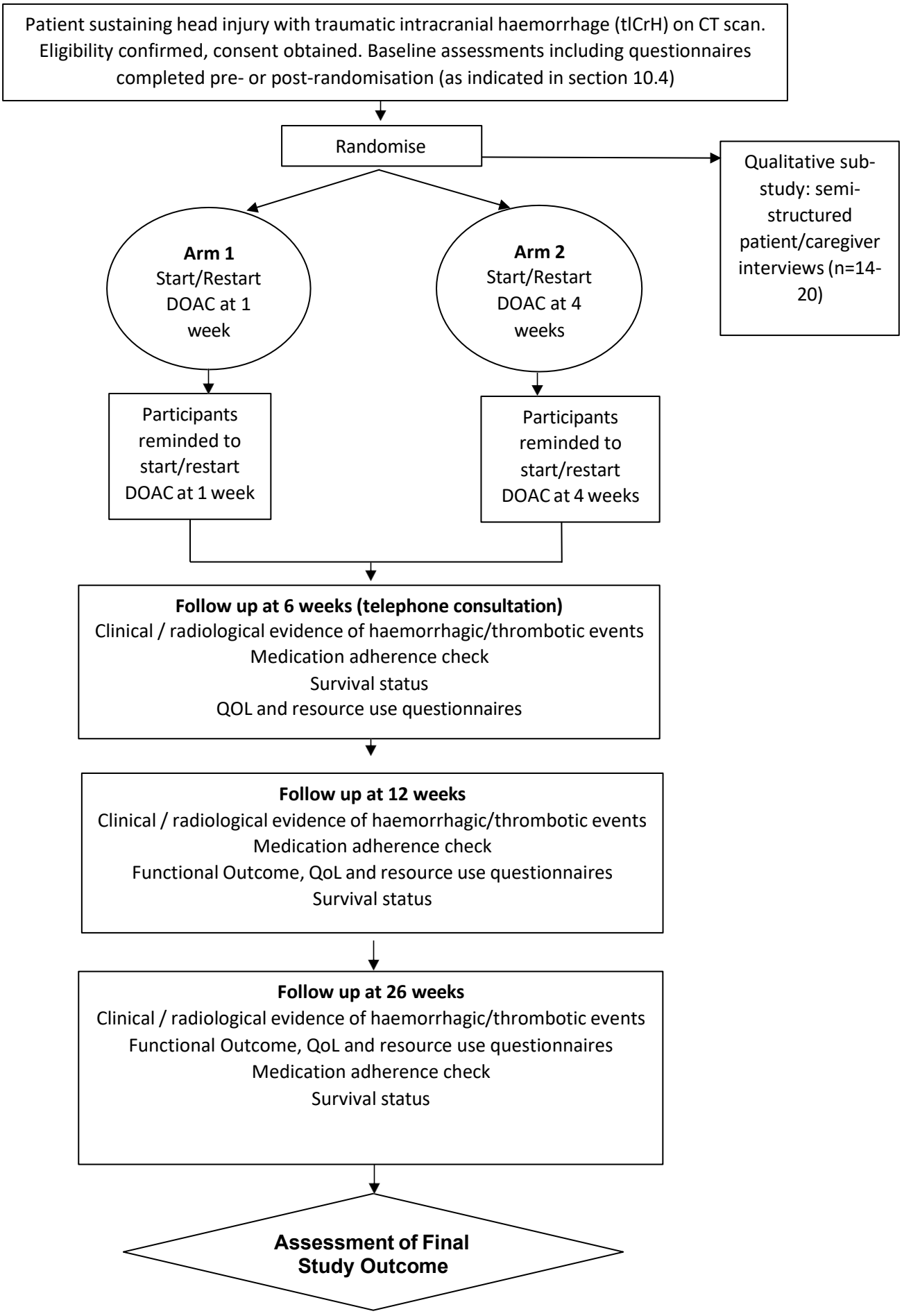
3 PROTOCOL OVERVIEW

Full Title:	Restart tICrH: A Randomised Trial of Timing to Restart Direct Oral Anticoagulants after Traumatic Intracranial Haemorrhage
Acronym:	RESTART-tICrH
Phase:	III
Target Population:	Adults with a traumatic intracranial haemorrhage (tICrH) who are taking oral anticoagulants (OAC)
Sample size:	1084
Inclusion Criteria:	1. Informed consent obtained from participant / participants' legal representative and ability to comply with the requirements of the trial 2. Adult ≥18 years with traumatic intracranial haemorrhage (tICrH) in the past 1 week who were taking oral anticoagulants (OAC) prior to admission (Oral anticoagulants include any DOAC or Vitamin K antagonist (e.g. Warfarin), prescribed for atrial fibrillation (AF) or venous thromboembolism (VTE) prior to admission for tICrH)
Exclusion Criteria:	1. Patients whose traumatic intracranial haemorrhage is a chronic subdural haematoma only 2. Patients with a mechanical heart valve 3. Patients with a plan to start/restart anti-platelet therapy within 12 weeks of tICrH 4. Abbreviated Injury Scale other than head with a score >3 5. Pregnant or nursing female 6. For participants of reproductive potential (males and females), not willing to use of a reliable means of contraception* 7. Participants with a hypersensitivity or contraindication to Direct Oral Anticoagulant (DOAC) as detailed in each IMP SmPC 8. Participant with bleeding where it would be unsafe to restart DOAC at 1 week 9. Participant with clinical reason to restart DOAC before 4 weeks or complete within 12 weeks 10. Indication to stay on VKA (Warfarin) rather than switching to DOAC (e.g. severe renal impairment)
Study Centres and Distribution:	Approximately 20 UK neurosurgery/neurotrauma networks
Individual Participant Trial Duration:	**Duration of treatment:** Restart/start DOAC at 1 week or 4 weeks post-tICrH depending on allocation **Duration of follow-up:** 26 weeks
IMP / Intervention:	Participants will start/restart DOAC based on local standard policy. DOACs commonly used are: • Apixaban

	• Dabigatran Etexilate Mesilate • Edoxaban • Rivaroxaban	
Objectives:		
Primary objectives	1. To compare the clinical effectiveness of restarting/starting DOAC early (1 week) versus late (4 weeks) following tICrH.	
Secondary objectives:	2. To evaluate the safety of treating patients restarting/starting DOAC early (1 week) in comparison to late (4 weeks) 3. To evaluate functional status and quality of life for patients restarting/starting DOAC early (1 week) in comparison to late (4 weeks) 4. To determine patient/carer attitudes to restarting/starting DOAC post-tICrH	
Economic objective:	5. To estimate the cost-effectiveness of restarting/starting DOAC early (1 week) in comparison to late (4 weeks)	
Outcomes:		**Corresponding objective:**
Primary outcome:	1. Proportion of patients with haemorrhagic or thrombotic event within 12 weeks following tICrH	1
Secondary Outcomes:	2. Time to first haemorrhagic or thrombotic event	1
	3. Time to first haemorrhagic event	1
	4. Time to first thrombotic event	1
	5. Time to death	2
	6. Functional outcome measured using Simplified Modified Rankin Scale (smRSq), Barthel Index and extended Glasgow Outcome Scale (GOS-E) at 12 and 26 weeks	3
	7. Quality of life measured with EQ-5D-5L at 6, 12 and 26 weeks	5
	8. Patient and caregiver attitudes to recommencing DOAC following tICrH.	4
Economic outcomes:	1. Incremental cost per quality-adjusted life year (QALY) gained	5

* See section 8 for list of acceptable methods of contraception

3.1 Schematic of Trial Design



3.2 Trial lay summary

Older people falling from a standing height is the most common cause of hospital admission for head injury. Up to 1 in 3 patients admitted are taking a tablet medication which thins the blood, known as an oral anticoagulant. This type of medication can increase the likelihood of bleeding in the brain. Many patients are taking oral anticoagulation due to having an irregular heartbeat (called atrial fibrillation) or because of having a previous stroke or blood clots. When a scan shows blood in the brain, oral anticoagulation is nearly always stopped. However, this leaves the question of when it is safe to restart them. The risk of making the bleeding in the brain worse must be balanced against the risk of having a stroke or blood clots.

There is no clear evidence on the safest time to restart oral anticoagulation, but most neurosurgeons advise restarting them 1-4 weeks after head injury. The number of people who have a bleed on their brain after a head injury is increasing and further brain bleeding or a stroke can have a serious effect on patients' lives and their on-going healthcare needs. Public and patient groups have highlighted that many patients want to stop taking oral anticoagulation after a bleed but they may be unaware of the vital importance of restarting this medication to prevent strokes and blood clots. The most popular oral anticoagulation prescribed has changed in recent years from warfarin to newer medications called Direct Oral Anti-Coagulants (DOACs).

The RESTART tICrH trial will recruit 1084 people who are admitted to hospital with a bleed on the brain caused by a head injury who were taking oral anticoagulation before their head injury and have been prescribed a DOAC for previously diagnosed medical condition (e.g., atrial fibrillation). Patients on other Oral Anti-Coagulants, such as Warfarin may also be able to take part.

The main purpose of the trial is to determine when the most beneficial time for people to start or restart a DOAC after their head injury is. People will be asked to start the medication either 1 week or 4 weeks after their head injury. This will be randomly assigned by a computer. They will then be followed closely for 12 weeks and any major bleeding events or a blood clots (thrombotic events) such as a stroke or heart attack will be recorded. The study will also look at the person’s overall quality of life, how they recover physically, the number of people who die, the costs of the treatment, and the attitudes of people and their caregivers to starting or restarting a DOAC.

