Trial Title: Oxford Acute Myocardial Infarction - Pressure-controlled Intermittent Coronary Sinus Occlusion in STEMI (OxAMI-PICSO study)

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No potential conflicts of interest to declare

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Oxford Acute Myocardial Infarction - Pressure-controlled Intermittent Coronary Sinus Occlusion in STEMI
Internal ref. no. (or short title)	OxAMI-PICSO
Clinical Phase	II
Trial Design	Prospective single centre observational cohort study

Trial Participants	Patients admitted for primary percutaneous coronary intervention for ST elevation myocardial infarction	
Planned Sample Size	75 patients	
Treatment duration	Maximum of 90 minutes	
Follow up duration	6 months	
Planned Trial Period	18 months	
	Objectives	Outcome Measures/Endpoints
Primary	To evaluate the effect of pressure intermittent controlled coronary sinus occlusion on the indexes of coronary physiology and on infarct size in STEMI patients at short and mid term follow up.	To evaluate the effect of pressure intermittent controlled coronary sinus occlusion on infarct size measured at cardiac magnetic resonance after 24-48 hours from revascularization.
Secondary	To evaluate the utility of individual biomarkers (blood components derived substances from cells, DNA, plasma etc) in the assessment of coronary artery disease and myocardial infarction investigating also how these individual biomarkers may be modified by PICSO treatment.	To evaluate the effect of pressure intermittent controlled coronary sinus occlusion on humoral biomarkers and on the evolution of parameters of coronary physiology at 24 hours and infarct size, microvascular obstruction at cardiac magnetic resonance after 6 months from revascularization.
Safety Endpoint	To evaluate the rate of PICSO failure deployment, coronary sinus complications, and additional time and radiation exposure associated to for PICSO deployment	
Device name	Pressure intermittent controlled coronary sinus occlusion (PICSO)	
Device Manufacturer	Miracor Medical System	
Device Classification	Interventional Cardiology	

Protocol version no.	Effective Date	Significant Changes	Previous protocol version no.
2.0	01.04.2015	- Clarification of follow up duration - Clarification for what group of patient CMR follow up is meant	v1.0 13.02.2015
3.0	20.06.2016	- Extension of sample size to 75 patients to achieve a minimum of 25 patients with complete dataset	v2.0 01.04.2015

Protocol version no.	Effective Date	Significant Changes	Previous protocol version no.
4.0	06.05.2016	- Change in information about regulatory status of PICSO technology from CE-marked to non non-CE mark - Extension of recruitment beyond the period specified in the IRAS application form	V3.0 20.06.2016
5.0	26.02.2018	- Extension of recruitment beyond the period specified in the IRAS application form - Extension of inclusion criteria to allow enrolment of all patients with ST elevation myocardial infarction, irrespectively of the coronary location of the culprit lesion	V4.0 06.05.2016

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CFR	Coronary flow reserve
CI	Chief Investigator
CMR	Cardiac magnetic resonance
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
FFR	Fractional flow reserve
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMR	Index microrcirculatory resistance
IRB	Independent Review Board

MI	Myocardial infarction
NHS	National Health Service
NRES	National Research Ethics Service
PCI	Percutaneous coronary intervention
PI	Principal Investigator
PICSO	Pressure controlled intermittent coronary sinus occlsuion
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford University Hospitals Trust / University of Oxford Trials Safety Group

4. BACKGROUND AND RATIONALE

Restoration of blood flow in the infarct related artery (IRA) is the cornerstone for the current treatment of ST elevation myocardial infarction (STEMI) [1]. However in a variable proportion of patients, ranging from 30 to 40%, myocardial reperfusion is impaired, despite the apparent successful achievement of epicardial coronary artery patency [2]. This condition, known as no reflow, is due to microvasculature dysfunction and/or obstruction and it is the result of the interaction of several pathophysiological mechanisms including ischemia injury, reperfusion injury, distal embolization and tissue oedema [3].

4.1 Diagnosis of no reflow

Identification of no reflow and microvascular obstruction can be obtained by application of different diagnostic tools. So far cardiac magnetic resonance (CMR) represents the gold standard for detection and quantification of myocardial damage and microvascular impairment [4]. Parameters easily derived from

CMR such as infarct size, area at risk, myocardial salvage and microvascular obstruction have been shown to be related to long term outcome.

A major limitation of CMR is the time-delay from percutaneous coronary intervention (PCI), being applied at the earliest at the end of the revascularization procedure [4]. Early identification of patients at higher risk of no reflow, during the PCI procedure, would be extremely useful and in such regard parameters of coronary physiology may have a role. Indeed, measurements of blood flow and coronary microcirculation function are now used in the catheter lab during routine PCI, using standard techniques (a pressure wire) that are incorporated into the PCI procedure itself (by replacing the PCI procedure wire with a pressure wire). An example of this is the measurement of the index of microcirculatory resistance (IMR), defined as distal coronary pressure divided by the inverse of the hyperaemic mean transit time (a correlate to absolute flow). It is measured simultaneously with the coronary pressure wire and it evaluates microvascular resistance, independently of epicardial stenosis [5]. IMR has become the catheter-based method of choice to independently assess coronary microcirculation [5-6]. Recent data suggest that IMR, measured acutely in patients with MI undergoing emergency PCI, provides useful prognostic information [7]. Specifically, a postprocedure IMR> 40 has been shown to be significantly associated with a worst long term prognosis in terms of cardiac death and re-hospitalization for heart failure [8].

We have conducted a preliminary study, in the setting of the Oxford Acute Myocardial Infarction (OxAMI) project, to understand the procedural aspects at PCI that may directly influence the microcirculation. The key findings are that:

1. Coronary stenting itself reduces IMR and is thus beneficial in terms of the microcirculation.

2. Patients with a low pre-stenting IMR tend to do have little change in IMR.

3. Conversely the reduction in IMR is largest in those with a higher IMR (> 40) before stenting

4. However, a proportion of patients with high IMR can continue to have a still high (> 40) or even further increased poststenting IMR.

This suggests that patients with a high pre-stenting IMR are at especially higher risk and may benefit from additional interventions.

4.2 Retroperfusion strategy and PICSO

So far many strategies have been proposed in order to prevent and/or to treat no reflow, but none have demonstrated a consistent beneficial effect. A new proposed approach being investigated is the retroreperfusion strategy [9] based on the principle that it is possible to reduce the ongoing ischemia by perfusing the myocardium through the coronary sinus.

