Trial Title: STENT **RETRIEVE**R THROMBECTOMY FOR THROMBUS BURDEN REDUCTION IN PATIENTS WITH **A**CUTE **M**YOCARDIAL **I**NFARCTION – RETRIEVE – AMI study

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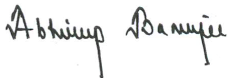
Statistician Signature: 

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2. KEY TRIAL CONTACTS

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3. Lay Summary

Heart attacks are caused by the sudden formation of a clot inside a diseased coronary artery which reduces blood flow beyond the blockage site. During conventional treatment of the blockage with what is known as a stent; a stainless-steel tube that keeps the artery open, the clot that has formed is disrupted and is pushed further down leading to damage in smaller blood vessels supplying the heart muscle. This additional damage can lead to long-term heart muscle damage influencing recovery and wellbeing. The original concept that was tested to prevent this 'clot shower' was that of a suction device to withdraw the clot before stenting. However, this approach has not translated to patient benefit.

Amongst the reasons put forward for the inefficacy of the suction device was that it does not remove the entire clot as it does not interact with it. A new device that physically interacts with the clot and traps it before pulling it out - the stent retriever - is now routinely used in stroke therapy to remove clots in the arteries supplying the brain. This device has been successfully used as a last resort to remove clots in a small number of heart attacks. We hypothesize that stent retriever therapy will be more effective in clot removal than the current standard of care; suction or stenting. To study this, we propose the RETRIEVE-AMI randomised controlled trial.

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4. SYNOPSIS

Trial Title	STENT **RETRIEVE**R THROMBECTOMY FOR THROMBUS BURDEN REDUCTION IN PATIENTS WITH **A**CUTE **M**YOCARDIAL **I**NFARCTION		
Internal ref. no. (or short title)	RETRIEVE – AMI study		
Trial registration	NCT05307965		
Sponsor	Oxford University Hospitals NHS Foundation Trust		
Funder	Medtronic & Terumo Inc		
Clinical Phase	Device Pilot		
Trial Design	Randomised controlled trial		
Trial Participants	ST elevation Myocardial Infarction Patients		
Sample Size	n=81		
Planned Trial Period	Start Date: 01/03/2022 End Date: 30/09/2025		
Planned Recruitment period	36 months		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Efficacy of thrombus burden reduction	Thrombus volume (mm^3) (OCT assessment)	Pre-stent
Co-primary	Safety of retriever thrombectomy	• Angiography-/OCT-defined device related target vessel complications, device deficiency • Rate of major adverse cardiac and cerebrovascular events (MACCE)	Pre-stent In hospital 30 days 6 months
Secondary	Efficacy of thrombus burden reduction	Thrombus area, flow area (mm^2) (OCT assessment)	Pre-stent
	Efficacy of thromboatheroma reduction	Thromboatheroma area, flow area (mm^2) (OCT assessment)	Post-stent
	Efficacy of stent implantation	Stent expansion & apposition (OCT assessment)	Post-stent
	Angiographic success rate	TIMI flow, Myocardial Blush Grade, Angiography derived coronary physiology indices	Post-stent
Intervention(s) • Other intervention(s)	Percutaneous coronary intervention with adjunctive use of stent retriever thrombectomy		
Comparator	Percutaneous Coronary Intervention alone or Percutaneous coronary intervention with adjunctive aspiration thrombectomy		

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5. ABBREVIATIONS

AE	Adverse event
ADE	Adverse device effect
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICH	International Conference on Harmonisation
IRB	Independent Review Board
MACCE	Major adverse cardiac and cerebrovascular event
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
RES	Research Ethics Service
OCT	Optical coherence tomography
OXTREC	Oxford Tropical Research Ethics Committee
PCI	Percutaneous coronary intervention
pPCI	Primary percutaneous coronary intervention
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RMP	Registered Medical Practitioner
SAE	Serious Adverse Event
SADE	Serious Adverse Defice Effect
SOP	Standard Operating Procedure
TIMI	Thrombolysis in myocardial infarction
TMF	Trial Master File
TSG	Oxford University Hospitals NHS Foundation Trust Trials Safety Group

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6. BACKGROUND AND RATIONALE

Ischaemic heart disease remains the leading cause of death across the globe despite sustained reductions in mortality rates.[1] However, cardiovascular morbidity following myocardial infarction remains a significant burden to healthcare systems. Our attempts during the last decade have thus shifted towards reperfusion therapies that reduce the extent of the myocardial infarction.[2]

Amongst the proposed adjuncts to angioplasty, aspiration thrombectomy has been proposed as a simple method of removing the in-situ clot prior to stent deployment. Aspiration thrombectomy was thought to reduce distal embolisation of athero/thrombotic debris, limiting the ensuing microvascular dysfunction and final infarct size.[3,4] Early randomised controlled trials of aspiration thrombectomy supported its routine clinical use,[5] but contemporary trials suggest no effect on mortality and a signal of increased stroke.[6,7] Amongst the reasons put forward to explain the lack of benefit of aspiration thrombectomy is its inefficacy in removing thrombi.[8] Indeed, the optical coherence tomography (OCT) sub-study of TOTAL suggested that there was no difference in pre-PCI thrombus volume in lesions treated with aspiration thrombectomy versus PCI alone.[9]

One of the reasons why thrombus-aspiration catheters failed to remove thrombotic debris in STEMI can be related to the inability of the devices to actually interact with the clot. In the coronary artery the clot develops on top of an ulcerated/ruptured plaque, meaning that the bulk of the clot is often in an eccentric position, eventually protruding towards the centre of the lumen. An additional element that must be taken into account is the disproportion between the vessel lumen-cross-section-area (which can potentially be filled with thrombus) and the aspiration-opening area at tip of the aspiration catheter. If an average size coronary artery (diameter: 3.0 – 3.5 mm) is considered, the vessel lumen-cross-section-area can range from 7.06 to 9.61 mm^2. Since the aspiration-opening area at tip of the aspiration catheter is on average 0.9-1.0 mm^2, that means that the thrombectomy device technically covers (on average) from 9.4 to 14.2% of the vessel lumen-cross-section-area. In a larger caliber vessel (for example large ectatic right coronary arteries) this ratio becomes even more unfavourable. As the caliber of the vessel increases, its "theoretical" ability to contain large thrombus-burden increases proportionally, meaning that

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paradoxically the currently available aspiration devices become less effective in those cases when they would be required to work at their best.

Another element to account for poor performance of the current aspiration-catheters is the "guidewire bias effect". This is a direct consequence of 1) the coronary arteries not being straight tubes, but having bends and curves and 2) of the thrombectomy-catheter sliding over an angioplasty-guidewire during the procedure. In a curved tube, like the coronary artery, the position of the wire can actually bias the aspiration device away from the clot. The "guidewire bias effect" can be minimally influenced by the operator. For this reason a clot-removal device that could interact with the whole vessel-lumen cross section area (and thus with the whole clot) and whose mode action is not affected by coronary artery caliber and by "guidewire bias effect" would be desirable and likely to be more effective in removing thrombus in STEMI patients.

Stent-retriever thrombectomy technology has this property and not surprisingly it has revolutionised the treatment of acute ischaemic stroke improving recanalization rates and clinical outcomes significantly.[10,11] Stent-retriever technology has been proved to be safe with low rates of vascular perforations (~2.1%) and iatrogenic dissection (1.7%-3.5%) in acute ischaemic stroke treatment.[10-14]

Isolated case reports of successful bailout stent-retriever thrombectomy in ST elevation myocardial infarction (STEMI) patients attest to the feasibility of a stent-retriever thrombectomy approach in STEMI.[15,16] However whether a stent-retriever strategy is more effective that conventional thrombus aspiration in STEMI has to be proved. Recently, stent retriever thrombectomy with the NeVa (Vesalio) device was evaluated in STEMI patients with large thrombus burden.[17]

We set out to study the efficacy and safety of retriever thrombectomy in a carefully selected cohort of patients with ST elevation myocardial infarction and compare it with current standard of care; standalone PCI or PCI with adjunctive thrombus aspiration. We expect that stent retriever thrombectomy will more effectively reduce the thrombotic burden when compared to the current standard of care (e.g. standalone PCI and/or PCI with adjunctive aspiration thrombectomy).