There is the potential for everyone in the trial to benefit from taking part, because regardless of which group they are in, everyone will start or be restarted on a DOAC by 4 weeks. Currently, many people are discharged after having a bleed on their brain without restarting oral anticoagulation. This can lead to delays in restarting if a clear plan has not been made and communicated to the person and their doctor. Being part of the study will also enable people to have closer follow-up and help to improve our understanding about recovery from brain injury in this patient group.

Patients diagnosed with a traumatic bleed on the brain are discussed with a head injury specialist (neurosurgeon) for advice but can usually be managed in their local hospital by medical doctors. Everyone will be reviewed by a neurosurgeon and if they are eligible for the study they will be provided with information about the study and invited to take part. This may happen in person, or over the phone/video call if the person is admitted to a hospital that does not have neurosurgeons on site.

There will be an opportunity to ask questions and discuss with family and friends before deciding whether to take part in the study. Due to the nature of the head injury some people may not be able to weigh up the pros and cons of the study for themselves for some time after the event, and people must be recruited within a week of their head injury. In such cases, we may ask the person’s relative to consent on their behalf if they feel the person would not object. If the person regains the ability to make decisions for themselves, they will be asked to confirm whether they are happy to stay in the study. Participants can choose to leave the study at any time, and it will not affect their clinical care in any way.

Everyone will be followed up for 6 months after their head injury. They will be reminded when it is time to start or restart their DOAC (at 1 or 4 weeks) and they will be contacted at 6 weeks to see if they have any concerns. Any

bleeding or thrombotic complications will be managed by the local medical team and reported to the study team for review. Health questionnaires to assess recovery from head injury will take place over the phone or online, at baseline, 6 weeks and 3 and 6 months. It will take four years to complete the study, but the information that we obtain will greatly improve our understanding and management of head injuries in this patient group to improve health for future patients.

4 ROLES AND RESPONSIBILITIES

4.1 Sponsor

The Walton Centre NHS Foundation Trust is the Sponsoring organisation and is legally responsible for the trial. They will formally delegate specific duties to the Chief Investigator (CI) and Liverpool Clinical Trials Centre (LCTC).

4.2 Funder

This trial is funded by NIHR Health Technology Assessment Programme NIHR152506

Table 1: Trial Funding

Funder(s)	Financial and Non-financial Support Given	Role
NIHR Health Technology Assessment Programme	Non-commercial financial support for delivery of project	This funding source had no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

4.3 Chief Investigator (CI)

Catherine McMahon (CI) and Michael Jenkinson (co-CI) are responsible for overall design and conduct of the trial in collaboration with other members of the trial team.

4.4 Principal Investigators (PIs)

In each participating site a PI will be identified to be responsible for identification, recruitment and data collection, along with follow up of trial participants and adherence to trial protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

4.5 Liverpool Clinical Trials Centre

LCTC is part of the University of Liverpool. In collaboration with the CI, the LCTC will have overall management responsibility and will be responsible for trial management activities including (but not limited to) trial planning, budget administration and Trial Master File (TMF) management (limited to budget and duties delegated to LCTC), safety reporting, data management, randomisation, statistical analysis, participating site initiation and monitoring.

4.6 Oversight Committees

This trial is subject to oversight from the following committees.

4.6.1 **Trial Management Group (TMG)**

A TMG will be formed comprising the CI, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management. The TMG will meet regularly, as defined in their terms of reference.

4.6.2 **Trial Steering Committee (TSC)**

The role of the TSC is to provide oversight for the trial and provide advice through its independent Chairperson. The TSC will consider recommendations of the Independent Data and Safety Monitoring Committee (IDSMC). The TSC assessment of IDSMC recommendations for the continuation or amendment of the trial will be communicated to the trial Sponsor and funder. The TSC will meet throughout the trial (at least annually) in accordance with their terms of reference/charter.

4.6.3 **Independent Data and Safety Monitoring Committee (IDSMC)**

The IDSMC will consist of at least three independent members encompassing expertise in biostatistics and in a field relevant to the trial.

The IDSMC will receive and review monitoring reports and interim analyses for the trial and provide recommendations on the conduct of the trial to the TSC in accordance with their terms of reference/charter.

5 INTRODUCTION

5.1 Background

Head injury in older patients is becoming increasingly common. The 2017 England and Wales trauma network review reports an older person falling from standing height as the commonest type of major trauma, and most frequently results in injury to the head[1]. By 2050, 1 in 6 people will be aged over 65, and with approximately 30% of older adults falling each year, the incidence of head injury will rise[2,3]. In conjunction, there is a high prevalence of oral anticoagulant (OAC) use in this older population, driven by increased incidence of atrial fibrillation (AF), the commonest heart rhythm disorder, which is related to aging. It increases the risk of stroke 5-fold[4,5] and should be considered for treatment with OACs depending on risk factor assessment by the CHA_2DS_2-VASc score[6,7]. OAC prescribing for such patients has more than doubled in the UK since 2000[8] and between 20-35% of older patients admitted with head injury causing intracranial haemorrhage (tICrH), are taking an OAC at the time of injury[9,10]. Standard care dictates that OACs should be stopped in the majority of cases to reduce the risk of progressive or new ICrH. Despite a low risk of new or on-going ICrH 48 hours after injury, there is a reluctance from clinicians to restart OACs for fear of evoking re-bleeding. This must be balanced against the increased risk of thromboembolism in patients not taking their OAC, predisposing AF patients to increased risk of stroke, systemic thromboembolism and all-cause mortality[11]. Currently there is no clear consensus on the optimal practice on the timing for restarting OACs post-tICrH. OAC medications are traditionally divided into vitamin K antagonists (e.g., warfarin) and Direct Oral Anticoagulants (DOACs). DOAC prescribing has increased substantially over the last decade[12]. Benefits include an immediate therapeutic effect, fixed dosing, fewer drug interactions and no monitoring when compared to warfarin[13]. Previous meta-analyses and trials demonstrate that DOACs are at least as effective as warfarin in the prevention of stroke in AF patients and have a lower rate of associated ICrH and mortality[13-18]. DOACs (eg Apixaban, dabigatran, edoxaban and rivaroxaban) are recommended by NICE for those over 65 with AF and a CHA_2DS_2VASc score of 2 or above and considered for men with AF and a CHA_2DS_2VASc score of 1[6]. For those already taking a Vitamin K antagonist (e.g., Warfarin) NICE recommends that the option of switching to a DOAC should be discussed. This study will focus on patients who are taking a DOAC or Vitamin K antagonist for AF or VTE at the time of tICrH which is stopped due to risk of further bleeding. Patients will then either be restarted on their DOAC, or the option of switching to a DOAC from their current Vitamin K antagonist will be discussed, as these have a superior safety profile (significantly reduced risk of haemorrhagic stroke and intracerebral haemorrhage compared to warfarin) and reflects best practice following tICrH[19].

Studies suggest evidence of early tICrH expansion (within 48hrs) on routine repeat imaging occurs in 10-37% of patients on OAC, indicating the need to stop OAC[20–22]. This risk reduces substantially over time. A recent trial assessing patients with a major bleed on OACs, reported re-bleeding rates of 4.3% within 30 days, when excluding the first 3 days from the initial bleed[23]. The bleeding rate was only 4.5% in those who restarted their OAC within 2 weeks, with a net benefit (Hazard ratio 0.384 combining thrombosis, bleeding and death rate) when compared to those that did not restart OAC within 2 weeks. Another study focusing on tICrH reported a 5% readmission rate for re-bleeding within 30-days in patients who did not restart their DOAC[24]. There is a paucity of high-level data on delayed (>72hrs) haemorrhage rates after tICrH and withholding OACs results in an elevated risk of thrombotic events such as stroke, MI and VTE. A trial of 352 patients suffering a major bleed whilst on a DOAC demonstrated that thrombotic events increase from around 4% at 1 week to 10% at 4 weeks[25]. At 3 months, patients who have restarted OAC have fewer strokes [Hazard Ratio (HR) 0.85, 95% CI 0.43-1.68] and deaths [HR 0.5, 95% CI 0.35-0.72], despite increased bleeding [HR 1.62, 95% CI 0.95-2.75] compared to those who have not restarted OAC[26].

A 2021 survey of UK Neurosurgeons reported that most advise restarting OAC 1-4 weeks following tICrH[27]. A live poll during a recent virtual UK neurosurgical conference confirmed acceptability of early (1 week) compared to late (4-weeks) recommencement of OAC after tICrH. We hypothesise that patients with tICrH restarting DOACs after 1 week will present with a lower combined rate of haemorrhagic and thrombotic events than those who restart at 4 weeks.

There are no ongoing trials addressing this research question (www.clinicaltrials.gov, accessed on 26th May 2023). A similar planned US trial[28] has not been funded.

5.2 Rationale

Readmissions or prolonged hospital stay due to complications such as re-bleeding or thrombotic events affect patient outcomes and are costly to the NHS. Optimising the timing of restarting a DOAC so that these critical complications are minimised, has the potential to make a difference to a large number of patient's lives, as well as an economic benefit to the NHS. There is the potential for all participants in the trial to benefit from taking part, as regardless of the group to which they are randomised, all participants will be (re)started on a DOAC by 4 weeks. Currently many patients are discharged soon after tICrH without restarting their OAC, which can lead to further delays in restarting due to clinical uncertainty, lack of timely follow up, slow or poor communication with community services (GP/pharmacist) and/or fear of restarting by clinicians not experienced in managing tICrH. To ensure the trial results are generalisable across the NHS, where management of tICrH is shared by the emergency department (ED), neurosurgeons and other medical specialists, all these specialties have contributed to the study design. Secondary outcomes focused on functional outcomes, quality of life and health economic impact will be measured. This provides data on the sequelae of head injury, highlighting areas of need for this older, multi-morbid patient population which is growing in the UK.

