Study Title: Multimodal Assessment to Optimise the Result of Percutaneous Coronary Interventions.

Short title: The **Ox**ford **Opt**imisation of **PCI** Study (OXOPT-PCI study).

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No potential conflicts of interest to declare

Confidentiality Statement

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1. AMENDMENT HISTORY

Protocol version no.	Effective Date	Significant Changes	Previous protocol version no.
1.1	25.07.2016	Primary outcome measure re-defined. Revision of chapter 13. Clarification on the patient identifier. (changes made as requested by the Ethics Committee	1.0
1.2	14.09.2016	2 Investigators added	1.1

2. KEY TRIAL CONTACTS

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3. SYNOPSIS

Study Title	Multimodal Assessment to Optimise the Result of Percutaneous Coronary Interventions. The OXOPT-PCI study
Study Design	Prospective single centre clinical trial

Study Participants	Pts aged 30-90 presenting for coronary angiography and PCI
Number of Participants	100
Treatment duration	Maximum of 30 minutes
Follow up duration	12 months
Planned Study Period	1 year
Primary Objective	To assess the impact of a study specific treatment algorithm on final FFR after PCI measured in the target vessel.
Secondary Objectives	The OXOPT-PCI study aims to assess the frequency of intracoronary pathologies after PCI that potentially lead to an impaired FFR using OCT according to CLI-OPCI II study criteria.
Tertiary Objectives	1. To assess the impact of a study specific treatment algorithm on final parameters of coronary physiology after PCI measured in the target vessel. 2. To assess the impact on clinical outcome.
Intervention (s)	Optimisation of PCI result according to a study specific algorithm

4. ABBREVIATIONS

BMS	Bare metal stent
CFR	Coronary flow reserve
CI	Chief Investigator
DES	Drug eluting stent
FFR	Fractional flow reserve
GCP	Good Clinical Practice
IC	Informed Consent
ICF	Informed Consent Form
IMR	Index of microcirculatory resistance
MACE	Major adverse cardiac events
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
POBA	Plain old balloon angioplasty
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

Fractional flow reserve (FFR) is the established gold standard used in the cardiac catheterisation laboratory to assess the haemodynamic relevance of coronary artery stenoses before stenting. Evidence from various clinical scenarios has shown that an FFR-guided PCI strategy reduces the need for stenting and improves clinical outcomes. Therefore, FFR has been incorporated in current revascularisation guidelines. [1-3]

Visual assessment of the interventional result by angiography and quantitative coronary angiography (QCA), has limited efficacy with respect to identifying patients with suboptimal PCI results and subsequent worse clinical outcomes.[4, 5] Post-PCI FFR measurement has been shown to be a useful indicator for the identification of a suboptimal PCI result in small observational studies using older techniques including plain old balloon angioplasty (POBA), bare metal stents (BMS) and first/ second generation drug eluting stents (DES).

5.1 Post-PCI FFR as an indicator of clinical outcome

In 1999, Bech et al. demonstrated that FFR was useful for stratifying patient outcome after plain old balloon angioplasty (POBA).[7] Receiver operating characteristics (ROC) curve analysis identified a post-POBA FFR of 0.89 as optimal predictor for worse clinical outcome at two years follow up (MACE rate: 40.6 vs. 11.5%; area under curve (AUC) = 0.69).

This was subsequently confirmed for PCI using bare metal stents. Pijls et al. showed that FFR after BMS implantation was an independent predictor of clinical outcome at 6 months.[6] In this study patients with a post-stent FFR <0.9 had a significantly worse outcome after 6 months than those with an FFR ≥0.9 (MACE rate: 20.3 vs. 5.5%). Analysing data for state of the art technologies showed that the FFR following implantation of drug-eluting stents (DES) predicted MACE at one year in a study reported in 2011.[7] Receiver operating characteristics (ROC) curve analysis identified an FFR <0.90 as optimal predictor for worse outcome at one-year follow up (MACE rate: 12.5 vs. 2.5%, ROC analysis: sensitivity = 67%, specificity = 58%, AUC = 0.69, 95% CI = 0.53–0.86).

5.2 Causes of persistently low FFR after PCI

Retrospective studies using intra-coronary imaging have identified possible underlying causes for a suboptimal FFR, including incomplete stent expansion, stent malapposition, “geographical miss”, plaque protrusion, edge dissection, and plaque shift at the stent edge.

(Figure 1).