The concept of retroperfusion is 100 years old it has been initially discarded after the advent of coronary artery bypass grafting and PCI. Different techniques of retroperfusion are available: intermittent coronary sinus occlusion (ICSO), synchronized retrograde perfusion (SRP) and simplified retroperfusion (SR) [10-13]. The common denominator is the temporal increase in coronary sinus pressure through the coronary sinus occlusion (ICSO) or retroperfusion with arterial blood (SRP and SR).

PICSO is a modification of the original time-dependent ICSO and it is applied through a dedicated catheter (PICSO Impulse catheter, Mirarcor Medical System GmbH, Vienna, Austria).

The catheter presents a balloon at the distal end. The balloon inflates and deflates cyclically once deployed in the coronary sinus, leading to intermitted coronary sinus pressure increase. This intermittent increase in coronary sinus pressure leads to an improved perfusion of the ischemic area with potential benefit in terms of myocardial salvage through 3 mechanisms: 1) redistribution of blood flow from the remote myocardium to the border zone of the ischemic myocardium [14]; 2) enhanced wash out of noxious, inflammatory factors and embolic material across the microvascular bed (suction effect upon balloon release) [15]; 3) improvement in collaterals through release of vascular growth factors as consequence of venous pressure increase [16-17].

The PICSO technology has revealed to be effective in several models by reducing infarct size (IS) [18] and a metanalysis on seven studies on animal models has confirmed a statistically significant -29% (CI95% -40.9 – -17.7, p<0.001) reduction in IS compared to control group [19]. Moreover, it has also been shown that the benefit from PICSO treatment is directly proportional to the pressure reached in the coronary sinus during the balloon inflation and thus to the increase in coronary wedge (CW) pressure, which is the pressure associated to the blood flow provided to the ischemic region by collateral branches [20].

The Prepare-PICSO study represents the first-in-man experience with the PICSO device [21]. On a small sample of 15 patients with stable angina the PICSO treatment showed to be firstly safe and, as observed in the animal models, was associated to a significantly increase in coronary sinus pressure as well in mean CW pressure in the distal left anterior descending (LAD) coronary artery [21].

These findings have triggered the Prepare-RAMSES study in which PICSO treatment was investigated for the first time in man in patients with STEMI [22]. The results of the study have been recently published. The study was initially designed to include 30 patients with anterior STEMI with PICSO treatment for 90 minutes after the completion of primary percutaneous coronary intervention (PPCI). The study enrolled only anterior STEMI since expected to be responsive to the PICSO device, being mainly the anterior wall of the myocardium drained by the coronary sinus. The device resulted to be safe, with a median implantation time of 12 minutes. The primary endpoint was the reduction in IS at cardiac magnetic resonance (CMR) at 2-4 days and 4 months. The PICSO group was compared with a matched control group of patients.

Although the study did not show an overall difference in the reduction in IS in the PICSO group [22], IS reduction appeared to be significantly related to the quantity of PICSO treatment (pressure achieved in the coronary sinus x time of treatment) and significantly higher in the small subgroup of patients receiving high PICSO quantity.

It is possible that the study did not reach the primary endpoint due to some limitations in its design. First of all the small sample size has to be acknowledged, since the investigators managed to fully deliver the PICSO treatment only to 12 patients (63% of the initially intended sample size). Moreover, the study

presented a potential “selection bias” that drove the investigators to include in the study “relatively healthier” patients in which anticipated benefit was limited: 40% of patients enrolled presented with a Thrombolysis In Myocardial Infarction (TIMI) flow > 1, e.g. presented with an open coronary artery at the time of primary PCI. Moreover the application of PICSO treatment at the end of the PPCI may have blunted the expected benefit: the device was deployed after stenting, the stage the procedure known to be at higher risk of distal embolization of atherothrombotic debris downstream the coronary microvasculature [22].

Identification of “higher risk” STEMI patients is thus crucial in order to confirm a clear benefit associated to the PICSO device.

4.3 Study Hypothesis

The Oxford Acute Myocardial Infarction - Pressure-controlled Intermittent Coronary Sinus Occlusion in STEMI (OxAMI-PICSO) study aims to analyze the potential benefit of PICSO in a selected population of STEMI patients. In patients with prestenting high IMR, and thus with larger infarct size and more compromised microvasculature status, PICSO treatment added to the conventional revascularization gold standard is expected to be associated to a better myocardial reperfusion. This will be assessed by measurement of indexes of coronary physiology and by CMR evaluation of indexes associated to infarct size, myocardial salvage and microvascular obstruction, and other biomarkers. The comparator group will be matched participants previously enrolled in the OxAMI study, with STEMI and with a prestenting IMR above 40.

5. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints

Primary Objective To assess the impact of PICSO on coronary physiology parameters, on infarct size, on myocardial salvage and on microvascular obstruction at CMR in a selected population of STEMI patients at higher risk of no reflow and with the theoretical prerequisites that make more likely to respond to PICSO treatment. The control group will be represented by a highly matched group of patients from the ongoing Ox-AMI (Oxford Acute Myocardial Infarction) project (Ethics Ref 11/SC/0397), who have undergone all other aspects of the study protocol, including assessment of coronary physiology at 24 hours post primary PCI, 24-48 hours and 6 months CMR, but who have not received PICSO treatment.	Area at risk, Infarct size, Myocardial salvage and microvascular obstruction measured by cardiac magnetic resonance at 24-48 hours
Secondary Objectives The OxAMI-PICSO study aims to evaluate the utility of individual biomarkers (blood components derived substances from cells, DNA, plasma etc) in the assessment of coronary artery disease and myocardial infarction. The OxAMI-PICSO may show also how these individual biomarkers may be modified by PICSO treatment.	Coronary flow reserve (CFR), Fractional Flow reserve (FFR), index of microcirculatory resistance (IMR) measured at 24 hours after PCI. Infarct size and microvascular obstruction extent measured by cardiac magnetic resonance at 6 months Individual Biomarkers related to coronary artery disease/myocardial infarction at three time points (PCI, 24/48 hours after PCI and 6 months). These include: blood biomarkers of myocardial injury, metabolism and inflammation.
Tertiary Objectives To evaluate the rate of PICSO failure deployment, coronary sinus complications, and additional time and radiation exposure associated to for PICSO deployment	Rate of PICSO failure deployment Rate of coronary sinus complications: perforation, dissection, thrombosis Time for PICSO deployment / additional screening time and radiation dose

6. TRIAL DESIGN

The OxAMI-PICSO study is a prospective single centre observational cohort study of the use of PICSO in patients presenting for primary PCI for acute myocardial infarction. The OxAMI- PICSO study is based upon the established framework of the OxAMI study (Ethics Ref 11/SC/0397).