5.3 Risk and Benefits

This trial is categorised as Type A (No higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the Medicines & Healthcare products Regulatory Agency (MHRA).

Currently clinical practice in the UK (based on national neurosurgery survey data) varies between advising restarting DOAC at 1 or 4 weeks after head injury. Since the trial is comparing 1 and 4 weeks, participants will not be exposed to any additional risk compared to normal clinical practice.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the TMF. The trial risk assessment is used to determine the intensity and focus of monitoring activity.

6 AIMS

6.1 Objectives

6.1.1 **Primary Objective**

1) To compare the clinical effectiveness of restarting/starting DOAC early (1 week) versus late (4 weeks) following tICrH.

6.1.2 **Secondary Objective(s)**

2) To evaluate the safety of treating patients restarting/starting DOAC early (1 week) in comparison to late (4 weeks) following tICrH
3) To evaluate functional status and quality of life for patients restarting/starting DOAC early (1 week) in comparison to late (4 weeks) following tICrH
4) To determine patient/caregiver attitudes to restarting/starting DOAC following tICrH
5) To estimate the cost-effectiveness of treatment with restarting/starting DOAC early (1 week) in comparison to late (4 weeks) following tICrH

6.2 Outcomes

Outcome	Timing of measurement	Method of measurement	Objective
Primary outcome			
Proportion of patients with haemorrhagic or thrombotic event within 12 weeks following tICrH.	12 weeks	Case Report Form	1
Secondary outcome(s)			
Time to first haemorrhagic or thrombotic event.	12 weeks	Case Report Form	1
Time to first haemorrhagic event	12 weeks	Case Report Form	1
Time to first thrombotic event	12 weeks	Case Report Form	1
Time to death	12 weeks and 26 weeks	Case Report Form	2
Functional outcome	12 and 26 weeks	Simplified Modified Rankin scale, Barthel Index, Extended Glasgow Outcome Scale, Rockwood Frailty Score	3
Quality of Life	6, 12 and 26 weeks	EQ-5D—5L	3
Patient/caregiver attitudes to (re)starting OAC	Within the first 9 months of recruitment start	Semi-structured interview	4
Healthcare resource use	6, 12 and 26 weeks	Case Report Form & Routine Data	5

6.2.1 **Event Definitions**

Definition of haemorrhagic and thrombotic events will meet the following criteria:

Haemorrhagic Events

a) Worsening tICrH or new tICrH as evidenced by all 3 of the following:
    1. Haematoma expansion or new ICrH demonstrated by CT or MRI, and;
    2. Causing a change in clinical status, and;
    3. Leading to cessation of anticoagulation if already re-started.

b) Extracranial major bleeding (defined as ISTH criteria[30]):
    ISTH major bleeding in non-surgical patients is defined as having a symptomatic presentation and
    a) Fatal bleeding, and/or
    b) Bleeding in a critical area or organ, such as intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
    c) Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more or leading to transfusion of two or more units of whole blood or red cells.

Thrombotic Events

a) Venous Thromboembolism (VTE),
b) Myocardial Infarction (MI),
c) Ischemic Stroke,
d) Systemic Embolism,
e) Non-bleeding Cardiovascular Death, defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, and death from other cardiovascular causes. A patient who has both this endpoint and another thrombotic endpoint will only be counted once as this endpoint.

6.3 Internal Pilot

RESTART-tICrH incorporates an internal pilot. This will take place over 9 months from the start of recruitment. The following 'Red, Amber & Green' criteria will be used to provide a clear decision on progression to the main trial (Part 2):

	Red	Amber	Green
Total recruitment	<50%	50-99%	≥100%
Average Recruitment rate/site/month	<0.82	0.82-1.64	≥1.65
Number of sites opened	<10	10-19	20

The following rules will apply:

- *Green target reached*: proceed to full trial
- *Amber target reached*: potentially proceed to main trial ensuring remaining sites open within 6 months and recruitment rate increases after discussion with TSC and funder. Reasons for declining trial participation will be noted and used to inform patient/clinician discussions regarding treatment options to promote recruitment.
- *Red target reached*: plan on how to revise the trial will be submitted to IDSMC and TSC prior to discussion with trial funders. The screening logs at all sites will be used to inform decisions. If the available patient population and consent rate are lower than expected and ultimately the recruitment rates are lower than that required

to end recruitment within the specified period, then a detailed plan of how the trial is to be amended will be provided or a recommendation that the trial should close.

If the trial is stopped at Part 1, all trial patients recruited to that point will be followed up as per the protocol. The intention is for Part 1 to progress seamlessly into Part 2 and for these patients to be included in the final analysis.

There will also be a check of the control group event rate used in the sample size calculation (proportion of patients experiencing the composite outcome in 4-week group) to ensure that the trial is adequately powered. The IDSMC will review the sample size assumptions. If these are met the trial will continue. The IDSMC may recommend that the sample size is increased but not decreased in response to the internal pilot.

7 TRIAL DESIGN

This trial is designed as a multisite, pragmatic, parallel-group, two-arm, superiority, randomised controlled trial (RCT), with 1:1 allocation ratio, stratified by recruitment site and severity of injury and frailty.

7.1 Trial Setting

Potential participants will be identified and recruited from at least 20 trauma networks in the UK. Follow up will occur with the participant/caregiver.

8 ELIGIBILITY CRITERIA

The RESTART tICrH trial target recruitment is based on the sample size calculations described in Section 12.1. All patients / Legal Representatives must provide written, informed consent before any trial procedures occur (see Section 11.2 for more information regarding informed consent processes).

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager restart.trial@liverpool.ac.uk before randomisation.

8.1 Inclusion Criteria

1. Informed consent obtained from participant / participants' legal representative and ability to comply with the requirements of the trial
2. Adult ≥18 years with traumatic intracranial haemorrhage (tICrH) in the past 1 week who were taking oral anticoagulants (OAC) prior to admission (Oral anticoagulants include any DOAC or Vitamin K antagonist (e.g. Warfarin), prescribed for atrial fibrillation (AF) or venous thromboembolism (VTE) prior to admission for tICrH)

8.2 Exclusion Criteria

1. Patients whose traumatic intracranial haemorrhage is a chronic subdural haematoma only
2. Patients with a mechanical heart valve
3. Patients with a plan to start/restart anti-platelet therapy within 12 weeks of tICrH
4. Abbreviated Injury Scale other than head with a score >3
5. Pregnant or nursing female
6. For participants of reproductive potential (males and females), not willing to use of a reliable means of contraception*
7. Participants with a hypersensitivity or contraindication to Direct Oral Anticoagulant (DOAC) as detailed in each IMP SmPC
8. Participant with bleeding where it would be unsafe to restart DOAC at 1 week
9. Participant with clinical reason to restart DOAC before 4 weeks or complete within 12 weeks
10. Indication to stay on VKA (Warfarin) rather than switching to DOAC (e.g. severe renal impairment)

* Contraception must be followed by study participants (males and females) for the duration of their participation in the clinical trial. Contraception requirements are only needed for female participants where they are women of child bearing potential (WOCBP). The definition of WOCBP is: "fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required".

The following are acceptable methods of contraception based on the clinical trials facilitation group (CTFG) guidance:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are NOT acceptable methods of contraception.

Monthly pregnancy test is also required in WOCBP for the duration of the participation in the trial (ie. until the final visit at week 26). It would be acceptable for a pregnancy test to be performed on-site or at the participants home.

8.3 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials during their participation in the trial. We have included a list of trials to which the CIs have already agreed co-enrolment on the sites area of the study website (https://restart-trial.org.uk/). Where recruitment into another trial is appropriate and without having any detrimental effect on this trial, it must be first discussed with the LCTC (restart.trial@liverpool.ac.uk) who will contact the CI if required.

9 TRIAL INTERVENTIONS

Eligible patients will be randomised to restart DOAC, or to start DOAC (if previously taking a Vitamin K antagonist, e.g., warfarin, and deemed clinically appropriate to switch to DOAC following patient discussion), early (1 week), or late (4 weeks).

9.1 Description of the Interventions

The type of DOAC prescribed should be in accordance with local Trust policy as part of standard care. There is no specific requirement to prescribe a particular DOAC for this trial.

9.1.1 **Starting/Restarting DOAC early (1 week)**

Participants will be restarted/started on DOAC 1 week post tICrH.

9.1.2 **Starting/Restarting DOAC later (4 weeks)**

Participants will be restarted/started on DOAC 4 weeks post tlCrH.

9.2 Assessment of Adherence

Medication adherence information will be collected during follow-up conversations with participants. A check will be made by the research team at the recruiting site to ensure that participants start their DOAC when they are supposed to, based on treatment allocation (i.e., either 1- or 4-weeks after tICrH). At the follow-up visits participants will be asked if they have missed any doses of their OAC since restarting it.

Participants or their legal representative/family member for those without capacity should be contacted by text, email or by a phone call/video call to remind them to restart DOAC according to their randomised allocation.