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7. HYPOTHESIS

We hypothesize that stent retriever thrombectomy will be more efficacious than aspiration or mechanical thrombectomy in thrombus burden reduction as assessed by OCT derived pre-stent thrombus volume (mm^3).

8. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objectives		
Efficacy of thrombus burden reduction	Thrombus volume (mm^3) (OCT assessment)	Pre-stent
Safety of retriever thrombectomy	• Angiography-/OCT-defined device related target vessel complications, device deficiency • Rate of major adverse cardiac and cerebrovascular events (MACCE)	Pre-stent In hospital 30 days 6 months
Secondary Objectives		
Efficacy of thrombus burden reduction	Thrombus area, flow area (mm^2) (OCT assessment)	Pre-stent
Efficacy of thromboatheroma reduction	Thromboatheroma area, flow area (mm^2) (OCT assessment)	Post-stent
Efficacy of stent implantation	Stent expansion & apposition (OCT assessment)	Post-stent
Angiographic success rate	TIMI flow, Myocardial Blush Grade, Angiography derived coronary physiology indices	Post-stent

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9. TRIAL DESIGN

RETRIEVE AMI is an investigator-initiated, multi-centre, exploratory three arms, randomised controlled trial. Patients over the age of 18 admitted for primary PCI (pPCI) for ST elevation myocardial infarction and meeting the inclusion criteria laid out in section 10.2 will be 1:1:1 randomised to receive either standalone PCI (Arm 1), thrombus aspiration + PCI (Arm 2) or retriever thrombectomy + PCI (Arm 3). Recruitment is expected to last for 18 months with the study finishing when the last follow-up of the last recruited patient is completed and all data is entered into the study. Each participant is expected to remain in the study for 6 months during which one telephone follow-up at 6 months will be arranged. (Figure 1, Appendix A)

The RETRIEVE AMI will enrol specifically patients with

- evidence of large thrombus burden on coronary angiography

- with culprit lesion located in a relatively large caliber (diameter > 3.0 mm) coronary artery

By only including a large caliber vessel, the retriever-stent will be tested in a setting where the currently available technology is perceived to be suboptimal as described in section 6. Our decision to expand recruitment to the left coronary system was driven by our experience with the device in this trial as well as from published reports of the systematic evaluation of the NeVa (Vesalio) stent retriever device. Indeed, the authors have shown that thrombectomy is safe in both the left and right coronary artery systems.[17] Procedurally, we are reducing the risk of a major interaction of the device by placing a coronary guidewire alongside the stent retriever allowing us to retain safe control of the vessel whilst the clot is retrieved.

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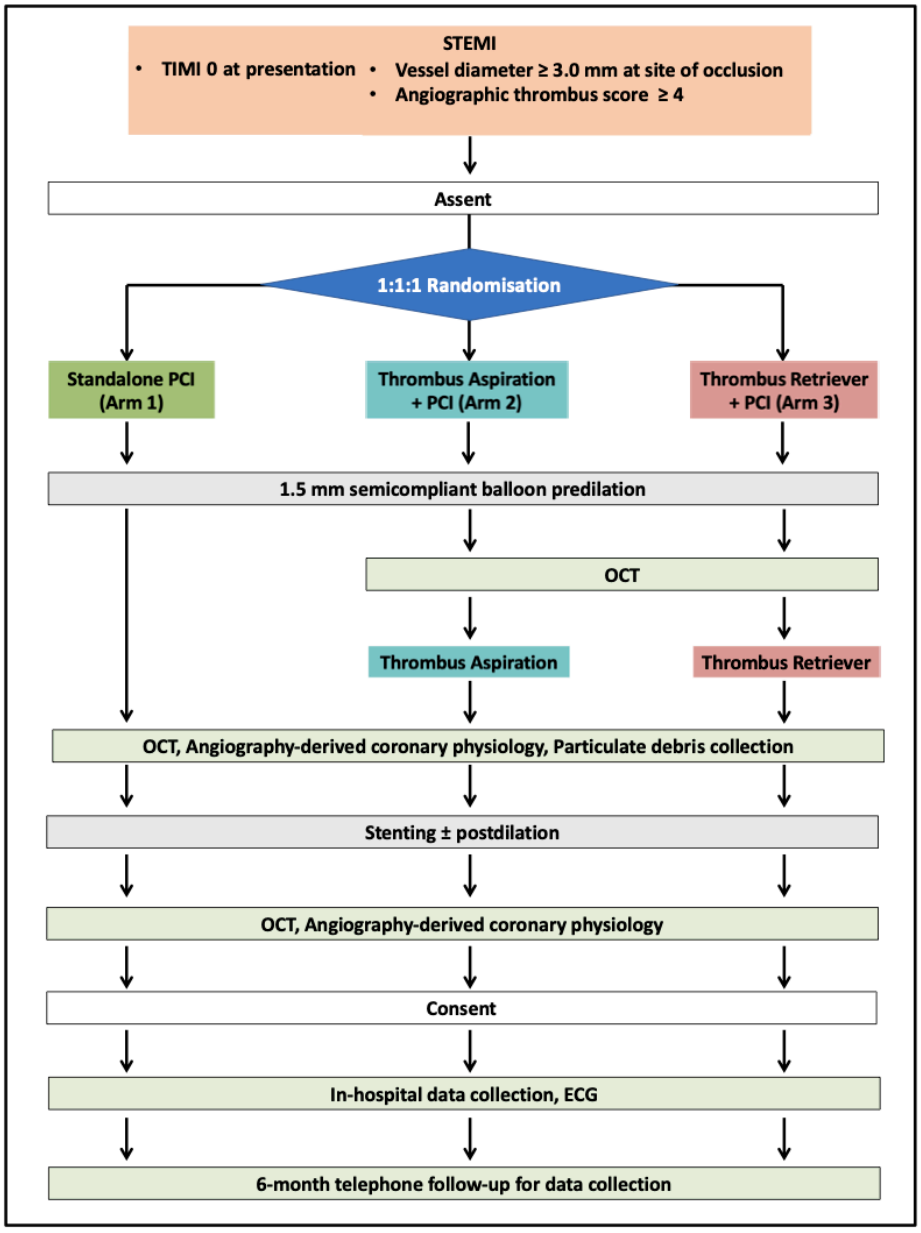

Figure 1: Trial flow chart

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10. PARTICIPANT IDENTIFICATION

10.1. Trial Participants

Patients over 18 years of age having pPCI for ST elevation myocardial infarction and meeting the inclusion criteria as listed below will be randomised to either retriever thrombectomy + PCI, or thrombus aspiration + PCI, or standalone PCI.

10.2. Inclusion Criteria

- Male or Female, aged 18-90 years.
- pPCI patient with ST elevation myocardial infarction.
- Angiographic criteria:
  - ◊ TIMI 0/1 flow at presentation
  - ◊ Angiographic thrombus score ≥ 4
  - ◊ Vessel diameter at site of occlusion ≥ 3.0 mm (measured by quantitative coronary angiography)

10.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Female participant who is pregnant or lactating
- Participant with known hypersensitivity to nickel-titanium
- Unconscious at presentation
- Late presenter (pain to wire time > 12 h)
- Class Killip III/IV and/or profound bradycardia (HR < 40 bpm)
- Known history of kidney failure
- Ostial occlusion

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- Highly tortuous vessel*
- Highly calcified vessel
- Suspected (angiographically) spontaneous coronary artery dissection
- Stent thrombosis
- Previous stent implanted proximal to the occlusion site
- Previous CABG
- Previous STEMI/TIA/Stroke
- Known anaemia (Hb <9).