Patients, age 30-90, presenting with ST elevation myocardial infarction will be considered for inclusion in the study. Measurement of IMR before stenting is an essential prerequisite for the study: only patients with pre-stenting IMR > 40 will be considered eligible for the PICSO treatment. Patients with IMR≤ 40 will remain in the study but will not undergo PICSO treatment. The procedure for consent in patients undergoing emergency PCI will be as already established in the ongoing OxAMI study, and is discussed below in Section 8.1.2.

The PCI procedure will be undertaken in a standard fashion, and include the use of pressure wire measurements before and after stent deployment. Aspiration or distal protection devices may be used if clinically indicated and where vessel anatomy is suitable. The devices used and the procedural techniques will be driven by clinical decision making at the patient and institutional level, and carried out in accordance with the Oxford University Hospitals NHS Trust (OUHT) departmental guidelines for PCI.

PICSO treatment will be added on top of the conventional treatment.

The protocol will constitute of 5 main stages described in details in the next sections (Section 8.3).

Only patients with pre-stenting IMR > 40 and who assent to receive PICSO treatment will undergo 24 hours coronary angiogram with coronary physiology measurement, 24-48 hours CMR scan and 6 months CMR scan. Patients who assent to participate in the study but in whom the prestenting IMR ≤ 40, or those in whom the prestenting IMR > 40 but the participant declines PICSO treatment will remain in the study for blood sampling and clinical data collection at the same follow up time points (24 hours, 48 hours and 6 months). A summary of the study design, indicating the time points and procedures, is shown in Section 8.3.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Participants aged 30-90 years old, referred for emergency diagnostic coronary angiography presenting with ST elevation myocardial infarction, with the intention to proceed to primary PCI with stenting.

7.2. Inclusion Criteria

Participants must satisfy the following conditions:

- Male or Female, aged 30 to 90 years,
- Clinical presentation with STEMI
- Referred for coronary angiography with view to proceed to PCI with stenting.

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following are known to apply:

- Patients in whom safety or clinical concerns preclude participation.
- Known anaemia (Hb <9).
- Pregnant or breast feeding females.
- Revascularization by mean of balloon angioplasty without stenting
- History of stroke, TIA or reversible ischemic neurological disease within last 6 months
- Known severe renal failure (eGFR < 30 ml/min/1.73m2) or history of dialysis or renal transplant
- Previous coronary bypass artery grafting
- Known severe valvular abnormalities
- Previous STEMI presentation
- Presentation with cardiogenic shock
- Severe bradycardia (Heart rate < 50 beats per minutes)
- STEMI due to stent thrombosis
- Unconscious on presentation

- Non-cardiac comorbidities and life expectancy < 1 year
- Use of warfarin
- Presence of pacemaker or other electrodes in the coronary sinus
- Contraindications to adenosine
- Additional exclusion criteria for participants undergoing CMR
  - claustrophobia which limits / prevents participants from remaining in CMR scanner.
  - patients who cannot lie flat on the scan table.
  - patients with metallic implants, pacemakers, implantable defibrillators etc, unless known to be CMR compatible.
  - patients with known allergy to medium of contrast (gadolinium)

8. TRIAL PROCEDURES

8.1. Informed Consent

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

8.1.1 Patients proceeding to emergency angiogram/PCI

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 a 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 8.1.1.2 below). This process includes an important role for a healthcare professional as a type of patient "advocate". This is discussed in section 8.1.1.2 below. We also seek approval from the REC for the waiver procedure.

8.1.1.1 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 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 as part of the research project he might undergo to some extra blood samples and to measurement of the index of microcirculatory resistance (IMR) which allows to have an indirect assessment of the entity of the ongoing heart attack. The patient will be also informed that in case IMR value will be greater than 40, thus suggesting a possible significant damage to the heart muscle that may benefit from additional treatment, he might be asked to provide assent for PICSO treatment. Patients with pre-stenting IMR ≤ 40 or those with prestenting IMR > 40 who elect not to receive PICSO treatment will be given the opportunity to continue to participate within the OxAMI-PICSO study, but without the use of the PICSO device.

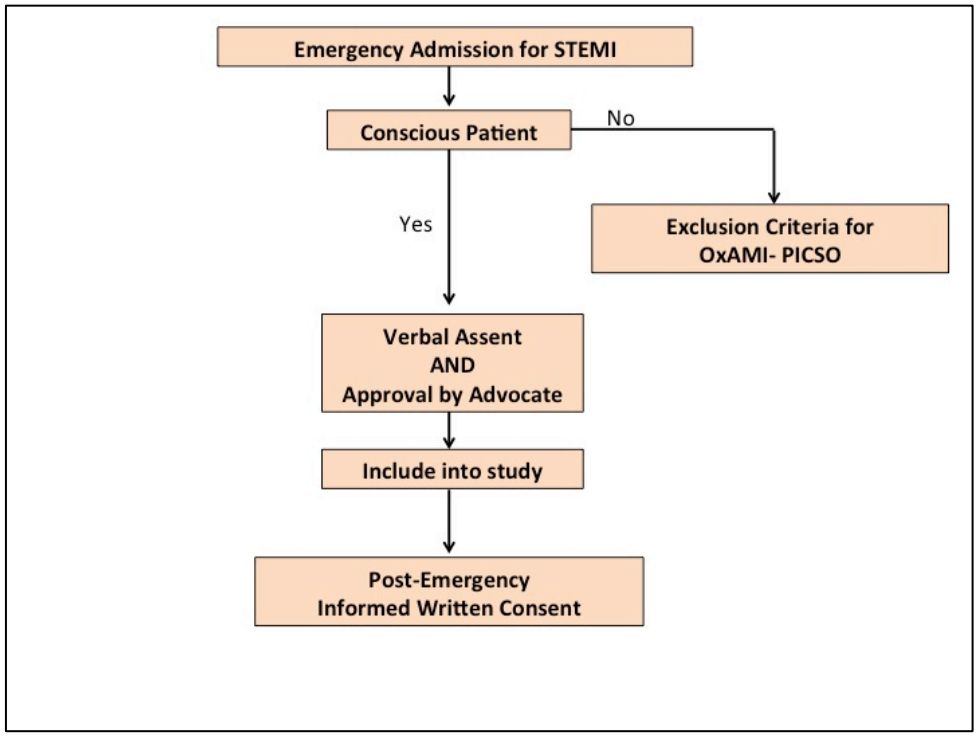
Participants will be reminded that they have the right to withdraw from the study at any stage and that this will not affect their treatment or human rights. The research and clinical team have extensive experience of patient assent, and the role of a Patient Advocate (see below), through the recruitment of approximately 250 participants undergoing emergency PCI for STEMI in the OxAMI study.