9.3 Trial Restrictions

There are no specific restrictions or contraindications for this trial apart from the exclusions detailed in the eligibility criteria.

9.4 Concomitant Medications/Treatments and Specific Restrictions

9.4.1 **Medications Permitted**

There are no specific restrictions to medications allowed during the trial.

9.4.2 **Medications Not Permitted / Precautions Required**

Caution must be undertaken on administration of a DOAC in patients receiving concomitant systemic treatment with strong inhibitors of CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) due to potential drug-drug interactions.

Precaution must be taken with **i**nducers of CYP3A4 and P-gp (including Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort).

For all DOACS, due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated except under specific circumstances. Precaution must be observed with concomitant use of platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs.

Please refer to sections 4.4 and 4.5 of the below SmPc documents for further details of medications not permitted or precautions required for each individual DOAC listed.

IMP/Intervention	**SmPC documents**
Apixaban	SmPC Bristol-Myers Squibb-Pfizer Eliquis 5 mg film-coated tablets
Dabigatran Etexilate Mesilate	SmPC Boehringer Ingelheim Limited Pradaxa 150 mg hard capsules
Edoxaban	SmPC Daiichi Sankyo UK Limited Lixiana 60mg Film-Coated Tablets
Rivaroxaban	SmPC Bayer plc Xarelto 20mg film-coated tablets

9.4.3 **Data on Concomitant Medication**

Concomitant medication data will not be collected for this trial.

9.4.4 **Specific Requirements / Restrictions.**

There are no specific restrictions to medications allowed during the trial.

9.5 Blinding

This is an open label trial with no blinding requirements.

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification and Screening

LCTC will provide an electronic screening log for completion during the trial to document all patients who have been screened or approached, this information is required for enrolling participants and for monitoring purposes. An electronic log will be maintained at each trial centre. Patients will be screened for the trial, and their eligibility and decision to participate will be recorded. Reasons for non-recruitment will be used for monitoring purposes and to inform on-going study conduct. As part of monitoring trial progress, the TMG will provide feedback to individual sites and clinicians to improve recruitment rates.

10.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent will be documented by a study team member but may be either written if the patient is consented face-to-face or be a witnessed document if consented over the phone or be an electronic document sent to the patient and/or legal representative.

Date(s) of informed consent processes (including date of provision of patient information, details of information provided (titles, version details), randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

The informed consent process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. Ideally potential participants will be given at least 24 hours to consider participation, but if they are due early discharge then consent can occur sooner to allow face-to-face discussions, if the participant is happy with this. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent, they do not have to give a reason.

10.2.1 **Informed Consent Process**

Written informed consent or electronic consent will be sought from potential participants / Legal Representatives. Where this is not possible, discussion can take place over the phone/video and a witness can sign the consent form. The potential particpant's or legal representative's email address may be shared with the LCTC by the site in order to facilitate sharing of the e-consent link with the potential participant/legal representative.

Potential participants / Legal Representatives will be approached by a member of the local research team during their initial referral to the neurosurgical unit or approached remotely by a member of the research team if admitted to a local hospital. Consent will be sought initially electronically following informed consent discussion, if it is not possible to collect consent electronically then an ethically approved written information sheet will be provided and written consent will be obtained. If this is not possible, due to distance and time constraints, then discussion can take place over the phone/video consultation and a witness can sign the consent form. Information includes a detailed explanation of the trial and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and electronic/written/ information has been provided, the individual seeking consent will ensure that the potential participant / Legal Representative has fully understood all the information and will ask if they are happy to agree to participation in the trial.

Where this is the case, electronic or written informed consent will be obtained by means of a dated signature on the electronic or paper consent form by the potential participant / Legal Representative. This should be

countersigned/confirmed electronically and dated by the person who obtained informed consent, i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

Where consent has been recorded on paper the original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the potential participant / Legal Representative for their information,
- One copy securely transferred to the LCTC
- One copy filed in the participant's medical records paper/electronic.

Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records, where remote recruitment has taken place, this should be documented in the online referral database where the neurosurgical referral was submitted.

To understand which consent processes are being utilised and are successful in recruiting patients we will collect information centrally on who provided consent (patient or legal representative) and where they were consented from (neurosurgical unit, remotely from district general hospital, or from home). This may aid future recruitment strategies.

10.2.2 **Adults Lacking Capacity – Information Provision**

Site staff responsible for obtaining consent should discuss the trial (processes and risks) with potential participants who are Adults Lacking Capacity (ALCs) and tailor that discussion to their level of understanding. Whilst consent for participation will be obtained from the potential participant's Legal Representative rather than the potential participant themselves, ***if they express a wish NOT to participate in the trial, this should be respected, and they should not be recruited.***

For ALCs every effort should be made by site staff to seek a personal legal representative in the first instance. The use of professional legal representatives should be a last resort and should only be considered where it has not been possible to appoint a personal legal representative.

10.2.3 **Regain / Loss of Capacity during Trial**

For participants who have consented to the trial and then subsequently lose mental capacity, agreement for them to continue in the trial must be sought from participants legal representative in accordance with the above-described processes. If the participants legal representative does not agree to continued participation, the participant must be withdrawn from the trial and no further trial-specific procedures should be performed, however, routine data can still be accessed as per consent.

For participants who lacked mental capacity at trial entry and consent was provided by their legal representative, if they regain capacity, and are still on follow-up, the site staff responsible for obtaining consent should seek written consent for continued participation at their next trial visit in accordance with the above-described processes. If the participant declines to consent, they must be withdrawn from the trial and no further trial-specific procedures should be performed.

10.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until fully informed consent is documented. Eligibility criteria are described in detail in Section 11.3

Eligibility confirmation must be documented in the participant's medical notes, where remote recruitment has taken place, this should be confirmed in the electronic referral database and then on the trial's Eligibility CRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation). Protocol eligibility waivers are not permitted.

10.4 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 11.7) in order to accurately complete the Baseline CRF and collect the necessary information for the trial analyses.

Pre-randomisation assessments; are required for stratification and therefore must be collected prior to randomisation);

- Glasgow Coma Scale (GCS)
- Rockwood Frailty Score

Other baseline assessments can be collected at any time up to around 1 week after head injury, with functional performance and quality of life assessed as close to the time of discharge from hospital as possible, or as close as possible to 1 week following head injury if still an in-patient at this time;

- Relevant medical history including indication for oral anticoagulants (OAC), type and dose of OAC before head injury and if a reversal agent was given at presentation or if a reversal was undertaken.
- Bleeding risk factors (with a view to calculating bleeding risk factor scores)
- Time in therapeutic range (TTR) data and international normalized ratio (INR) value on presentation (for participants on warfarin only)
- Head injury characteristics (Mechanism of injury and head injury score)
- Liverpool Head Injury Tomography Score (Liverpool HITS)
- Demographic data and social information prior to admission
- Functional performance: Simplified Modified Rankin Scale, Barthel Index and Extended Glasgow Outcome Scale,
- Quality of Life – EQ-5D-5L
- Resource use questionnaire

10.5 Randomisation

10.5.1 **Randomisation Process**

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to restart DOACs early (1 week) or late (4 weeks) in a ratio of 1:1. Randomisation should occur once the following have been confirmed:

a) Eligibility criteria have been fulfilled (and full eligibility confirmed by a medically qualified person)

b) Informed written consent has been obtained (and appropriately documented) from the participant or their proxy

c) Pre-randomisation baseline assessments have been undertaken.

A personal login username and password, provided by the LCTC, will be required to access the randomisation system. Designated research staff will be issued with their personal login and password upon completion of training in the use of the system. This training will be coordinated by the LCTC.

When the system requirements (i.e., consent, eligibility) are confirmed the participant's treatment allocation and a unique trial number (randomisation number) will be displayed on a secure webpage. An automated email confirmation will be sent to the authorised randomiser, the Principal Investigator (PI), and LCTC central trial email.

Following randomisation, participants should be notified when they will be able to restart their own DOAC as soon as possible. Members of the research team at site will contact the participant either by text message, email or phone to

remind participants to start/restart DOAC. Participants will be asked on recruitment if they would prefer a text message, email or phone call reminder and the preferred method will be issued post-randomisation.

10.5.2 **Randomisation System Failure**

In the event of a randomisation system failure, the site should contact the LCTC (Monday to Friday between 9:00 to 17:00 excluding bank holidays and University of Liverpool closed days) to try to resolve the problem.

10.6 Trial Treatment

Once the research team are made aware of what arm the participant has been randomised to, participants will restart/start DOAC at 1 week or 4 weeks following their tICrH. The type and dose of DOAC prescribed should be done as per local Trust policy as part of standard care and aligned with the approved SmPCs.

10.7 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

	Follow-Up Schedule					
Procedures	Screening	Pre-randomisation	Baseline at discharge/ 1 week	6 weeks*	12 weeks*	26 weeks*
Written Informed Consent		X				
Confirmation of consent				X	X	X
Assessment of Eligibility Criteria	X					
Pregnancy test (if applicable)	X	X				
Confirmation of Full Eligibility		X				
Baseline GCS and Rockwood frailty score		X				
Review of Medical History (indication for OAC, type/dose of OAC, reversal agents)			X			
Head injury characteristics (mechanism of injury and head injury score)			X			
Liverpool Head Injury Tomography Score (Liverpool HITS)			X	X#	X#	X#
Bleeding risk factors, time in therapeutic range and international normalized ratio on presentation (for warfarin only)			X			
Demographic data and social information			X			
Randomisation			X			
Trial IMP designation to re-start DOAC at 1 or 4 weeks			X			
Medication Adherence				X	X	X
Functional performance: Simplified Modified Rankin Scale, Barthel Index and Extended Glasgow Outcome Scale			X		X	X
Functional performance: Rockwood Frailty Score at follow up					X	X
Clinical/Radiology evidence of Haemorrhagic and Thrombotic Events				X	X	X
Quality of Life – EQ-5D-5L			X	X	X	X
Resource use questionnaire			X	X	X	X
Monitoring of Related Adverse Events and all Serious Adverse Events				X	X	X
Process Evaluation Interview**				X		

(X) – As indicated/appropriate.