*A highly tortuous vessel is defined by the presence of ≥3 consecutive curvatures of 90° to 180° measured at end-diastole in a major epicardial coronary artery ≥2 mm in diameter.[18] In our protocol tortuosity will lead to a participant's exclusion if it is affecting the vessel at the target lesion or proximal to it.

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11. TRIAL PROCEDURES

11.1. Informed Consent

Informed consent will be obtained, with the recruitment approach to the patient, as described below.

11.1.1. Waiver request for patients having emergency angioplasty procedure

The clinical treatment of these patients is in the emergency context and delays to treatment are detrimental. It is necessary to administer prompt emergency treatment and it is not always possible to identify and approach a Consultee beforehand. Thus we would seek a waiver, as described in Section 32(9) of the Mental Capacity Act, since

a) the treatment needs to be given urgently,

b) it is necessary to take the action for the purpose of the research urgently,

but

c) it is not reasonably practicable to consult prior to enrolling the patient.

In this situation the Mental Capacity Act allows the participant to be enrolled with an agreement of a registered medical practitioner (RMP) not involved in the research or in accordance with a procedure agreed with the appropriate body (i.e. REC). Since this is only applicable for the duration of the emergency we will seek written informed consent as soon as reasonably practicable (see diagram and Section 11.1.1.2 below). This process includes an important role for a healthcare professional as a type of patient "advocate". This is discussed in section 11.1.1.2 below. We also seek approval from the REC for the waiver procedure.

11.1.1.1. Verbal assent

Because of the urgency of the situation it is not feasible to obtain fully informed written consent. Fully informed consent requires that the potential participant have time to read and reflect on a patient information sheet which in this context is clinically inadvisable. We therefore propose to obtain verbal assent so as to optimize the amount of appropriate information conveyed to potential participants

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acutely and minimize the clinical risks involved with substantial delay. The research study will be discussed verbally with the patient and the risks and benefits explained.

In detail the patient at the time of verbal assent process will be informed that the particular pattern of heart attack they are having would be suitable for recruitment in our research trial which investigates a new device to remove the blood clot that is causing the heart attack. We will explain that as part of the trial they will receive either standard of care procedures or the investigational device. We will also briefly mention that we will be obtaining some extra pictures from within the arteries, a sample of the clot and measurements of flow and resistance in the small net of capillaries feeding the heart.

Participants will be reminded that they have the right to withdraw from the study at any stage and that this will not affect their treatment or human rights. The research and clinical team have extensive experience of patient assent, and the role of a Patient Advocate (see below), through the recruitment of approximately 500 participants undergoing emergency PCI for STEMI in the OxAMI [Ethics Ref 11/SC0397] and OxAMI PICSO [Ethics Ref 15/SC0167] studies. Newcastle upon Tyne Hospitals NHS Foundation Trust is a participating site to the OxAMI Study.

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Only conscious patients, able to provide verbal assent will be enrolled in the study.

11.1.1.2. Patient Advocate

Because of the urgency of the situation it is not feasible to obtain written informed consent from the patient prior to enrolment, so an RMP or patient "advocate" will be identified to act in accordance with section 32(9). The Patient Advocate will act as witness and documenter of the verbal assent process for all conscious potential participants and/or overseer of the waiver process as a whole. This RMP will be present at the time of emergency treatment, but is not part of the research team. The Advocate will ensure that the verbal assent process is undertaken, that the patient does not object (i.e. the patient "assents" rather than "dissents"), and that the researcher has taken practical steps to explain the study, risks and benefits, within the context of the emergency clinical situation, and in accordance with the clinical status of the patient. The Advocate in this situation will be a healthcare professional such as a

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specialist nurse. Assessment of patients in this context is within their professional capacity and the role here will be to witness verbal assent.

Most of the nursing staff at the Oxford Heart Centre has already attended a series of seminars to make them aware of their specific roles and responsibilities in this situation, and they have acted as patients' advocates through the recruitment of approximately 500 participants undergoing emergency PCI for STEMI in the ongoing OxAMI and OxAMI PICSO studies. The seminars have been directed by an ethicist who is not directly involved with the research project. We will continue to provide this training and draw on the extensive experience of the members of the clinical team currently acting as a Patient Advocate. Staff training at the Newcastle upon Tyne University Hospitals NHS Foundation Trust is ongoing.

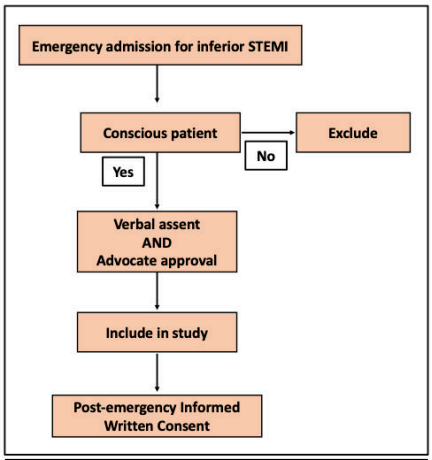

Figure 2: Informed consent in emergency research

11.1.1.3. Post-emergency phase

Once the emergency phase is over and treatment has been delivered, we will seek full written informed consent as soon as practical. For most patients this means within 12 hours of admission. This consent will be a two parts process:

a) We will seek consent to allow use of data already acquired during the emergency phase

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b) We will seek consent for ongoing participation in the study.

Written Informed Consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant and another copy will. Be filed in their medical records. The original signed form will be retained at the trial site.

If the participant elects to withdraw from the study at this point then we will present them with three withdrawal options as outlined in section 11.2.1.

If a patient is unable to provide informed consent at this stage due to deterioration in clinical condition, then advice may be sought from a relative/carer/friend acting as a consultee. When reasonable steps have been taken to identify a consultee and one is unavailable, then the researcher must nominate a person to act as in their stead. This person may be involved in the patient's care in a professional capacity but they must have no connection with the research project. A suitable person who might act as a nominated consultee is an independent doctor working with the patient or nominated by the healthcare provider. Consent from the patient will be obtained directly, if they recover promptly, at the earliest opportunity.

11.2. Discontinuation/Withdrawal of Participants from Trial Treatment

11.2.1. Study Withdrawal

We anticipate and have made provision for withdrawal when the emergency exception period is complete; if a patient is assessed and has capacity then they may completely or partially withdraw at any time. This possibility will be made clear as a part of seeking of full written informed consent after the initial emergency procedure. Participants may have the following three options for withdrawal:

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1) Participants may withdraw from active follow-up and further communication but allow the trial team to continue to write to their GP and access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., Radiology/diagnostic test, blood results and disease progression data etc.
2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

The type of withdrawal and reason for withdrawal will be recorded in the case report form (CRF).

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

11.2.2. Participant death

If the participant dies before giving full written consent then we propose to continue using the data obtained. We would not seek further 'consent' from relatives at the risk of causing undue distress.

11.3. Recruitment

RETRIEVE-AMI is a multi centre study recruiting at the John Radcliffe Hospital and the Newcastle upon Tyne Hospitals NHS Foundation Trust sites. Participants will be identified as they are being admitted for primary PCI. They will be approached by a research team member (a primary PCI operator who is also a member of the clinical care team) who will verbally assent them as explained in section 11.1.1.1. Upon assent, participant will be randomised to one of the three study arms, by a system based on sealed Envelope system. Consent will be completed at the post-emergency phase as described in section 11.1.1.3.