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

8.1.1.2 Patient Advocate

Because of the urgency of the situation it is not feasible to consult prior to enrolment, a RMP or patient "advocate" will be identified to act in accordance with 32(9). The Patient Advocate will act as witness and documenter of the verbal consent process for all conscious potential participants and/or overseer of the waiver process (8.1.2.3) 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 consent 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 specialist nurse. Assessment of patients in this context is within their professional capacity and the role here will be to witness verbal consent or assent.

Most of the nursing staff 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 250 participants undergoing emergency PCI for STEMI in the ongoing OxAMI study. These 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.



8.1.1.3 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 and samples already acquired during the emergency phase

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

If the participant elects to withdraw from the study at this point then we will seek consent to use the data and samples already acquired. If this is not given, then all research data and samples acquired during the emergency treatment will be destroyed, otherwise only data acquired in the emergency situation will be retained in the study.

If a patient is unable to provide informed consent at this stage due to deterioration in clinical condition, we propose to keep the data and samples acquired under the assent phase. We would not seek further 'consent' from relatives at the risk of causing undue distress.

8.2. Discontinuation/Withdrawal of Participants from Trial Treatment

8.2.1 Study Withdrawal

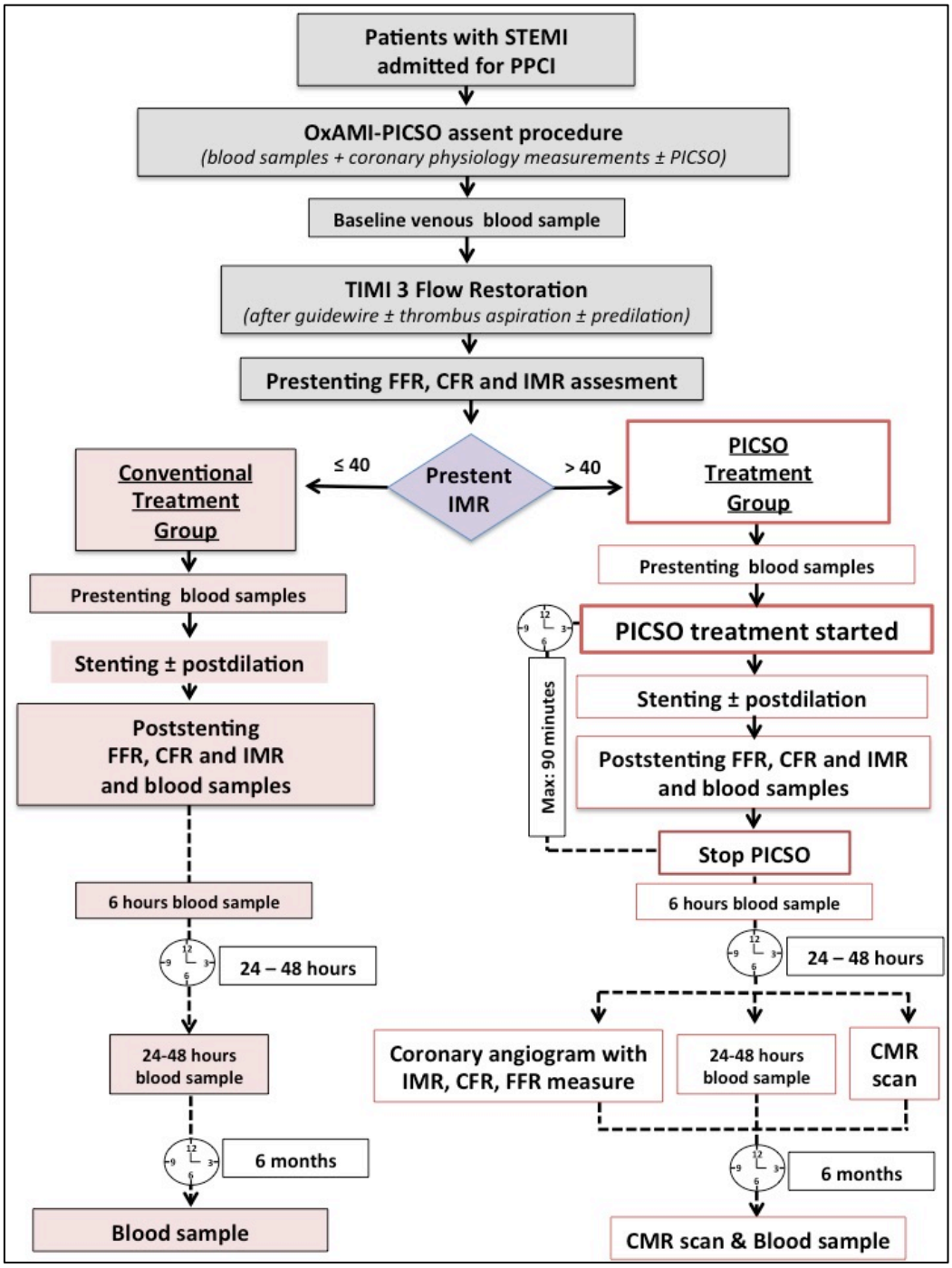
We anticipate and have made provision for withdrawal when the emergency exception period is complete; if a patient is assessed and has capacity then they may completely or partially withdraw at any time. This possibility will be made clear as a part of seeking of full written informed consent after the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

8.2.2 Participant death:

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

8.3 Study timeline (see "Integrated flowchart for OxAMI-PICSO study" as below)

The OxAMI-PICSO study will take place beside an ongoing large prospective observational study in STEMI patients (OxAMI study). Patients fulfilling the OxAMI-PICSO criteria will be invited to participate in the study. OxAMI-PICSO study will constitute of 5 main stages:



8.3.1 Stage 1: Pre-Stenting

1. Diagnostic angiography will be performed in the standard manner using appropriate catheters.
2. Bivalirudin will be administered (0.75mg/kg bolus followed by an infusion of 1.75 mg/kg/min for up 4 hours after the procedure as clinically warranted), as routinely used for PCI. The lesion will be

crossed with a coronary guide wire in the usual manner for PCI. Normal blood flow will be rapidly achieved by thrombus aspiration and/or predilation

3. Pre-stenting coronary physiology parameters, namely FFR, CFR and IMR, will be measured, using a pressure wire, as used for routine clinical measurements in patients undergoing PCI.
4. If pre-stenting IMR is > 40, patients will be invited to receive the PICSO device. If pre-stenting IMR is ≤ 40 PICSO device will not be proposed, but the patient will be invited to remain in the study for serial blood sampling (procedural-6 hours-24 hours and 48 hours) and routine clinical data collection.