*Post-randomisation

** To be conducted by a member of The University of Liverpool research team within 60 days of study approach

to be repeated at 6, 12 and 26 weeks only if an additional haemorrhagic event is recorded

10.7.1 **Summary of Follow-up Visits**

All follow-up visits will adopt a pragmatic approach. Site can use any of telephone, in person or video depending on the patient / clinician preference. We have proposed that telephone consultations should suffice for most participants.

Research nurses will contact participants/carers at 6, 12 and 26 weeks from randomisation. This should be done within 2 weeks either side of the follow-up date at 6/12 weeks and within 4 weeks either side at 26 weeks. Consultations will be arranged and conducted by local research teams. The following information should be collected and recorded:

6 weeks

- Confirmation of consent
- Medication adherence
- Clinical/Radiology evidence of Haemorrhagic Event and Thrombotic Events
- Liverpool Head Injury Tomography Score (Liverpool HITS) – only if there is an additional haemorrhagic event
- Quality of Life – EQ-5D-5L
- Resource use questionnaire
- Related Adverse events
- Serious Adverse events
- Process evaluation interview (To be conducted by a member of The University of Liverpool research team within 60 days of study approach)

12 weeks

- Confirmation of consent
- Medication adherence
- Functional Outcomes: Simplified Modified Rankin Scale, Barthel Index, Extended Glasgow Outcome Scale and Rockwood Frailty Score
- Clinical/Radiology evidence of Haemorrhagic and Thrombotic Events
- Liverpool Head Injury Tomography Score (Liverpool HITS) – only if there is an additional haemorrhagic event
- Quality of Life – EQ-5D-5L
- Resource use questionnaire
- Related Adverse events
- Serious Adverse events

26 weeks

- Confirmation of consent
- Medication adherence
- Functional Outcomes: Simplified Modified Rankin Scale, Barthel Index, Extended Glasgow Outcome Scale and Rockwood Frailty Score
- Clinical/Radiology evidence of Haemorrhagic and Thrombotic Events
- Liverpool Head Injury Tomography Score (Liverpool HITS) – only if there is an additional haemorrhagic event
- Quality of Life – EQ5D-5L
- Resource use questionnaire
- Related Adverse events

- Serious Adverse events

Premature discontinuation

- Clinical/Radiology evidence of Haemorrhagic and Thrombotic Events
- Liverpool Head Injury Tomography Score (Liverpool HITS) – only if there is an additional haemorrhagic event

10.7.2 **Health Economic Evaluation**

The economic evaluation aims to estimate the cost-effectiveness of restarting DOACs at 1 or 4 weeks post-tICrH. Besides the differences in the costs of the DOAC regimens, potential differences in haemorrhagic and thrombotic event rates and their implications on long-term sequelae, will impact significantly on both lifetime costs and QALYs. The analysis will adopt the perspective of the NHS and personal social services (PSS).

A resource use measure will be developed to include items of resource use relating to primary, community and personal social care services. Resource use questionnaires will be administered during clinic visits or calls at Baseline, 6-, 12- and 26-weeks. Questionnaires will be provided to trial participants who are able to complete resource use and health utility questionnaires independently. If a participant's condition prevents self-completion, caregivers will be given the questionnaires and may assist in completing them on the participant's behalf where possible, ensuring the participant's input is captured.

A bespoke resource use measure will be developed from existing questionnaires catalogued in our Database of Instruments for Resource Use Measurement[31] and include items from the generic, modular resource-use measure (ModRUM)[32]. Principal items of resource use will include primary, community, hospital and social care services. Resource use questionnaires will be administered at baseline, 6-, 12- and 26 weeks.

For trial participants receiving care in England, use of secondary care services will be obtained via requests for bespoke HES to NHS England at the end of the trial. HES data will be categorised into Health Resource Group codes, and will include information on outpatient, inpatient (including critical care) and A&E attendances by each participant from 6 months immediately prior to the date of the first participant being randomised, to the date of last participant completing follow-up. Participants will be fully and unambiguously informed as to the transfer of any personal data associated with obtaining and processing their HES data and will agree to these processes by signing the mandatory statement on the consent form. Participants will explicitly be made aware that they have the right to withdraw consent, and how to go about withdrawing their consent, for disclosure of HES data. Participant information (postcode, date of birth, NHS number and randomisation number) will be collected by the LCTC in order to process requests to NHS England for HES data. These direct identifiers will be stored at LCTC separately to other trial data and access will be restricted to authorised personnel. At the time of HES data request, the required identifiers will be securely transferred to NHS England, then Bangor University will securely receive the HES data from NHS England. The data provided to Bangor University will have had removed the NHS number, date of birth, postcode and other identifiers. The HES data will be stored securely and destroyed in accordance with Bangor University and NHS England Data Sharing Framework Contract. For trial participants receiving care outside of England, use of secondary care services will be obtained via trial CRF data and the resource use questionnaire. Unit costs will be obtained from standard sources, including the NHS reference costs[33] for hospital costs, and PPSRU's Unit Costs of Health and Social Care[34] for primary, community and social care, and the British National Formulary and Prescription Costs Analysis data for medicines. Costs will be based on the most recent available at the time of analysis. Health outcomes will be based on participants' responses to the EQ-5D-5L questionnaire, administered at baseline, 6-, 12- and 26-weeks. Utilities will be calculated using NICE's preferred method at the time of analysis (currently the EEPRU 5L/3L cross-walk tariff.)[35] A lack of baseline utility score will be considered in the analysis.[36]

10.7.3 **Embedded Qualitative Sub-study**

The qualitative sub-study will explore patient and caregiver attitudes to recommencing a DOAC following tICrH. A Public and Patient Involvement (PPI) focus group of 6-8 tICrH survivors and caregivers will be undertaken to inform the topic guide for the qualitative sub study as there is currently limited qualitative data available in this patient group[37]. Purposive sampling will be undertaken to obtain 10-20 patients and/or caregivers (of those patients lacking capacity to consent) randomised to receive a DOAC at 1 or 4 weeks post-tICrH, to represent diversity in terms of site, age, gender, ethnicity, presence of a caregiver and other patient characteristics (PROGRESS+ criteria)[38]. Patient-carer dyads are not required. During the pilot phase, reasons for declining trial participation will be noted and those who decline (n=10 patient/caregivers) will also be invited to take part in an interview to discuss reasons for declining a DOAC and to inform patient-clinician discussions regarding treatment options. An individual semi-structured interview, lasting 30-60 minutes with a qualitative researcher will be undertaken to elicit their perceptions and beliefs

about DOACs, in relation to stroke prevention and risks of recurrent tICrH. The interview will be conducted in person/remotely (depending on participant preference) within 60 days of the study approach. The topic guide will be iterative and informed by earlier interviews and adapted accordingly. Interviews will be concurrently transcribed verbatim and anonymised. Data collection will continue until data saturation is reached, with Nvivo Pro used to manage and analyse the data using framework analysis[39].

10.7.4 **CT Scan Data**

As part of standard clinical care all patients who experience traumatic intracranial haemorrhage will have a CT scan and often several follow-up CT scans, to guide management of the head injury.

In this trial we want to collect images from these standard clinical care scans at baseline and up to 12 weeks (or premature discontinuation if sooner than 12 weeks). Images, including participant name, NHS number and date of birth will be transferred electronically (by IEP) from recruiting sites to the University of Plymouth to generate an imaging repository which will be held at the University of Plymouth. Consent forms will be sent from LCTC to the University of Plymouth securely so that the images can be linked to the participant. An administrator at the University of Plymouth who is independent from the study will link the images to study participant number and anonymise them after which time they will only contain the participant study number.

CT scans will not be used to confirm eligibility or to provide data on disease response. Standard clinical care scans will be collected only, no additional scans are to be completed as part of the trial. Analysis of CT scans will be completed under a separate NIHR Clinical Research Fellowship application.

10.8 Intervention Discontinuation and Participant Discontinuation / Withdrawal

In consenting to the trial, participants / Legal Representatives agree to all trial activities including timing of recommencement of DOAC / follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

10.8.1 **Premature Discontinuation of Trial Intervention**

Participant in RESTART-tICrH will be on a DOAC. The type and dose of DOAC will be determined on clinical grounds by the local medical team. Any discontinuation of the DOAC will be made on clinical grounds by the local medical team. Patients will remain on trial and the reason for discontinuation will be recorded on the eCRF.

Treatment discontinuation criteria include but are not limited to:

- AEs
- use of prohibited medication
- pregnancy
- or occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient, including serious or intolerable AE that prevents the patient from continuing with study participation.

10.8.2 **Participant Withdrawal**

Participants / Legal Representatives are free to withdraw at any time without providing a reason, though a reason should be recorded if one is given. LCTC should be informed via email to the LCTC and via completion of a Withdrawal CRF to be returned to LCTC within 7 days. When a participant / Legal Representative has expressed a wish to withdraw from further trial activities, the research team at site should ascertain if this is for all elements of trial follow-up, or if for example data from routine assessments can still be collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable.