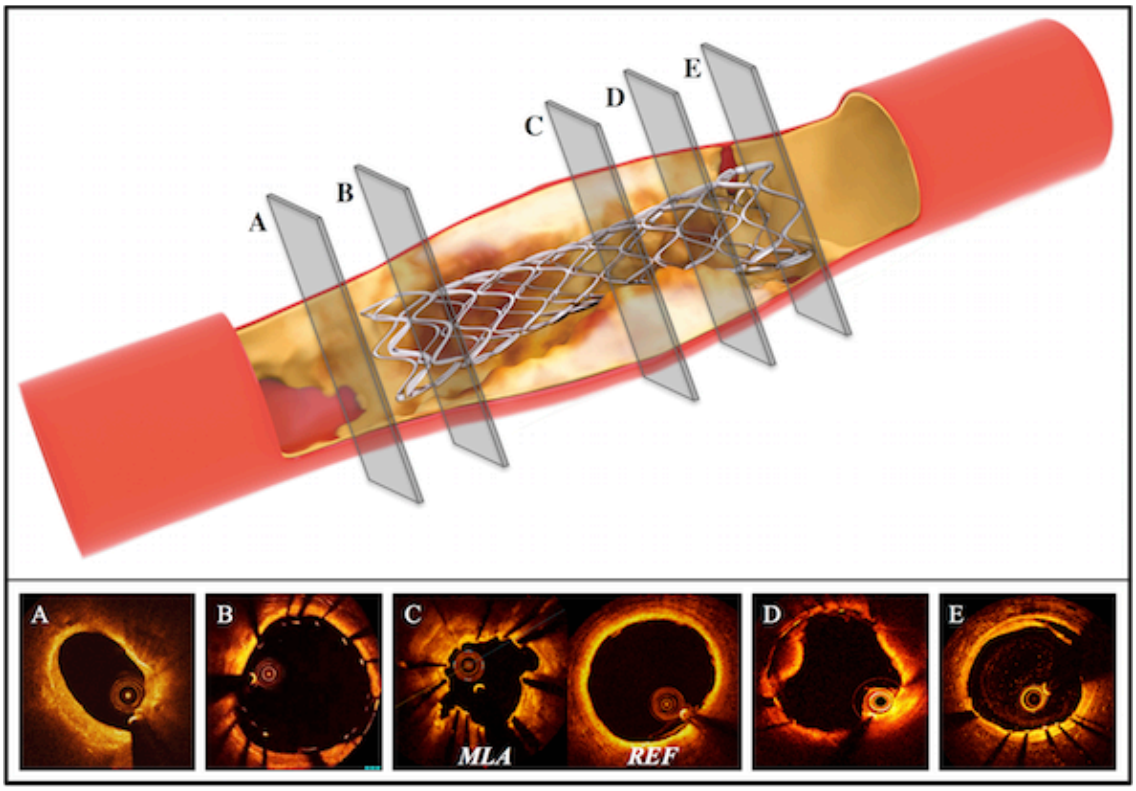

Figure 1. Potential causes of suboptimal FFR after percutaneous coronary interventions. Panel A: 'geographical miss' (diseased reference segment). Panel B: stent mal-apposition. Panel C: stent under-expansion. Panel D: intrastent plaque-protrusion/thrombus. Panel E: edge dissection. MLA - minimal lumen area, REF - proximal reference segment.

5.3 Assessment of coronary physiology (coronary pressure/flow)

Coronary flow and pressure measurements are widely recognised to determine the degree of disease for epicardial vessels and for the microcirculation.[8] The pressure wire is interchangeable with the coronary guide wire used in all PCI procedures, so is incorporated in to the procedure. Measurements that assess the integrity of the small blood vessels of the heart are made at the end of the PCI in response to administration of clinically used drugs such as adenosine to increase coronary flow. Saline is flushed through the guide catheter to measure coronary flow using the transit time calculation. Incorporating these parameters are recognised to support the clinical decision making but no standardized guidelines for their application after stenting has been established.

5.4 Imaging Modalities Used to Evaluate Coronary Artery Disease

5.4.1 Optical coherence tomography (OCT)

OCT is a high resolution intravascular imaging modality that can accurately characterise coronary morphology.[9] Recently a study evaluating the relationship between final stent dimensions, determined by optical coherence tomography (OCT), post-stent FFR, and clinical outcome the intrastent area stenosis (AS) was positively correlated with post-stent FFR (r^2 = 0.49; P < 0.001), and both parameters were good predictors of MACE rate at 20-month follow up.[10] The optimal thresholds to predict MACE was 0.905 for post-stent FFR, based on ROC analysis (sensitivity 71.4%, specificity 85.0%, AUC 0.77, 95% CI 0.56–0.97).

5.5 Background Summary

Based on available evidence a persistently low FFR following PCI is associated with an adverse clinical outcome. Small observational studies using intra-coronary imaging have suggested different underlying causes for a suboptimal FFR. The aim of this prospective clinical trial is to confirm that these are the responsible mechanisms and to examine whether additional simple procedures can influence post-stent FFR and potentially improve clinical outcome.