8.3.2 Stage 2: PICSO treatment

1. In patients with IMR >40 who assent to PICSO treatment, the PICSO device will be deployed as already previously described in the literature [22] (Section 9.2). The overall duration of PICSO will be no less of 60 minutes up to a maximum of 90 minutes in order to ensure a PICSO delivery dose of 800 mmHg.

8.3.3 Stage 3: Stenting

1. Stenting is performed as usual clinical practice.
2. Post-dilation is left to operator's discretion, as in clinical routine.
3. At the end of the procedure a final reassessment of coronary physiology parameters is performed again as previously described.

Blood samples may be taken, (by 5 or 10 ml syringes), at the following time-points, from both peripheral vein (V), using the venous cannula, from the coronary sinus (CS) using a CS sampling catheter, or the PICSO delivery sheath, and from the coronary artery (C) either via the guide catheter used for the procedure or an aspiration catheter placed through the guide catheter:

Sampling point (1): beginning of procedure	V, C
Sampling point (2): placement of PICSO device	V, CS, C
Sampling point (3): end of procedure	V, CS, C
Sampling point (4): end of PICSO treatment period	V, CS,
Sampling point (5): 6 hours after 1st stent deployment	V

For patients in whom an aspiration catheter or protection device is used during PCI, blood, thrombus and/or atheromatous plaque material may be retrieved during the procedure. These materials, which are usually discarded, will be retained for analysis. Data on the PCI procedure and any device or technology used will be collected.

8.3.4 Stage 4: 24-48 hours post PCI

Full written consent to take part to the OxAMI-PICSO study is obtained as soon as practicable. The following study assessments may be carried out:

1. Repeat coronary angiogram for assessment of coronary physiology parameters assessment – for participants who receive the PICSO device only
2. Cardiac magnetic resonance - for participants who receive the PICSO device only
3. Venous blood sampling for biomarker measurement
4. Data Collection, Patient Reported Outcomes and Cardiovascular Outcomes

8.3.5 Stage 5: 6 months post PCI

Participants will be invited to attend the hospital as an outpatient at approximately 6 months post-PPCI for the following research assessments

1. Cardiovascular MRI - for participants who receive the PICSO device only
2. Blood sampling for biomarker measurement
3. Data Collection, Patient Reported Outcomes and Cardiovascular Outcomes

8.4 Definition of End of Trial

Recruitment to the study will cease as soon as 25 participants have undergone PICSO treatment and have completed follow-up at 6 months. The study will end on the date of the last CMR at 6 months follow up of the last participant recruited.

9. STUDY ASSESSMENT

9.1 Data Collection, Patient Reported Outcomes and Cardiovascular 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 may be accessed by the study team. Clinical outcomes and MACE will be ascertained during the follow-up appointment with the patient, by accessing relevant sections of the medical notes, ONS database and existing databases of cardiac outcomes and treatment (such as the CCAD and MINAP databases), or by contacting the GP if appropriate.

9.2 PICSO device

See Section 10

9.3 Analysis of CMR

Cardiac related parameters will be derived for further analysis. Analyses will be performed according to published methods and will be focused on the assessment of different cardiac components including anatomy, function, tissue, flow and metabolism (i.e. ventricular volumes, wall motion, infarct size, area at risk, myocardial salvage and microvascular obstruction) [23]. These parameters are partly used both clinically and in research settings (e.g. heart volumes, myocardial mass).

9.4 Analysis of cardiac physiological measurements

Cardiac and/or coronary flow and pressures will be measured, before and after stenting and during the repeat coronary angiogram at 24 hours post-PPCI, using commercially available measurement guidewires

according to standard techniques that are in routine use in current PCI practice. The guidewire contains a pressure-temperature sensor to allow for calculation of the physiological parameters. The guide wire is calibrated at the beginning of the PCI and then advanced into the distal third of the culprit artery. Calculations will be based on measurements of proximal and distal coronary pressure(s) and mean transit time (in seconds) during maximal hyperemia, as previously described. Briefly a pressure wire (Radi; St Jude Medical, St Paul, MN, USA) is placed in the LAD distal to the lesion. Baseline mean aortic pressure (Pa), mean distal pressure (Pd) and Pd/Pa ratio will be recorded. Thermodilution-based measurement of CFR and IMR will be performed by injecting in the IRA 5 ml of room temperature saline solution and recording mean transit time (meanTt) at baseline and after induction of maximal hyperaemia by intravenous infusion at a rate of at a rate of 140 mg/kg/min. Once hyperaemia is achieved the following parameters will be obtained: FFR (Pd/Pa during hyperemia), CFR (meanTtbaseline/meanTthyperaemia) and IMR (Pdhyperaemia* meanTthyperaemia).

9.5 Analysis of blood samples

Blood samples collected at the respective time points will be prepared under standard laboratory protocols, blood and its derived components will be aliquoted and stored, as necessary, in appropriate conditions for further analyses. The samples will be analysed for known and novel biomarkers related to coronary artery disease and myocardial infarction, using techniques such as enzyme immunoassay, flow cytometry etc. Samples may be assayed using novel platforms to investigate the potential utility against the existing techniques. Samples may be stored and sent to other centres, outside the UK, for specific analyses, according to the availability of specialist techniques. Depending on specific informed consent being given by participants, blood will be stored for DNA extraction and future genetic analysis, including typing of SNPs and for whole genome analysis. Specific genetic variants may be used to guide invitations to participate in future studies.