Where a participant / Legal Representative decides that they do not want any further data to be provided for trial purposes, data already collected up to the point of withdrawal will still be used in trial reports and analyses, but no further data will be collected unless required by law (e.g. safety reporting regulatory requirements).

10.8.3 **Participant Transfer**

If a participant moves from the area, every effort should be made for them to be followed-up at another participating trial site and for this trial site to take over responsibility for the participant or for follow-up via their General practitioner (GP).

A copy of the participant's CRFs should be provided to the new site. The participant remains the responsibility of the original site until the new site PI has signed the electronic transfer CRF.

10.8.4 **Loss to Follow-up**

If a participant fails to attend/facilitate a required trial visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit within 2 weeks and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable, they should be considered withdrawn from the trial with a primary reason of lost to follow up and this should be recorded on the appropriate CRF.

10.9 End of Trial

The End of the Trial is defined to be database lock.

Trial closure activities will begin once all participant treatment and follow-up are complete. Alternatively, the trial may be closed prematurely by the TSC, on the recommendation of the IDSMC.

Site and trial closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely.

11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site via the electronic SAE CRF or to lctcsafe@liverpool.ac.uk. Any trial specific SAE reporting exceptions are detailed in section 11.3.

11.1 Terms and Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Serious Adverse Reaction (SAR)	An adverse reaction which meets the definition of serious (see Section 11.2) is a SAR. A SAR event that has been assessed as 'expected' (see Section 11.6 Expectedness) according to the Reference Safety Information (see below) will remain classified as a SAR only, however some Serious Adverse Reactions that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

11.2 Adverse Events

Related Adverse events will be collected for this trial. Adverse events **related to thrombotic or haemorrhagic events** will be collected as part of primary outcome and do not need duplicate reporting as a related adverse event.

The assessment of seriousness of safety events must be performed by an appropriately delegated, medically qualified member of the site research team.

An Adverse Event or Adverse Reaction is assessed as serious if it:

- Results in death
- Is life-threatening
    - (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death)
- Requires hospitalisation or prolongation of existing hospitalisation
    - (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE)
- Results in persistent or significant disability or incapacity
    - (i.e. substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect
    - (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis)
- Is another important medical event
    - (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

11.3 Trial Specific SAE Reporting Requirements

All events that meet the criteria of serious should be reported to the LCTC within 24 hours of knowledge of the event apart from serious adverse events **related to thrombotic or haemorrhagic events** which will be collected as part of primary outcome and do not need duplicate reporting as an SAE. Recording and reporting of SAEs will be performed from consent until the last study visit (week 26 or premature discontinuation). **These should be completed in the participant's notes and reported to the LCTC**

11.4 Severity of Adverse Events

All reportable adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator (or medically trained delegate) responsible for the care of the participant using the definitions in the table below.

Severity Grading

Severity	Description
Mild	Does not interfere with routine activities
Moderate	Interferes with routine activities
Severe	Impossible to perform routine activities
Life-Threatening	Placed the subject at immediate risk of death from the experience as it occurred

Death	Resulted in death

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 11.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

11.5 Assessment of "Causality" - Relationship to Trial

The assessment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. Assessment should be made against the IMPs administered to the participant.

Table 3: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be classed as "Related" (i.e. having a reasonable possibility of being a causal relationship), and events assessed as unrelated or unlikely will be classed as "Unrelated" (i.e. having no reasonable possibility of being related).

Assessment of causality should be made based on known safety profiles of the IMPs in question (e.g. SmPC) or of other drugs in the same class.

In the case of discrepant views on causality between the treating investigator and others, **the causality assessment of the treating investigator will never be downgraded** and the MHRA & REC will be informed of both points of view.

11.6 Assessment of "Expectedness"

There is no requirement for a reporting investigator to assess expectedness. Assessments of expectedness are sponsor's responsibility and are delegated to the LCTC and Medical Reviewer.

An event will be considered unexpected if it is not listed within the relevant document as detailed in the table below, which is current and approved for the trial at the time of the event's onset. Participants will start or restart one of the medications listed below, decision on which medicine will be made by the treating doctor as per standard practice.

IMP/Intervention	Document to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Apixaban	SmPC Bristol-Myers Squibb-Pfizer Eliquis 5 mg film-coated tablets	Section 4.8

Dabigatran Etexilate Mesilate	SmPC Boehringer Ingelheim Limited Pradaxa 150 mg hard capsules	Section 4.8
Edoxaban	SmPC Daiichi Sankyo UK Limited Lixiana 60mg Film-Coated Tablets	Section 4.8
Rivaroxaban	SmPC Bayer plc Xarelto 20mg film-coated tablets	Section 4.8

The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event will be assessed as unexpected. Fatal or life-threatening events related to the IMP/Intervention by nature, are deemed unexpected (unless specified in the RSI as such).

11.7 Time Period for Active Monitoring of Safety Events

Active monitoring of safety events experienced by trial participants will be from the period from consent until the last study visit (week 26 or premature discontinuation).

11.8 Notes on Safety Event Recording

The following adverse events must be recorded for the purposes of the trial:

- Related adverse events
- All Serious Adverse events that are <u>not</u> thrombotic or haemorrhagic events recorded for primary outcome

Do not record:

- Thrombotic or haemorrhagic events which will be captured separately as part of primary outcome and do not need duplicate reporting as an SAE
- Non serious adverse events that are not related
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery[1]
- Overdose of medication **without signs or symptoms***[2]
- The disease being treated or associated symptoms/signs unless more severe than expected for the participant's condition

[1] Cosmetic elective surgery is cited here as example of an event that is not reportable as an AE, however such an occurrence may need to be reported elsewhere in the CRF; this should be addressed in the trial protocol

[2] Note that although overdose of medication without signs or symptoms may be excluded from AE reporting it may still require investigation to ensure other protocol and regulatory requirements are met to ensure participant safety.

*N.B. If overdose occurred **with** resulting signs and symptoms that meet the protocol criteria for AE/AR/SAE/SAR/SUSAR then they should be reported accordingly, and the overdose highlighted to the LCTC team.

The events above do not need recording as the trial is considered low risk this was determined by the TMG and is documented in the TMF.

11.9 Reporting of Pregnancy

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital

malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the LCTC to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP.

If pregnancy occurs whilst the participant is on the trial this must be notified to the LCTC 24 hours of the research team becoming aware using a pregnancy report CRF. The pregnancy must be followed up by the site research team until birth and details reported to LCTC on the pregnancy report CRF.

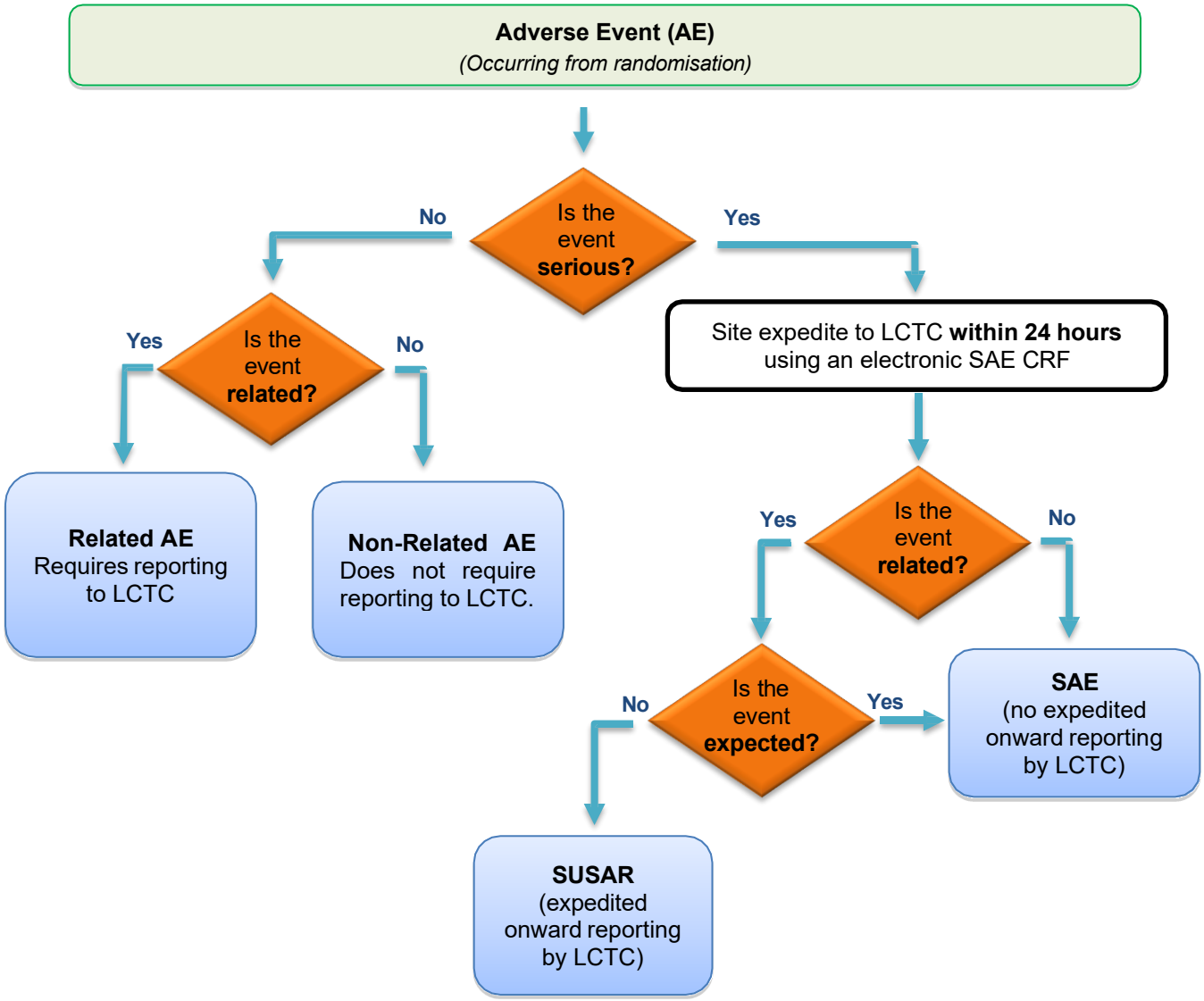
Any pregnancies which result in a safety event assessed as "serious" (e.g. birth defect) must also be reported separately on a serious safety report in accordance with processes described in section 11.1. All pregnancies and outcomes reported to LCTC will be notified to the trial Sponsor and monitored by trial oversight committees.