11.4. Randomisation

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Upon assent, participant will be randomised to one of the three study arms, by a system based on sealed envelopes. Randomization will take place in the cathlab once both inclusion and exclusion criteria are verified and assent provided.

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11.5. Blinding and code-breaking

Due to the interventional nature of the trial, masking and code-breaking procedures are not applicable.

11.6. Study timeline

Stage 1 – Screening, Assent & Randomisation

Participant identification and assent will proceed as described in sections 10 and 11.1.1.1-11.1.1.2 respectively.

- Diagnostic angiography will be performed in the standard manner using appropriate catheters. Heparin will be administered as routinely used for PCI. Angiograms will be reviewed to ensure participation eligibility according to angiographic inclusion/exclusion criteria (section 10.3)
- Once eligibility is confirmed patients will be assented and randomised.

Stage 2 – Baseline assessments

- Once the lesion has been crossed with a coronary guidewire, flow will be established with a 1.5mm semicompliant balloon predilation.
- OCT measurements will be performed using a dedicated OCT catheter over the coronary guide wire in the usual manner for clinical OCT assessment. For Arm 1, the OCT measurements in the baseline assessment will be treated as the pre-stent measurements as thrombus modification will not be performed in this group.

Stage 3 – Post-thrombus modification pre-stent assessments

Patients randomised to Arm 2 (thrombus aspiration) or Arm 3 (thrombus retrieval) will undergo the assessments in this stage.

- Thrombus aspiration (Arm 2) will proceed according to standard clinical practice. In brief, a thrombus aspiration device (i.e. Export Catheter) will be advanced over the coronary guidewire. Aspiration will then proceed.

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- Retrieval thrombectomy (Arm 3) will proceed according to the manufacturer's manual. In brief, a microcatheter (e.g. Phenom™, Marksman™) is advanced over the guidewire. Once the microcatheter has traversed the thrombotic occlusion the Solitaire™ X revascularisation device is advanced through the microcatheter until the usable length of the stent extends past each side of the thrombus in the vessel. Then the microcatheter is retracted to the proximal radiopaque marker of the stent. As this retraction occurs the stent self-expands and entangles the thrombus. Next, the microcatheter and Solitaire™ X Revascularisation Device are withdrawn as a unit into the guide catheter under continuous aspiration (Appendix C).
- OCT measurements will be performed using a dedicated OCT catheter over the coronary guide wire in the usual manner for clinical OCT assessment.
- Angiography-derived coronary physiology measurements will be performed with up to two angiographic views (complementary and separated by an angle of at least 25 degrees) at a frame rate of 15 frames per second. Maximal hyperaemia will be achieved with an intravenous infusion of adenosine at a rate of at a rate of 140 mg/kg/min. Since stage 3 is the same as stage 2 for Arm 1 participants, these measurements will be performed at Stage 2.
- Extracted thrombus from aspiration/stent retriever at any stage of the procedure will be collected, and imaged *ex-vivo*.

Stage 4 – PCI & post-PCI assessments

- PCI will proceed according to clinical practice. Post-dilation will be performed at the operator's discretion.
- OCT measurements will be performed following a successful angiographic PCI result using a dedicated OCT catheter over the coronary guide wire in the usual manner for clinical OCT assessment.
- Angiography-derived coronary physiology measurements will be performed with up to two angiographic views (complementary and separated by an angle of at least 25 degrees) at a frame rate

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of 15 frames per second. Maximal hyperaemia will be achieved with an intravenous infusion of adenosine at a rate of at a rate of 140 mg/kg/min.

Stage 5 – Consent & data collection

Patients will be approached for consent according to procedures detailed in section 11.1.1.3. Once consent has been obtained in-hospital data collection will be completed (section 11.7.1.). ECGs will also be stored.

Stage 6 – 6 month follow-up

At 6 months patients will have a scheduled telephone follow-up to gather relevant clinical information as detailed in section 11.8.

11.7. Trial Assessments

11.7.1. Data Collection, Patient Reported Outcomes and Clinical Outcomes

Data on the clinical procedures and any devices and/or imaging technologies used will be collected. Medical history will be taken from the patient once informed consent has been given and relevant sections of the medical notes and scans may be accessed by the study team. Clinical outcomes and MACCE will be ascertained at the 6-month telephone follow-up, by accessing relevant sections of the medical records or by contacting the GP if appropriate.

11.7.2. Optical Coherence Tomography

OCT is a high-resolution intravascular imaging modality that can accurately characterise coronary plaque morphology and quantify atherothrombotic burden.[4,19] It also has the capability to accurately define the inner lumen of the native coronary artery allowing to measure the flow area and monitor the structural integrity of the artery. It is expected therefore to play a key role in identifying target vessel complications (e.g. dissection, intramural haematoma) and aspects of stent deployment (e.g. stent apposition, expansion, edge dissection).[20] Finally, OCT has the advantage of having a fast acquisition frame rate and being relatively inexpensive.

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11.7.3. Angiography-derived coronary physiology

Coronary physiology measurements during emergency PCI can be used to assess the coronary microvascular function which is affected amongst other factors by the pre-stenting thrombotic burden and distal embolisation of atherothrombotic material during angioplasty.[3] Indeed, coronary physiology measurements under adenosine-induced hyperaemia can be employed to characterise microvascular obstruction and predict the extent of myocardial infarction.[21] Contemporary work enables us to derive cardiac physiology indices such as quantitative flow ratio non-invasively using coronary angiograms.[22,23]

11.7.4. Extracted Thrombus Imaging

Intracoronary thrombus/plaque material obtained with the use of aspiration/stent-retriever thrombectomy as part of the procedure will be imaged *ex-vivo*. Images will be obtained in the catheterisation laboratory and stored in a pseudonymised format. The extracted thrombus will not be stored by the study team and will be discarded.

11.7.5. Electrocardiography (ECG)

ECG refers to the measurement of the electrical activity of the heart. It is a routine non-invasive assessment carried out in patients with suspected or known coronary artery disease.

11.8. Subsequent telephone follow-ups

Participants will have a scheduled telephone follow-up 6 months after their randomisation to the study. This telephone follow-up will gather information on concurrent medication therapy, patient reported outcomes, study outcomes and serve as an opportunity to log a participant's recovery progress.

11.9. Definition of End of Trial

Recruitment to the trial will cease as soon as 81 participants have been randomised in the study and have completed follow-up at 6 months. The trial will end when the last patient exits the study. To ensure that

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the scientific integrity of the trial is maintained, should the target recruitment not be reached by the pre-specified study end-date we will seek an extension of the study

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12. IDENTIFICATION & DESCRIPTION OF THE INVESTIGATIONAL DEVICE & COMPARATORS

12.1. Investigational Device & Comparators

12.1.1. Standalone PCI (Arm 1)

Participants randomised to the standalone PCI arm of the RETRIEVE AMI trial will have standard of care treatment. Participants will undergo PCI with devices and techniques driven by clinical decision making at the patient level and institutional level, and carried out in accordance with local guidelines.

Commented [FK(O3]: This should be made applicable to both organisations so perhaps"carried out in accordance with the hospital department guidelines."

Commented [RK4R3]: Thank you. Addressed.

12.1.2. Aspiration thrombectomy and PCI (Arm 2)

Participants randomised to Arm 2 of the RETRIEVE AMI trial will have standard of care treatment with manual thrombectomy catheter and PCI. Participants will undergo PCI with devices and techniques driven by clinical decision making at the patient level and institutional level, and carried out in accordance with local guidelines.