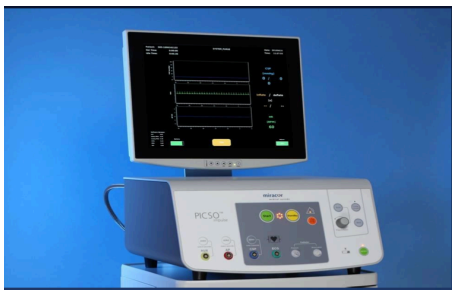
9.6 Analysis of particulate debris

Intracoronary thrombus / plaque material obtained with the use of thrombus aspiration at any stage of the procedure will be prepared under standard laboratory protocols and stored at -80ºC for further analyses. Snap frozen debris may be analysed using immunohistochemical stains, including antibodies to CD68, smooth muscle actin, CD3, and CD20, Tissue Factor [24], Vascular Endothelial Growth Factor (VEGF) [25], MMPs 2 and 9 [26], cellular proliferation and apoptosis [27-29]. Samples may also be analysed by extraction of mRNA for RT-PCR, or for levels of proteins/lipids using proteomics/lipidomics approach or other molecular markers using novel technologies.

10. IDENTIFICATION & DESCRIPTION OF THE INVESTIGATIONAL DEVICE

10.1 Device description

The PICSO Impulse System consists of the PICSO Impulse console (101.100.000.000) and PICSO impulse catheter (300.100.000.010) by Miracor Medical Systems (Gumpendorferstrasse 139, Top1.05 Vienna, A-1060).



PICSO Impulse Console

PICSO Impulse Catheter

Each PICSO Impulse catheter will have a serial number, which will be recorded for traceability during and after completion of the study.

The PICSO Impulse catheter presents a balloon at the distal end. The balloon inflates and deflates cyclically once deployed in the coronary sinus, leading to intermitted coronary sinus pressure increase. This intermittent increase in coronary sinus pressure leads to an improved perfusion of the ischemic

area with potential benefit in terms of myocardial salvage through 3 mechanisms: 1) redistribution of blood flow from the remote myocardium to the border zone of the ischemic myocardium [14]; 2) enhanced wash out of noxious, inflammatory factors and embolic material across the microvascular bed (suction effect upon balloon release) [15]; 3) improvement in collaterals through release of vascular growth factors as consequence of venous pressure increase [16-17].

The PICSO Impulse catheter is a 8F double lumen catheter with a 15.5x20mm long balloon at the distal end. The catheter is connected to the console through two pneumatic tubes in which helium is shuttled to and from the balloon. In addition, the coronary sinus pressure is monitored through the center lumen of the catheter. The catheter is placed in the coronary sinus over a 0.025' wire by a 8.5Fr pre-shaped delivery long steerable sheath (Oscor Destino Steerable Sheath DS856750/22) inserted in the femoral vein. Femoral vein access is obtained as routine practice according to Seldinger technique. Once the catheter is placed, the guidewire is removed and the steerable sheath is retracted in the right atrium for support. PICSO deployment median time has been estimated to be of 12 minutes (Interquartile Range 9-18 minutes)

The PICSO Impulse Catheter is then connected to the PICSO Impulse console. The PICSO Impulse Console automatically operates the PICSO Impulse Catheter. The balloon is intermittently inflated and deflated using helium, based on coronary sinus pressure and synchronized with the ECG. The monitor displays the inflation/ deflation state of the balloon, as well as trend graphs and time counters; Live graphs display curves and numeric values of ECG, coronary sinus pressure, aortic pressure and auxiliary input. It is easy to use and provides direct feedback on the patient's individual therapy using the 'PICSO Dose', which is defined as the sum of the coronary sinus pressure modulation for all PICSO cycles applied. All data are automatically stored and can be retrieved for later analysis for each patient. The unit is transportable and runs on battery supply if needed during patient transportation.

Once the PICSO Impulse catheter is connected to the consoled, by activating the "START" button, the distal balloon will be cyclically inflated. Each cycle starts with a balloon inflation triggered by QRS

complex on ECG monitoring. During balloon inflation coronary sinus pressure will progressively increase till reaching a plateau, then coronary sinus occlusion is stopped by balloon deflation. For security, each balloon inflation has a maximum limit of 30 seconds in duration. The deflation interval between two cycles has a minimum duration of 3 seconds.

In the OxAMI-PICSO the PICSO Impulse system will be adopted in a highly selected population of patients with ST elevation myocardial infarction, characterized by a possibly impaired microvasculature impairment at the time of the PCI, as expressed by a prestenting elevated index of microcirculatory resistance (> 40). The aim is to assess the extent of infarct size after 24-48 hours in such specific group of patients. Propensity-score matched historical patients from the ongoing OxAMI study will be controls in the OxAMI-PICSO study.

All the investigators using the PICSO device will undergo a specialist training programme completion, including the performance of the first cases under the supervision of a proctor expert. Educational training sessions for use of the PICSO will be provided to all clinical staff (nurses, radiographers, physiologists) involved in the care of patients who have received PICSO.

10.2 Device Safety

PICSO treatment is safe. Potential complications associated to PICSO may include:

a) Bleeding due to damage to the coronary sinus where the PICSO catheter is placed

b) Bleeding in the groin from the femoral vein access.

c) Long term blockage of the coronary sinus where the PICSO catheter sits.

d) Helium leak from the catheter into the blood. A leak of helium into the patient could occur with a balloon rupture or hole. However the risk is significantly mitigated since the system can automatically detect any leakage and stop the procedure. The maximum helium volume that could enter the patient using the PICSO system is less than 10 ml. This volume is approximately 1/3 of the volume that could leak from a bursting intra-aortic balloon pump (IABP) catheter, that are used in routine clinical practice in the aorta (i.e arterial circulation), whereas the PICSO catheter is used exclusively in the venous

circulation.. A helium leak from the PICSO system is therefore regarded to constitute a low risk to the patient.

Data about PICSO are continuously increasing and in the two main studies performed in man so far (PREPARE-PICSO and PREPARE-RAMSES) only one procedure adverse event (tamponade secondary to coronary sinus perforation) has been described. This rate (<3%) of complication is further lower than that associated to the routine elective electrophysiological procedures to the coronary sinus in the context of tachycardia ablation or cardiac resynchronization therapy.

It is possible that the PICSO balloon may be dislodged from the coronary sinus into the right atrium. This event has no known safety implications for the patients, but it may affect the efficacy of the PICSO treatment. The PICSO console will detect the occurrence of such event and alert the clinical team. In such a scenario balloon repositioning will only be considered if the treatment time-interval is less than 60 minutes. In order to minimize the risk for the patient, repositioning will be performed under fluoroscopic guidance in the catheterization laboratory. Once the balloon is repositioned, the PICSO treatment will be continued to achieve a minimum total treatment time of 60 minutes to a maximum of 90 minutes from the time of stent deployment.