11.10 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the Notification of Death CRF within 24 hours of becoming aware. An SAE form will also need to be submitted if death is the outcome of an SAE.

11.11 Reporting Procedures

All reportable safety events which are recorded for the trial should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine trial visits, from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. SAEs are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below as an overview of reporting procedures for different types of safety events.


Adverse Event (AE)
(Occurring from randomisation)
Is the event serious?
No
Yes
Is the event related?
Yes
No
Related AE
Requires reporting to LCTC
Non-Related AE
Does not require reporting to LCTC.
Site expedite to LCTC within 24 hours using an electronic SAE CRF
Is the event related?
Yes
No
Is the event expected?
No
Yes
SAE
(no expedited onward reporting by LCTC)
SUSAR
(expedited onward reporting by LCTC)

11.11.1 **Site Responsibilities**

Initial Reports

In addition to the below requirements to report to the LCTC, safety events should also be reported to the site R&D team in accordance with local policy.

The site PI is responsible for ensuring that all serious adverse events which the local research team becomes aware of are recorded on CRFs for trial purposes and reported to LCTC. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events.

Events which are assessed as "serious" must be recorded in more detail on an electronic SAE CRF; a single form is used for each main individual event, though multiple symptoms can be recorded. Electronic SAE CRFs collect additional data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The SAE CRF must be completed **immediately and in no circumstances later than 24 hours from becoming aware**.

The electronic SAE CRF should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately authorised medically qualified doctor. The following is considered the regulatory minimum reporting information and must be provided in initial reports:

- Participant study number
- Study site identifier and name of reporting site staff member
- Description of the event, including date of onset
- Suspect intervention or research procedure
- Seriousness assessment
- Causality assessment

N.B. In the absence of a delegated medically qualified doctor the electronic SAE CRF should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the electronic SAE CRF, make amendments as appropriate, initial report shall be followed by detailed follow-up reports.

Follow-up Reports

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable. Where additional information on an SAE is received by site after submission of an initial electronic SAE CRF to LCTC, this should be provided on a follow-up electronic SAE CRF within 24 hours of becoming aware of the information.

Sites must respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event.

11.11.2 **LCTC Responsibilities**

The trial Sponsor, the Walton Centre NHS Foundation Trust, have delegated to LCTC the duty of onward reporting of safety events to MHRA and REC.

Safety events which are assessed as "serious", "related" and "unexpected", will be classed as SUSARs and will be onward reported in an expedited manner to MHRA and REC within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** of receipt at the LCTC. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of receipt at the LCTC

Additionally, SUSARs will be reported to the trial Sponsor within agreed timelines.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline as per LCTC Safety Processing Plan.

The LCTC will submit annual reports containing safety information to REC and MHRA.

Information on safety events will also be reported to TSC and IDSMC. Inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported safety events in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

11.12 Urgent Safety Measures (USMs)

An USM is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and MHRA via the usual amendment process.

The LCTC will notify the REC and MHRA immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and the MHRA, further action will be agreed, which may include submission of a temporary halt, or permanent termination of the trial.

Following notification of a USM, a substantial amendment should be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the trial is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the trial is halted or permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA,) the LCTC will notify the REC and MHRA within 15 days of the date of halt/termination.

11.13 Contact Details and Out-of-hours Medical Cover

As this trial is pragmatic emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size

12.1.1 Sample Size Calculation

The primary outcome of the trial is the proportion of participants who experience a haemorrhagic or thrombotic event within 12 weeks. Using a control group success rate for first-line treatment of 12% we aim to detect a 6% reduction using a group sequential design with a single interim analysis planned following 50% of the recruitment target once they have completed 12 weeks or observed an event (whichever is sooner). Sample size calculations were undertaken in SAS with the O'Brien-Fleming spending function based on standardised Z-statistics used to determine the efficacy and futility boundaries (non-binding). Based on an overall two-sided 5% significance level, and 90% power 487 participants are required per group. To allow for 10% loss to follow up, the sample size has been inflated by 10% to 542 participants per group (1084 participants in total).

12.1.2 Feasibility of Sample Size

10-20 patients with tICrH on DOAC are referred to neurosurgery units/ month. Assuming each unit screens 5 patients/month and 33% of eligible patients are recruited, this totals a conservative estimate of 20/unit/year. A recruitment period of 42 months is sufficient to reach the target.

12.2 Method of Randomisation

12.2.1 Allocation Sequence Generation

Randomisation lists will be generated using block randomisation with random variable block length, stratified by site, severity of injury and frailty. The lists will use a 1:1 randomisation ratio. The lists will be produced by an independent statistician (who is not otherwise involved in the RESTART study) at LCTC.

12.2.2 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed. The randomisation system will be set up, maintained and monitored independently of the trial statistician or other trial staff.

12.3 Interim Analyses

A single interim analysis will be undertaken after 50% of the total participants have been recruited and followed up to 12 weeks or observed an event (whichever is soonest). Non-binding stopping boundaries were determined using the O'Brien-Fleming spending function based on standardised Z-statistics, giving stopping bounds for efficacy and futility of 2.963 and 0.345 respectively. If the trial stops early for efficacy or futility, treatment of all participants already randomised will continue until the planned end point to enable meaningful outcome data to be collected.

12.4 Analysis Plan

The trial will be analysed using the International Conference on Harmonisation E9 guidelines and reported using the 'Consolidation Standard of Reporting Trials' (CONSORT) guidelines. A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms.

All analyses will be conducted using the intention to treat principle, based on all randomised participants, in the group to which they were allocated, and for whom the outcomes of interest have been observed or measured. A p-value of

0.05 or less will be used to declare statistical significance for all analyses and results will be presented with 95% confidence intervals.

Baseline characteristics will be presented but no comparisons will be undertaken, rather the clinical importance of any imbalance will be noted.

The primary outcome will be analysed using logistic regression adjusted for the factors included within the randomisation process. A Z score of 1.969 will be used for the final analysis and a p-value of 0.05 will be required to determine statistical significance. A secondary analysis will be conducted using the win-ratio approach.

Time to event secondary outcomes will be analysed using Cox Proportional Hazards adjusting for randomisation factors, or competing risks analysis as appropriate. Quality of life and other functional measures will be analysed using longitudinal analysis, joint modelling will be considered if appropriate.

Missing data will be monitored, and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform the handling of missing data.

12.5 Health Economics Analysis Plan

A full Health Economic Analysis Plan will be specified prior to data lock[40]. Patient-level cost and utilities will be analysed using regression models to estimate mean values associated with clinically meaningful health states. These states will be the basis of a Markov model to extrapolate costs and consequences over patients' lifetime[41]. The specification of the economic model will be informed by, and require data derived from, purposive searches of the literature. Parametric functions will be used to model overall survival. Different functional forms will be tested for suitability based on goodness of fit criteria and informed by external data from published sources[42]. Whilst the base-case economic evaluation will adopt a lifetime horizon of analysis, we will also report costs and QALYs, and estimate the ICER over the 26-week follow-up period of the trial."

A stochastic sensitivity analysis will be carried out to estimate the incremental cost-effectiveness ratio, and to assess the probability of cost-effectiveness for given threshold values of willingness to pay. This will consider simultaneous uncertainty in parameter inputs and provide evidence suitable to decision makers on the cost-effectiveness of restarting DOACs. Additional sensitivity and scenario analyses will be undertaken to account insofar as possible, different sources of uncertainty. A stratified cost-effectiveness analysis will be conducted for valid subgroups that will be specified a priori.

12.6 Qualitative Data Analysis Plan

Audio-recorded interviews will be transcribed verbatim to produce transcripts for analysis. Data will be analysed using Framework analysis[34] as this allows the combination of inductive and deductive analysis. NVivo Pro software (or similar) will be used to facilitate data management. Framework analysis will performed in five stages: familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation. First, the transcripts will be read to aid familiarity and re-read with the thematic framework in mind. The thematic framework will be identified by separating the data into manageable chunks so it can be analysed further during the indexing stage. A matrix will be created that allows the data to be structured by theme, code, or participant. The researchers will make a value judgement on which parts of the data align with which theme (indexing) and then data will be transposed from the original transcripts and placed in the matrix underneath the corresponding themes (charting). The thematic framework created will be applied to the entire data set and the data will be interpreted in the wider context of existing literature (mapping and interpretation) to identify the over-arching themes. The process of indexing is largely subjective, and will be discussed collectively by the qualitative team, and reflexivity will be utilised. The results of the qualitative analysis will present the over-arching themes and sub-themes and provide verbatim quotes to support them.