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12.1.3. Investigational arm (Arm 3)

Participants randomised to the stent-retriever thrombectomy arm of the RETRIEVE AMI trial will undergo stent-retriever thrombectomy with the Solitaire™ X Revascularisation Device (Figure 3). The Solitaire™ X revascularisation device has been clinically approved and CE marked for use in acute ischaemic stroke endovascular intervention.[14] Solitaire™ X works by mechanically retrieving the thrombus and restoring blood flow to the area distal to the occlusion. The Solitaire™ X Revascularisation Device is a self-expanding stent designed for dynamic clot integration with radiopaque markers that enhance visualisation of the optimal working length. Features including the range of stent diameters and usable lengths are presented in Appendix B. The device can be used in vessels with a diameter between 2.0mm and 5.5mm at the thrombotic occlusion site (Appendix B).

Figure 3: Solitaire™ X device

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After a thrombotic occlusion has been identified and crossed with a guidewire, the stent-retriever thrombectomy proceeds as described below (see Appendix C for schematic diagram).[15] A microcatheter (e.g. Phenom™, Marksman™) is advanced over the guidewire. Once the microcatheter has traversed the thrombotic occlusion the Solitaire™ X revascularisation device is advanced through the microcatheter until the usable length of the stent extends past each side of the thrombus in the vessel. Then the microcatheter is retracted to the proximal radiopaque marker of the stent. As this retraction occurs the stent self-expands and entangles the thrombus. Finally, the microcatheter and Solitaire™ X Revascularisation Device are withdrawn as a unit under continuous aspiration into the guide catheter. PCI will then proceed with devices and techniques driven by clinical decision making at the patient level and institutional level, and carried out in accordance with local guidelines.

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Commented [RK8R7]: Addressed.

12.1.4. Masking (blinding)

Due to the interventional nature of the trial, masking is not applicable.

12.1.5. Storage of investigational devices

The Solitaire™ X Revascularisation Device and Phenom microcatheters will be provided by Medtronic. The OFDI catheters will be provided by Terumo Inc. We will be documenting the number of devices, with their lot numbers, that will be shipped to the John Radcliffe Hospital and Newcastle Upon Tyne Hospitals NHS Foundation Trust. After their delivery, the kit will be stored in designated spaces at both sites and kept in a cool, dry place. We will document on the CRF the LOT number and expiry date for each device for each patient.

12.2. Retriever thrombectomy safety

Stent-retriever thrombectomy is clinically tested and licensed for endovascular intervention in acute ischaemic strokes with large vessel occlusions involving the internal carotid and the first segment of the middle cerebral artery.[14,24] Our proposed pilot in acute coronary syndrome – STEMI patients would therefore represent an off-license application for the Solitaire™ X Revascularisation Device. Endovascular intervention for acute ischaemic stroke bears similarities to coronary intervention for acute myocardial

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infarction. Off license use of retriever thrombectomy in STEMI patients is reported twice in the literature with no reported complications and a successful recanalization outcome.[15,16]

From an anatomical perspective, the Solitaire™ X revascularisation device is licensed for interventions in vessels with a minimum diameter of 2mm and a maximum of 5.5mm depending on the device model used (see appendix A). The diameter of internal carotid and middle cerebral arteries (arteries for which Solitaire™ X intervention is licensed) is reportedly 3.38±1.34mm and 2.45±0.85mm respectively.[25] Our pilot study is designed to include patients with heart attack due to thrombotic occlusion of a "large caliber" coronary artery (diameter at the site of occlusion ≥ 3.0 mm). The size range of the target vessel is thus well within the safety range proposed by the manufacturer (e.g. between 2.0 and 5.5 mm).

From a device perspective, in stroke patients Solitaire™ X revascularisation device failure was reported in one case (0.8%) in the two pivotal trials that examined this end-point with no significant sequelae.[14,26] Regarding device related complications in patients randomised to the Solitaire™ X revascularisation device, arterial dissection or perforation was reported in 5/211 (2.3%). Perforations, albeit in the coronaries are encountered in routine PCI practice in 0.37% of patients[27], while edge dissections following stent deployment in 7.7% of patients.[28] The relatively higher perforation with the Solitaire™ X device can be explained by the tortuosity of the intracerebral vessels that are treated as well as the early stage of the thrombectomy experience in the RCTs and the small sample size. To minimise the potential for coronary perforations in our trial, we will include patients with thrombotic occlusions involving the right coronary artery prior to the crux, e.g. in a vessel segment with minimal, if any, tortuosity. Nonetheless, in the event of a coronary perforation the treatment – angioplasty – is similar to the definitive treatment for the myocardial infarction.

Finally, stroke in the context of pPCI is reported in 0.25% to 0.5% of STEMI cases[29-31] and in ~0.8% of STEMI patients with aspiration thrombectomy and PCI.[30] In the Solitaire™ X device trials, the rate of embolisation to vascular fields proximal to the target vessel is not reported. It is therefore not possible to estimate the risk of stroke for our trial. However, from a mechanistic perspective stent-retriever thrombectomy is based

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on the concept of integration of the stent scaffold into the thrombus which in combination with the withdrawal of the stent into the microcatheter and the continuous aspiration on withdrawal renders embolisation of thrombotic material less likely.

12.3. Other Interventions

Not applicable

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13. SAFETY REPORTING

13.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in participants, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or comparator, events related to the procedures involved (any procedure in the protocol). For users or other persons this is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or form intentional misuse of the investigational device.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • Results in death • Is life-threatening, • Requires inpatient hospitalisation or prolongation of existing hospitalisation, • Results in persistent or significant disability/incapacity, or • Is a congenital anomaly/birth defect. • Other important medical events.

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	Included herein are device deficiencies that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) circumstances had been less fortunate. These are handled under the SAE reporting system. Planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event. Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

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Serious Adverse Device Effect (SADE)	Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above. *Unanticipated Serious Adverse Device Effects (USADE)* Any serious adverse device effect which, by its nature, incidence, severity or outcome, has not been identified
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling. Device deficiencies that did not lead to an adverse event, but could have led to a medical occurrence if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate
User error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.

Severity definitions

The following definitions will be used to determine the severity rating for all adverse events:

Mild: awareness of signs or symptoms, that does not interfere with the subject's usual activity or is transient that resolved without treatment and with no sequelae.

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Moderate: a sign or symptom, which interferes with the subject's usual activity.

Severe: incapacity with inability to do work or perform usual activities.

Arterial injury classification scheme

Coronary dissections and perforations will be classified according to the established NHLBI and Ellis classification schemes.[32,33] A significant coronary dissection is defined as a dissection leading to coronary flow impairment or coronary occlusion.

13.2. Causality

The relationship of each adverse event to the trial device may be determined by the manufacturer and/or a medically qualified Investigator according to the following definitions:

Not related: The event is clearly related to other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication.

Unlikely: The event is probably produced by other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication and does not follow a known response pattern to the device

Possibly: The event follows a reasonable temporal relationship form the time of placement/administration and/or follows a known response pattern to the device but could have been caused by other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication.

Most probable: The event follows a reasonable temporal relationship form the time of placement/administration and/or follows a known response pattern to the device and could not have been caused by other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication. Further the event immediately follows the administration/placement of the device and improves on stopping or removing the device.

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13.3. Procedures for Recording Adverse Events

All adverse events (including ADEs) and device deficiencies occurring during the course of the study will be recorded on the CRF whether or not attributed to the trial device. The information recorded will include but not be limited to:

- A description of the event
- The dates of the onset and resolution
- Action taken
- Outcome
- Assessment of relatedness to the device
- Whether the AE is serious or not
- Whether the AE arises from device deficiency
- Whether the AE arises from user error

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The CI shall submit to Medtronic a report of AEs and ADEs that occur in Arm 3 of this study. AEs/ADEs considered related to the device as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE/ADE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE/ADE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

13.4. Reporting Procedures for Serious Adverse Events

Reporting of all Serious Adverse Events will be done in accordance with the European Commission Guidelines on Medical Devices Serious Adverse Event Reporting (MEDDEV 2.7/3; December 2010).