All the investigators using the PICSO device will undergo a specialist training programme completion, including the performance of the first cases under the supervision of a proctor expert. Educational training sessions for use of the PICSO will be provided to all clinical staff (nurses, radiographers, physiologists) involved in the care of patients who have received PICSO. Patients undergoing PICSO treatment will be strictly monitored, according to the standard clinical care guidelines, during and after the PICSO treatment in order to minimize or to early detect possible issues associated to the treatment. After the procedure, when the PICSO treatment is still ongoing, the patients will be monitored in the Recovery Assessment Area in order to guarantee a rapid access to the Catheterization Laboratory, if required.

The additional x-rays used for the placing of the device is extremely low in the context of the exposure associated to the standard primary PCI procedure. The radiation dose associated with the placement

of the device is estimated to be 4.3 mSv, which is approximately equivalent to 22 months exposure to UK background radiation. This may theoretically be associated with an increased lifetime risk of developing a cancer of 0.06%. This compares with the risk of developing a cancer in the general population of around 30% to 40%. So overall this represents a very small addition to the underlying cancer risk from all causes.

The radiation exposure in case of repositioning the PICSO balloon is estimated to be less than that associated with the device implantation. Therefore patients undergoing repositioning would have a global radiation dose associated to the PICSO device of no more of 8 mSv.

10.3 Device Accountability

PICSO Impulse console and PICSO Impulse catheter will be provided by Miracor Medical Systems. We will be documenting the number of devices, with their lot numbers, that will be shipped to the John Radcliffe Hospital. PICSO Impulse console will be placed in the Catheterization Laboratory of the John Radcliffe Hospital, connected to electric supply in order to assure full charge of the battery. After their delivery, the PICSO Impulse catheters will be stored in the storage room of the Catheterization Laboratory f the John Radcliffe Hospitals and kept in a cool, dry place.

We will document on the CRF the LOT number and expiry date for each balloon for each patient.

11 SAFETY REPORTING

11.1 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)	An adverse event that: • Led to death • Resulted in serious deterioration in the health of the subject that: o resulted in a life-threatening illness or injury o resulted in a permanent impairment of a body structure or a body function o required in-patient care or prolongation of hospitalisation o resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

	This includes 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.
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 labeling. 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.

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

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

11.2 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.

11.3 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.

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.

11.4 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).

SAEs/SADEs that pose an immediate risk to patient health or safety, will be reported to the trial DSMC/Sponsor immediately or no later than 24 hours after the Investigator is aware and to the device manufacturer, competent authority and the REC within 2 calendar days of the Chief Investigator becoming aware of the event.

All other reported SAEs/SADEs will be reported to the trial DSMC and Sponsor competent authority 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 going from verbal assent/PICSO device adoption to 30 days following the use of the device.

11.5 Expectedness

Expectedness will be determined according to the Manufacturers risk analysis report

11.6 Safety Monitoring Committee

The Oxford University Hospitals Trust 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
- To evaluate the risk of the trial continuing and take appropriate action where necessary

11.7 Safety for PICSO

See 10.2

11.8 Safety for CMR

CMR is a safe and non-invasive technique with no known risk when appropriately supervised. It does not involve ionising radiation. Potential participants with ferromagnetic objects in their bodies or with implanted devices which can be damaged by the CMR magnet will be excluded. All participants entering the scanner room are screened for such objects. Gadolinium contrast is widely used for clinical indications in CMR and is safe. Occasionally it may cause a mild headache, nausea, itching and very rarely (< 1 in 1000) a more severe allergic reaction. It is cleared within hours by the body. Gadolinium has recently been associated with nephrogenic systemic fibrosis in patients with severe renal dysfunction; hence, as per departmental guidelines based on Food and Drug Administration guidelines, all patients with glomerular filtration rate (GFR) < 30 ml/min (stage 3-5 renal disease) should be not be given gadolinium. Participants for whom there is a possible history of metal in the eye and we are unable to find documented clinical evidence that the metal has been removed, will be offered an orbital (eye) x-ray prior to their cardiac CMR scan to confirm or negate presence of metal in the eye. This will add 0.1 mSv additional radiation exposure; this is 1/260 of that incurred during a standard coronary angiogram procedure. There are no contraindications to short periods of supplementary oxygen in appropriately selected patients.

11.9 Safety of cardiac physiological measurements

Coronary pressure wire studies are routinely performed during PCI procedures. The repeat catheterizations 24-48 hours after PCI are not part of routine practice and special attention will be paid to minimize radiation and use of contrast agent. The risk of repeating cardiac catheterization is low; a commonly occurring consequence is bruising at the site of vascular access which can be treated with simple analgesia. Based on local audit data, the average radiation exposure for a patient during routine angiography is 5 mSv. The additional IMR measurement adds on average only 1.6 mSv to the procedure. The follow up visits for IMR measurement also allows a valuable clinical opportunity to assess the result of initial PCI, which not otherwise be performed.

11.10 Safety of blood sampling

Blood sampling performed during the procedure will be performed through either the femoral venous sheath, coronary sinus catheter or coronary artery catheter. The femoral artery sheath and coronary artery catheter are required for and routinely used for PCI to be carried out. Some discomfort and possible complications are associated with placement of the femoral arterial sheath, but this is already clinically indicated as a necessary part of the PCI. The femoral venous sheath is not routinely placed for all PCI procedures, but is used whenever additional venous access during PCI is required clinically, for example to place catheters in to the venous system, or catheters or pacing electrodes in to the right side of the heart, or infusion of drugs during the PCI procedure. Potential risks and complications associated with venous sheath placement are much less than arterial sheath placement, because blood is not under arterial pressure and because other potential risks are intrinsically lower in the venous circulation. Placement of a coronary sinus catheter is not routinely used during PCI, but is used routinely using during other commonly performed cardiac interventions. The risk of additional complications is very low. The average volume of blood samples for research analyses taken at each sampling point would not exceed 40 ml.