13 DATA MANAGEMENT

13.1 Source Documents

The case report form (CRF) will be considered the source document for data where the information cannot be obtained from the medical records and is recorded directly in the trial specific CRF.

The trial Source Data Checklist will document where the source data for the trial is routinely held. The investigator is required to confirm that the information held in the checklist is an accurate reflection of data collection practices at site. A copy of this checklist must be retained in the Investigator Site File

13.2 Data Collection Methods

Data are to be entered into an electronic secure web-based trial specific system by approved members of the research team at site.

14 MONITORING

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, whether central or on site and what level of detail monitoring will be conducted.

Site monitoring visits may be 'triggered' in response to concerns regarding trial conduct, participant recruitment, outlier data or other factors as appropriate. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the trial protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- Source data verification.

15 CONFIDENTIALITY & DATA PROTECTION

This trial will collect and process Personal Data of participants. All data will be handled in accordance with applicable data protection legislation, including the UK General Data Protection Regulation (GDPR) and Data Protection Act (DPA) 2018.

The Data Controller organisations for this trial are The Walton Centre NHS Foundation Trust, Bangor University, Liverpool Clinical Trials Centre (LCTC) and Plymouth University. The Data Processors for this trial include trial sites.

LCTC is part of the University of Liverpool, which is registered as a Controller with the Information Commissioner's Office (ICO).

Data will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.), thereby ensuring data minimisation and purpose limitation. At all times, this data will be handled confidentially and securely.

Data collected at sites and transferred to LCTC will include direct identifiers (e.g. participant names on Consent Forms and NHS number/contact details on Contact Forms) and Special Category data (i.e. participant medical information on main CRFs). Medical data is subject to a duty of confidence under Common Law. Trial participants consent to the disclosure of their data to researchers as part of the trial's recruitment and consent process.

Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to LCTC by recruiting sites. This transfer of identifiable data is disclosed in the Participant Information. Main CRFs collecting medical data (i.e. Special Category) will be pseudonymised and labelled with a unique trial randomisation number. This data will be collected and stored separately to direct identifiers to ensure pseudonymisation.

Breaches of data protection principles or regulations identified by LCTC will be notified to the trial Sponsor and applicable Data Protection Officers.

Health Episode Statistics (HES) data is required for trial analysis. This data is obtained from NHS England. As part of the data request process, participant direct identifiers (including NHS number) and unique study number will be securely transferred to NHS England by LCTC. NHS England will use these identifiers to extract the appropriate HES data and will pseudonymise this data by removing all patient identifiers and identifying the patient by unique study number only before securely transferring the data directly to Bangor University. Participants are informed of, and agree to, this transfer as part of their trial consent process.

16 QUALITY ASSURANCE & CONTROL

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each site will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- The Trial Manager at the LCTC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended the trial-specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual site.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG may monitor screening and consent rates between sites and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

16.1 Records Retention

All essential documents created for this trial will be retained for the trial-specific archive period as defined in the trial contracts (25 years). This archive period will begin on the official End of Trial date (defined in section 10.9 above).

The PI at each site is responsible for ensuring their site-specific records (trial files, data and source documents) are securely and confidentially retained during the full archive period. If a PI leaves their site (e.g. retires or changes employer) before the end of the archive period, they must transfer responsibility, in accordance with the local site processes and in compliance with the trial contract.

In addition to sites, each team who are delegated duties for the trial will be responsible for securely and confidentially retaining their own trial records for the whole archive period, unless their contracts with Sponsor permit different arrangements (e.g. provision of records to Sponsor for archiving).

17 REGULATORY & ETHICAL CONSIDERATIONS

17.1 Statement of Compliance

This trial will be run in accordance with all applicable legislation, including, but not limited to:

- Principles of GCP
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)
- UK GDPR & DPA 2018
- UK Policy Framework for Health & Social Care Research
- UK Mental Capacity legislation

17.2 Ethical Considerations

The trial will abide by the principles of GCP and Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone peer review and ethical and regulatory review by an independent REC.

17.3 Approvals

The protocol, participant information & consent materials and any proposed public-facing material will be submitted to an appropriate REC, the Health Research Authority (HRA), MHRA and trial sites for approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

17.4 Non-Compliances

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and REC requirements are handled based on their nature and severity.

17.4.1 **Protocol Deviations**

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees. The handling of protocol deviations will be documented in the SAP.

Protocol deviations and other non-serious breaches of GCP, etc. will be managed according to local site and LCTC procedures as appropriate.

17.4.2 **Serious Breaches**

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants. The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

18 INDEMNITY

The Walton Centre NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated trial, the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation may therefore be available in the event of clinical negligence being proven.

Clinical negligence is defined as: “A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process “.

19 PUBLICATION AND DISSEMINATION

19.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

19.2 Authorship

Contributors to all four of the following (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the RESTART-tICrH Consortium which will also be named at the manuscript head.

19.3 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and results will be submitted to the REC. The trial results will be published regardless of the magnitude or direction of effect. A Lay Summary will be produced and made available via the HRA website. The findings of the study will be presented to healthcare professionals at scientific conferences and published in medical journals. People who participated will also be thanked and informed of the results by letter. Social media will be used to share the results with all groups.

19.4 Data Sharing

At the end of the trial, after the primary results have been published, the individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers.

IPD will only be shared with external researchers if the participants have consented to this onward disclosure in accordance with the Common Law Duty of Confidentiality, or if the external researchers obtain approval to waive this Common Law requirement (i.e. Section 251 Approval via the Confidentiality Advisory Group (CAG) / approval from the Public Benefit & Privacy Panel for Health & Social Care (PBPP)) or if the IPD has been fully anonymised prior to sharing.

All requests for access to the IPD will be assessed by the Sponsor and must be agreed by all Data Controller organisations.

20 AMENDMENT HISTORY

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
Prior to submission for approvals	V2.0	19/07/2024	Section 10.7.4 updated to clarify the details of how the CT scan data would be processed and anonymised at the University of Plymouth for the CT Scan repository.
In response to MHRA, HRA and REC comments	V3.0	07/10/2024	Section 3 Protocol Overview updated to remove reference to consultees in inclusion criteria 1 to avoid confusion and to clarify exclusion criteria 7. Section 8 Eligibility Criteria updated to remove reference to consultees in inclusion criteria 1 to avoid confusion and to clarify exclusion criteria 7 and to add further information about contraception requirements for the study. Section 9.4.2 updated to add details of Medications Not Permitted/ Precautions required and to include reference to the relevant SmPC documents. Section 10.6 updated to indicate that the type and dose of DOACs should be as per local trust policies and aligned with SmPCs. Section 10.7 updated in the Schedule of Assessments and Follow-up table and in section 10.7.1 Summary of Follow up visits to indicate that we will now monitor Related Adverse Events as well as Serious Adverse Events and that these will be monitored up to the last study visit at 26 weeks. Section 10.8.1 updated to add details of treatment discontinuation criteria. Section 11.2 updated to indicate that we would collect Related Adverse events. Section 11.3 updated to indicate that we would record and report SAEs from consent until the last study visit. Section 11.8 updated to clarify events that should be reported. Reference to consultees removed throughout the protocol to avoid confusion.

Amendment 2 (substantial)	V4.0	11/12/2024	Lay Summary updated to clarify that questionnaires will be completed at baseline in addition to the follow up timepoints. Glossary updated. Section 3.1 Schematic of Trial Design updated to clarify when baseline assessments would be completed to be consistent with those stated in section 10.7. 'Modified Rankin Scale' updated to 'Simplified Modified Rankin Scale' throughout to clarify the version of the questionnaire that will be used for the study. Section 10.2.2 updated to emphasise that professional legal representatives should be a last resort for participants who lack capacity and that every effort should be made by sites to appoint a personal legal representative first. Sections 10.4 and 10.7 updated to clarify that we will collect Liverpool Head Injury Tomography Score (Liverpool HITS) at baseline and also at follow up where patients have had a further haemorrhagic event Section 10.7.2 updated to clarify data flow and remove a secondary analysis and duplicated paragraph. Section 15 updated to clarify data controllers and process for transfer of health economics data Formatting changes
Amendment 7 (substantial)	V5.0	10/09/2025	Sections 3 and 8 - Removal of the inclusion criteria "At high risk for thromboembolic complications (CHA2DS2-VASc ≥2 in men and ≥3 in women) OR patients taking long term OAC for deep vein thrombosis (DVT) / pulmonary embolism (PE)" and exclusion criteria "Concomitant p-gp and CYP3A4 inducers/inhibitors" Section 8.3 updated to add that trials with agreed co-enrolment will be listed on the RESTART trial website. Section 10.2.1 updated to clarify that LCTC may be provided with the potential participant's/ legal representative's email address in order to facilitate sharing of the e-consent link Section 10.5 updated to clarify when baseline assessments can be undertaken Section 10.7.2 updated to clarify the details of the health economics analysis and how the questionnaire should be administered

			Section 11 updated throughout to clarify that thrombotic or haemorrhagic events will be captured separately as part of primary outcome and do not need duplicate reporting as an SAE Section 12.5 updated to clarify details of the health economics analysis

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