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SAEs/SADEs that pose an immediate risk to patient health or safety will be reported to the trial TSG/Sponsor immediately or no later than 24 hours after the Investigator is aware and to the device manufacturer, the MHRA and the REC within 2 calendar days of the Chief Investigator becoming aware of the event. The SAE form should be emailed to ouhsae.reports@ouh.nhs.uk.

All other reported SAEs/SADEs will be reported to the trial TSG, the Sponsor, device manufacturer and the MHRA within 7 calendar days of notification, if appropriate. This will not include SAEs that may be expected as part of the risks of routine care. Adverse device events (SADEs, USADEs) and device deficiencies will also be reported to the device manufacturer. All SAEs will be followed up to resolution.

SAEs/SADEs will be recorded for a time period starting from verbal assent/investigational device deployment to 30 days following the use of the device.

13.5. Expectedness

Expectedness will be determined according to the Manufacturers risk analysis report

13.6. Trial cessation rules

The trial will be halted early if any of the following occur:

- >2 transient ischaemic attack /ischaemic stroke-related SADEs
- >2 coronary perforation-related SADEs
- > 2 significant coronary dissection-related SADEs

13.7. Safety Monitoring Committee – Trial Safety Group (TSG)

The Oxford University Hospitals Trust Trial Safety Group (TSG) will conduct a review of all SAEs/SADEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required

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- To evaluate the risk of the trial continuing and take appropriate action where necessary

13.8. Safety of stent-retriever thrombectomy

See Section 12.2.

13.9. Safety of intravascular imaging

Intravascular imaging using OCT is often performed during PCI to assist in the procedure. The utilization of this modality typically adds up to 5 minutes to the procedure duration. Use of any intra-coronary device including OCT can cause ischaemia, chest discomfort or, rarely, other local coronary complications during the PCI. However, this is in the context of a PCI procedure where significant interventions such as balloon expansion and stent deployment are already being carried out in the coronary artery, which themselves may cause ischaemia, chest pain that may require the use of analgesia, or other local coronary complications.

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14. STATISTICS

14.1. Number of participants

Based on estimates from previously published work[9,34] and our stipulation for inclusion of patients with high thrombotic burden, we anticipate a mean pre-stent thrombus volume of 9.6mm^3 with a standard deviation estimate of 5.1 mm^3 in the standard of care arms. Since this is the first pilot of stent retriever in acute coronary syndromes there is no previous published work that can inform on the expected pre-stent thrombus volume reduction with retriever thrombectomy. We have therefore hypothesised a 33% reduction in mean pre-stent thrombus volume. Using a 1-way pairwise ANOVA with a 2-sided equality, accounting for 2 pairwise comparisons with an α of 0.05, a sample size of 72 patients would have 80% power to detect a 33% reduction in pre-stent thrombus volume with retriever thrombectomy.[35] The approach that was used accounts for two pairwise comparisons. Indeed, for one such comparison a sample size of n=48 (n=24 for Arm 1 and 24 for Arm 3) would maintain the desired α of 0.05 and β of 0.2. Given that aspiration thrombectomy was not shown to differ from no thrombus modification,[9] a sample size of n=48 (n=24 for Arm 2 and n=24 for Arm 3) would maintain the desired α of 0.05 and β of 0.2 for this comparison. The overall sample size is therefore increased by a further n=24 patients for the aspiration thrombectomy group. This leads us to n=72 patients required to show a 33% reduction in pre-stent thrombus burden with a power of 80%. Assuming 12.5% of patients will not have analysable OCT imaging, we plan to enrol 81 patients (n=27 in each group) to ensure the study remains adequately powered.

14.2. Analysis of Endpoints

In keeping with our usual practice, we will obtain expert statistical advice from the Centre for Statistics in Medicine (or equivalent) for each specific task. A flow diagram detailing number of participants screened and randomised will be provided. Analysis of the OCT-derived primary and secondary endpoints (including angiography-derived) will be conducted offline in a blinded fashion. Summary statistics, including means, medians, and variances, will be calculated at each time point and for each type of data and group (e.g. baseline characteristics, parameters derived from OCT, angiography-derived coronary physiology). The distribution of the levels will be described. For each parameter an analysis of variance will be carried out.

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An analysis evaluating for a between group difference in pre-stent thrombus volume will first use an 1-way ANOVA with a 2-sided equality test to assess for an overall trend. Post-hoc analyses exploring the following hypotheses i) retriever thrombectomy (Arm 3) is different to no thrombus modification (arm 1) and ii) retriever thrombectomy (Arm 3) is different to aspiration thrombectomy (Arm 2) will be performed using the Dunnett test. Control of the Type I error at 5% two-sided significance level due to multiple testing will be achieved using Dunnett's method.[36] . Missing data for the primary analysis will be dealt with complete case analysis if data missingness is <10% (<3 cases per group). If missingness is higher, multiple imputation will be performed instead. Major adverse cardiac and cerebrovascular events will be analysed using proportions statistical testing (Fisher's exact or $\chi 2$ tests), yet they represent an exploratory analysis.

14.3. Interim Safety Analysis

Based on the reported coronary perforation (0.37%), coronary dissection (7.7%) and transient ischaemic attack/ischaemic stroke (0.25-0.8%) rates in contemporary STEMI practice, in a 27-patient arm study, 1 coronary perforation, 1 significant coronary dissection and 1 transient ischaemic attack/ischaemic stroke may be expected by chance. If >2 (>10%) coronary perforation-related SADEs or >2 significant coronary dissection-related SADEs or >2 transient ischaemic attack-/ischaemic stroke-related SADEs occur in the investigational device arm this will be considered too high.

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15. DATA MANAGEMENT

15.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), ECGs, radiographic and OCT images and correspondence. Access to relevant source data will be sought for members of the research team.

15.2. Data recording and Record Keeping

The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. This will be achieved by assigning participants a unique trial ID number that will be used in case record forms (CRFs), ECGs, radiographs, OCT and extracted thrombus images (pseudonymisation). A contact record form linking a participant's unique trial ID number with their personal identifiable data (name, hospital ID, personal address, emails or telephone numbers) will be used. This form will be kept in the code break folder, separate from other documents. This form is needed to perform the 6 months telephone follow-up and to ensure that in case of an emergency participants can be identified and contacted. The written informed consent form that contains personal data (name and signature) can not be anonymised, but will be kept in a separate folder to the pseudonymised data and stored securely at the Oxford University Hospitals NHS Foundation Trust and the Newcastle upon Tyne Hospitals NHS Foundation Trust.

Study data will be entered into the CRFs by members of the research team after reviewing source data and/or seeking information from the patient. This data will then be securely stored in an on-site location with restricted access and will only be accessible by study staff and authorised personnel. Pseudonymised data from non-Oxford sites can be transferred using appropriately encrypted means to Oxford University Hospitals NHS Foundation Trust. Source ECG data will be copied, identifiable data will be removed and subsequently labelled with the trial participant ID number. ECG's will be securely stored alongside the

Commented [GS(O9]: How will this be done?

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participant's CRFs in an on-site location with restricted access and will only be accessible by study staff and authorised personnel. Radiographic and OCT imaging data will be de-identified using the unique trial participant ID number before downloading them on to encrypted electronic transfer media and transferred to be stored on to password protected NHS computers in an on-site location with restricted access. Pseudonymised data from non-Oxford sites can be transferred using appropriately encrypted means to Oxford University Hospitals NHS Foundation Trust. In Oxford, extracted thrombus imaging data will be stored in a de-identified format using the trial participant ID number on to password protected NHS computers in an on-site location with restricted access.