12 STATISTICS

12.1 Number of Participants

The OxAMI-PICSO study aims to investigate the potential benefit of PICSO in a highly selected population of STEMI patients. In line with the data reported by Sayeed et al in a previous metanalysis on 7 studies about PICSO application in animal models, the recently published Prepare-RAMSES study also observed a 30% reduction in IS in the treatment arm, however such reduction was not statistically significant in comparison to the control arm [19]. The study, however could still show a benefit of PICSO in terms of IS reduction at six months follow up in the subgroup of patients receiving high PICSO quantity. The study, however, was significantly hampered by the inclusion of relative low risk patients and by a small sample size. The author managed indeed to deliver full PICSO treatment only in 63% of the initial planned cohort (12 patients, of the 30 planned, received a prolonged treatment with PICSO) [22].

In order to address the first limitation of the Prepare-RAMSES study, OxAMI-PICSO study will select patients with a prestenting higher IMR. In this way PICSO is meant to be applied only in a population at higher risk and highly likely to get benefit from its application.

In this regard assuming that the stricter inclusion criteria may allow to detect a substantial benefit from PICSO compared to the control group and expecting that this will allow to achieve a significant 29% reduction in IS as shown in Sayeed's metanalysis [19], we initially calculated a final sample size of 12 patients with complete final data per each group with an interval of confidence at 95% and a 80% power. However considering that this was the final same sample size enrolled in the Prepare-RAMSES study, initially meant to recruit 30 patients per arm, we propose to double the actual sample size from 12 to 25 per arm.

Allowing for participants who do not wish to undergo repeat cardiac catheterisation, or cardiac MRI, we anticipate that approximately 75 patients may be recruited to the study in order to achieve full participation and complete follow up in 25 subjects.

12.2 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. Summary statistics, including means, medians, and

variances, will be calculated at each time point and for each type of data (e.g. parameters derived from coronary physiology and CMR). The distribution of the levels will be described. It may be necessary to log transform the data before further statistical analysis. For each parameter an analysis of variance will be carried out at each time point.

Control group in OxAMI-PICSO study is represented by a highly matched group of patients underwent to primary PCI, with a prestenting IMR > 40 and with available 24 hours recath and 24-48 hours/6 months CMR data. Matching will be performed by application of a propensity score matching analysis including the following predictors in the model: age, sex, pain to wire time, thrombotic burden (assessed as angiographic thrombus score), thrombus aspiration performance, stent volume, glycoprotein IIbIIIa inhibitors adoption.

13 DATA MANAGEMENT

13.1 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), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

13.2Access 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.

13.3 Data Recording and Record Keeping

Study data will be entered on case record forms (CRF). The department SOP on database design will be followed. Data will be uploaded into SPSS or equivalent statistical software for statistical analysis. The participants will be identified by a study specific participant number in any database. The name and any other identifying detail will NOT be included in any study data electronic file. All data will be made non patient-identifiable as soon as is practical to do so via the participant ID.

14 QUALITY ASSURANCE PROCEDURES

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

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. Following written standard operating procedures, 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.

15 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.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 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 consent and assent, 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).

16.2 Possible risks and/or discomfort for patient

Patients referred for cardiac catheterization and PCI will undergo this procedure as would routinely be performed. Patients will therefore be consented for the standard of care procedure and its associated risks.

Overall the PCI procedure time may be lengthened by around 20 minutes to complete the selected study procedures (cardiac physiological measurements + PICSO catheter placement). In the context of a PCI procedure that typically last approximately 60 minutes; the additional time taken 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.

CMR is an established cardiac imaging technique in our institution and is generally very well tolerated. Specific considerations for safety are reflected by the additional exclusion criteria listed in section 7.3. All local protocols will be adhered to and only fully trained staff will carry out procedure according to departmental SOPs.

16.3 Collaboration and Partnership with Commercial Companies

The University of Oxford, the Oxford University Hospitals NHS Trust (OUHT) and the OxAMI-PICSO study may work in partnership with, and receive support from, commercial companies who provide the devices

and technologies related to PCI and other research investigations. As part of this partnership we may make available research data to the company specifically related to the use of their device or technology. All data will be supplied in a fully anonymised format and participants would not be identifiable from this.

16.4 Feasibility

16.4.1 Facility

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 these studies.

16.5 Declaration of Helsinki

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

16.6 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

16.7 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

16.8 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), 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.

16.9 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

16.10 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

16.11 Potential Benefits

The information derived from coronary pressure/flow measurements is often very useful to the interventional cardiologist in optimising PCI strategy, and the use of vasodilators (e.g. adenosine) as part of the coronary pressure/flow measurements often results in useful clinical improvements in coronary flow.

Finally PICSO treatment, according to pre-clinical literature evidences, is expected to provide a benefit in terms of infarct size reduction. According to animal models this advantage should amount around a 29% in reduction of the infarcted area. The application of PICSO treatment in a highly selected, high risk population of STEMI patients should amplify the potential benefits of this therapy.

17 FINANCE AND INSURANCE

17.1 Funding

The study will be supported by British Heart Foundation, NIHR Biomedical Research Centre programme. Miracor Medical Systems will support the study by providing PICSO catheters, PICSO Impulse Console and an unrestricted grant.

17.2 Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If the patient is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team a liability cover would apply. Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

18 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 British Heart Foundation, NIHR Biomedical Research Centre programme and Miracor Medical Systems. 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 OXAMI-PICSO investigators.

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20. APPENDIX A: SCHEDULE OF PROCEDURES IN PICSO GROUP

	PICSO group								
Procedures	**Pre-PCI**	**During PCI**				**6 hours**	**24 hours**	**48 hours**	**6 months**
		Start of procedure	**PICSO start**	**End of PCI**	**PICSO stop**				
Verbal assent	X								
Blood samples		X	X	X	X	X	X	X	X
PICSO			X	X	X				
Coronary physiology measurements (IMR, CFR, FFR)		X		X		X			
Informed written consent						X			
Coronary angiogram with coronary physiology measurements (IMR, CFR, FFR)							X		
CMR								X	X
ECG	X			X		X			
Echocardiography							X		
Medical history Demographic data collection								X	

21. APPENDIX B: SCHEDULE OF PROCEDURES IN NON-PICSO GROUP

	NON-PICSO group						
Procedures	**Pre-PCI**	**During PCI**		**6 hours**	**24 hours**	**48 hours**	**6 months**
		Start of procedure	**End of PCI**				
Verbal assent	X						
Blood samples		X	X	X	X	X	X
Coronary physiology measurements (IMR, CFR, FFR)		X	X				
Informed written consent				X			
ECG	X		X	X			
Echocardiography					X		
Medical history Demographic data collection						X	