Personal data (contact record form) will be stored for 12 months after the study has ended, while pseudonymised research data generated by the study and any research documents with personal information, such as the consent forms, will be stored for 10 years. All study data and documents will be stored securely in an on-site location with restricted access. Study data will only be accessed by study staff and authorised personnel. After analysis is completed, data will be archived in a secure location with restricted access. After the specified data storage period elapses, the data custodian will agree a date for destruction and data will be destroyed confidentially at that time.

15.3. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

15.4. Approval to share imaging data with third parties

De-identified research data including imaging data may be shared with the University of Oxford or other specialised centers in partnership with RETRIEVE-AMI, according to the availability of specialist analysis techniques that may not be available to the local research team. Data transfer and storage should follow the processes described in 15.2. Participants will be informed in the information leaflet and sign in the consent form (if they approve) that their pseudonymised images may in the future be sent to third parties

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for specialist processing. It will be clearly stated that no identifying information will be sent with these imaging data.

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16. QUALITY ASSURANCE PROCEDURES

16.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

16.2. Monitoring

Regular monitoring will be performed by the sponsor according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

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17. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. All deviations will be reported to the MHRA.

18. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree -

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

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19. ETHICAL AND REGULATORY CONSIDERATIONS

19.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

19.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

19.3. Medical Device Regulations

The Investigator will ensure that this trial is conducted in full conformity with:

- European Commission Medical Device Guidelines relating to the application of the EU Directives on Medical Devices
- Guide to European Medical Device Trials and BS EN ISO 14155

19.4. Approvals

Following Sponsor approval the protocol, informed consent form and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

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19.5. Specific Ethical Considerations for participants in emergency situations

Research in emergency situations is ethically complex because of the urgent nature of the interventions and the often severely compromised capacity of the patient. The processes of enrolment and consent described above, including verbal assent and the involvement of the Advocate represents our attempt to develop a thorough, ethically justified process that both protects patients' rights and interests and enables important research to be done. These processes have been developed in the light of and guided by the provisions laid out in the Mental Capacity Act with special reference to Section 32(9).

19.6. Possible risks/discomfort to participants

Patients referred for emergency cardiac catheterization and PCI will undergo this procedure as would routinely be performed. Patients will therefore be informed of the standard of care procedure and its associated risks. All local protocols will be adhered to and only fully trained staff will carry out procedure according to departmental SOPs.

From a research perspective, the PCI procedure time may be lengthened by around 10 minutes to complete the selected study procedures (OCT acquisitions, angiography derived physiology & aspiration/stent retriever thrombectomy). In the context of a PCI procedure that typically lasts approximately 60 minutes. The additional time should not result in any clinically significant difference to the participants. Very occasionally this additional time can result in some back discomfort for patients having to lie on the angiography bed for the additional time period.

Stent-retriever thrombectomy with the Solitaire X revascularisation device is clinically tested and licensed for endovascular intervention in acute ischaemic strokes. Device failure was reported in one case (0.8%) in the two trials that examined this endpoint with no significant sequelae. Device related complications such as arterial dissection or perforation was reported in 5/211 (2.3%) of ischaemic stroke patients randomised to stent-retriever thrombectomy with the Solitaire X revascularisation device. Perforations and edge dissections are encountered in routine PCI practice in 0.37% and 7.7% of patients and interventional cardiologists are familiar with their management. Coronary perforations and significant

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dissections are usually treated with a stent which is the treatment these patients will eventually receive for their heart attack.

Finally, stroke in the context of pPCI is reported in 0.25% to 0.5% of STEMI cases and in ~0.8% of STEMI patients with aspiration thrombectomy and PCI. In the Solitaire X device trials, the rate of embolisation to vascular fields proximal to the target vessel is not reported. From a mechanistic perspective, stent-retriever thrombectomy is based on the concept of integration of the stent scaffold into the thrombus which in combination with the withdrawal of the stent into the microcatheter and the continuous aspiration on withdrawal renders embolisation of thrombotic material less likely.

Patients having a heart attack have a higher risk of cardiac mortality, heart failure, periprocedural myocardial infarction and access-site complications (haematoma, bruising, discomfort) by virtue of the underlying condition and its treatment with PCI. Additionally, participants who have suffered a heart attack are frequently re-admitted for a pre-planned procedure to complete revascularisation of their coronary artery disease. We expect that some combination of these events will be noted in trial participants during the study follow-up period. Adverse event reporting will proceed as described in section 13.

19.7. Collaboration and Partnership with Commercial Companies & Third parties

The Oxford University Hospitals NHS Foundation Trust (OUHT), the Newcastle upon Tyne Hospitals NHS Foundation Trust and the RETRIEVE-AMI study receive support from, commercial companies who provide the devices and technologies related to PCI and other research investigations.

To futureproof our study, we may also share research data, including imaging data, with the University of Oxford or other specialised centres (academic or commercial) in partnership with The Oxford University Hospitals Trust, the Newcastle upon Tyne Hospitals NHS Foundation Trust and the RETRIEVE-AMI study for specialist analysis techniques that may not be available to the local research team. We will ensure that participants are not identifiable from the shared research data.

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19.8. Feasibility

The Oxford Heart Centre is a state-of-the-art facility which incorporated services in cardiology and cardiac surgery. The cardiac catheter laboratories are fully equipped to support this study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is a high volume institution with considerable experience in acute cardiology research.

19.9. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, the HRA (where required), Medtronic, Terumo Inc, the host organisation, and the Sponsor. A progress report will also be submitted on a semi-annual basis to Medtronic and Terumo Inc. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor. The CI shall make the generated results available to Medtronic and Terumo Inc up to 14 days before publication or dissemination to the public.

19.10. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exceptions of i) the contact record and ii) consent forms. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. Data management is described in detail in section 15.

20. FINANCE AND INSURANCE

20.1. Funding

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RETRIEVE AMI will be supported in kind by Medtronic (Minnesota, US) through the provision of medical devices and assistance with the MHRA application process. RETRIEVE AMI will also be supported in kind by Terumo corporation (Tokyo, Japan) through the provision of OFDI (second generation OCT) catheters.

20.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If participants are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

21. PUBLICATION POLICY

Data will be owned and supervised by the trust. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Medtronic and Terumo. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Copies of any publications connected to this study are available on request from the RETRIEVE-AMI investigators.

22. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

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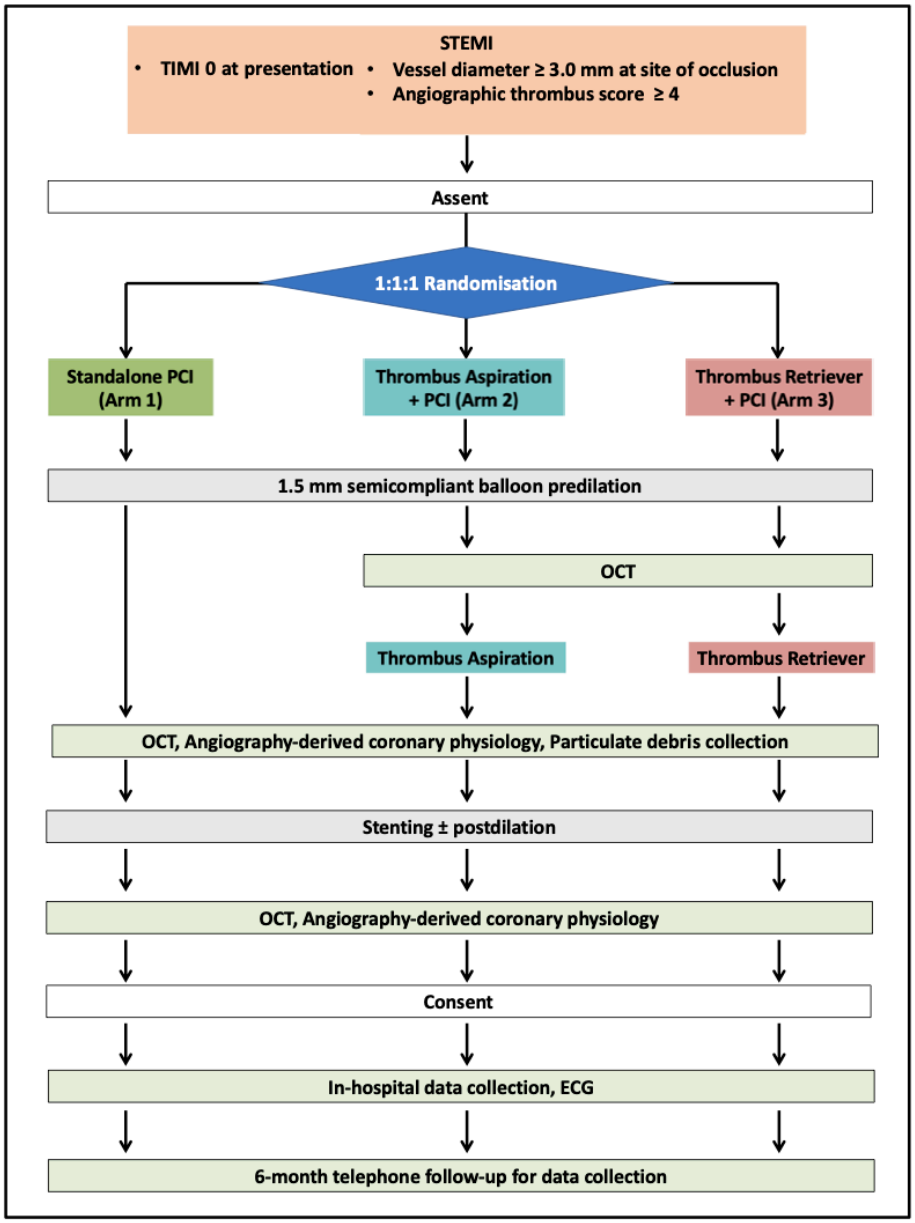
24. APPENDIX A: Trial flow chart



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25. APPENDIX B: Vessel reference diameters for device sizing

SOLITAIRE™ X REVASCULARIZATION DEVICE ORDERING INFORMATION[4]

Model	Recommended Vessel Diameter[A] (mm)		Minimum Microcatheter ID (inch)		Push Wire Length	Stent Diameter	Usable Length[B]	Stent Length	Length from Distal Tip to Flourosafe Marker	Radiopaque Markers		Radiopaque Stent Markers Spacing
	(min)	(max)	(min)	(max)	(cm)	(mm)	(mm)	(mm)	(cm)	Distal	Prox.	(mm)
SFR4-4-20-05	2.0	4.0	0.021	0.027	200	4.0	20.0	31.0	<130	3	1	5
SFR4-4-20-10	2.0	4.0	0.021	0.027	200	4.0	20.0	31.0	<130	3	1	10
SFR4-4-40-10	2.0	4.0	0.021	0.027	200	4.0	40.0	50.0	<130	3	1	10
SFR4-6-20-10	2.0	5.5	0.021	0.027	200	6.0	20.0	31.0	<130	4	1	10
SFR4-6-24-06	2.0	5.5	0.021	0.027	200	6.0	24.0	37.0	<130	4	1	6
SFR4-6-40-10	2.0	5.5	0.021	0.027	200	6.0	40.0	47.0	<130	4	1	10

A. Based on the smallest vessel diameter at thrombus site.
B. Usable length that is at least as long as the length of the thrombus.

Up to 3 retrieval passes[4]

1. TR-NV16168 Rev A. **2.** TR-NV12692 Rev A. **3.** Compared to Solitaire™ Platinum. **4.** 71042-001 Rev B. **5.** Umansky, F. et al. Microsurgical anatomy of the proximal segments of the middle cerebral artery. **6.** TR-NV13807 Rev A. **7.** TR-NV12180 Rev A. **8.** DWGSFG13XXX-YYyy-Zz Rev B. **9.** DWGSFG15XXX-YYyy-Zz Rev B. **10.** Solitaire™ FR Received CE Marking 2009. **11.** TR-NV15666A Rev A. **12.** Phenom 21 Catheter. **13.** STRATIS, SWIFT PRIME, ESCAPE, Nasa Registry, THRACE, MR CLEAN, STAR, EXTEND IA, HERMES, SEER, REVASCAT, DEFUSE 3.
Note: The Solitaire™ X Revascularization Device was not evaluated in these studies.

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26. APPENDIX C: Schematic diagram of device operation

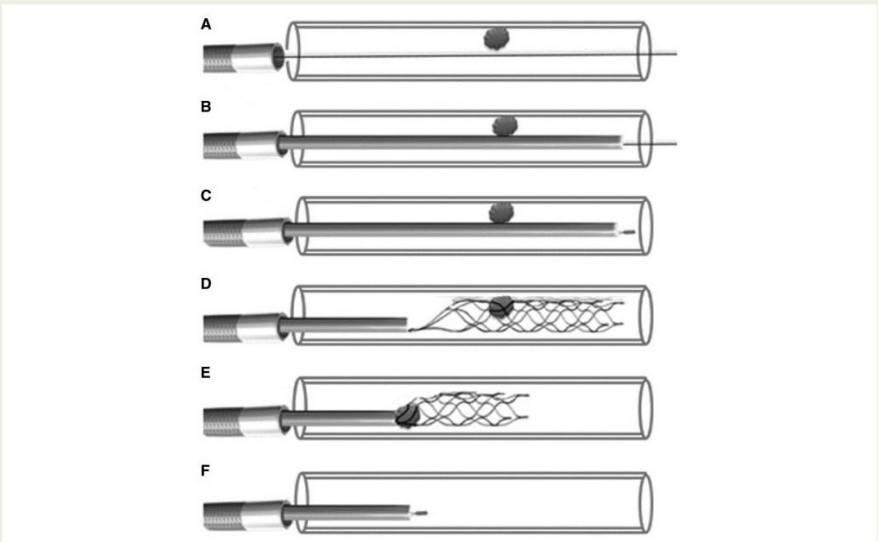

Figure 4 Line diagram to illustrate the technique of using the thrombus retrieval device. (*A*) The vessel with thrombus is crossed with a workhorse wire that was pre-loaded with a Rebar micro-catheter. (*B*) Rebar micro-catheter was advanced beyond the thrombus. (*C*) The wire was removed; an appropriate sized Solitaire AB device was back loaded and advanced to the tip of the micro-catheter positioned beyond the thrombus. (*D*) The micro-catheter was pulled back maintaining the tip of the device at the same position. This makes the stent expand and trap the thrombus between its struts. (*E*) The stent device is then pulled back into the micro-catheter along with the trapped thrombus. (*F*) Once the device is completely within the micro-catheter the whole system is pulled out.

Schematic diagram of device operation[15]

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27. APPENDIX D: Amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V1.3	21/01/2022	Rafail A Kotronias Giovanni L De Maria	Sample size increase
2	V2	21/12/2022	Rafail A Kotronias Giovanni L De Maria	Changes in inclusion and exclusion criteria
3	v3.0	02/10/2023	Rafail A Kotronias Giovanni L De Maria	Inclusion of an additional site Extension of recruitment period

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