5.6 Study Hypothesis

1) A post PCI FFR < 0.9 is linked to a suboptimal stent deployment. 2) Using a dedicated algorithm incorporation FFR measurements and intracoronary imaging will improve interventional result.

6. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints
Primary Objective To assess the impact of a dedicated treatment algorithm on final FFR after PCI measured in the target vessel.	Proportion of patients with FFR >0.9 at baseline versus proportion of patient with FFR measured at the end of optimisation procedure (final FFR)
Secondary Objectives The OXOPT-PCI study aims to assess the frequency of intracoronary pathologies after PCI that potentially lead to an impaired FFR using OCT according to CLI-OPCI II study criteria.	1. Frequency of: - Stent-edge dissection - Geographical miss/Reference lumen narrowing - Stent-malapposition - In-stent minimum lumen area (MLA) < 4.5 mm^2 - In-stent MLA <70% of the average reference lumen area - Intrastent plaque/thrombus protrusion 2. Frequency of a significant pressure step up during pressure wire pullback during maximal hyperaemia.
Tertiary Objectives 1. To assess the impact of a dedicated treatment algorithm on final parameters of coronary physiology after PCI measured in the target vessel. 2. To assess the impact on clinical outcome.	1. Coronary flow reserve (CFR), index of microcirculatory resistance (IMR) measured at the end of PCI. 2. Composite of death, myocardial infarction and target vessel revascularisation after 12 months of follow up.

7. TRIAL DESIGN

The OXOPT-PCI study is a prospective single centre clinical trial investigating the use of a dedicated, study specific treatment algorithm on the final result of PCI in patients with suspected or known coronary artery disease, including acute myocardial infarction (except for ST elevation myocardial infarction), who present for coronary angiography with the usual expectation of proceeding to PCI.

Patients, age 30-90, will be included in the study. Informed consent will be obtained prior to the angiography/ PCI procedure.

A flowchart of the study design, indicating the time points and procedures, is shown in Appendix A.

All PCI procedures, coronary imaging and coronary physiology measurements will be performed in a standard fashion. A specific treatment algorithm incorporating parameters of coronary imaging and coronary physiology will dictate further optimisation of the stent result (Figure 2, Chapter 10.5.). After stenting all patients will undergo intravascular imaging with OCT and in all patients the FFR will be assessed in the stented vessel. The initial stent result will be optimised based on intravascular imaging if clinically indicated by the CLI-OPCI II study criteria (see chapter 10.5.3). Following optimisation of the stent result the OCT assessment and the FFR measurement in the target vessel will be repeated. At this stage the study population will be divided into two groups according to the latter FFR recording.

Group A includes patients with an FFR value <0.9. In these patients the OCT images will be used to decide according to the CLI-OPCI II criteria whether and how to optimise the stent result (see chapter 10.5.5). If further optimisation was carried out the intervention will be concluded by repeated assessment of coronary physiology (FFR, CFR, IMR) and intravascular imaging. If no further stent-optimisation was performed the intervention will be concluded by the assessment of CFR and IMR.

Group B includes all patients with an FFR ≥0.9. As this FFR value can be considered satisfactory, no further optimisation of the interventional result will be attempted and the PCI will be concluded by the assessment of CFR and IMR. Procedural details including details of the PCI, the coronary physiology measurements and intravascular imaging studies (OCT-studies) at all stages of the study and of all study patients will be recorded. The total procedure and PCI/ OCT/ coronary physiology study times will be also collected. Post-PCI

assessment and discharge strategy will be carried out according to routine clinical practice. Telephone follow-ups will be then
performed at 12 months to assess current symptoms and cardiovascular events. The end of the study for each patient will be the date of the 12 months telephone follow-up.

This is a clinical trial in attempt to give some insights regarding the utility of a specific multi-modal algorithm to improve the result of PCI. In view of the absence of data on this topic, it has been designed as pilot study for power analysis and sample size calculation of a further main study.[11] Based on this assumption it was designed as a non-randomised clinical trial.

Comments from an external peer review have been considered when finalising this protocol.

8. STUDY RISKS AND BENEFITS

8.1 Study risks

8.1.1 Standard PCI procedure

The patients taking part in this study will undergo a standard percutaneous coronary intervention with stenting on the basis of clinical reasons.

Standard risks associated with a PCI procedure include:
- bruising in the groin, which are usually self-limiting, occur in 1 in 10-20 people;
- femoral vascular injury requiring a minor surgical repair occurs in 1 in 200 people;
- TIA or stroke occurs approximately 1 in 300 people;
- cardiac perforation requiring a drain at the time of the operation occurs in 1 in 500 people;
- emergent surgery occurs approximately 1 in 500 people;
- fatal complication (death in the catheter laboratory) is estimated to be 1 in 2000 people;
- cancer secondary to fluoroscopy exposure during the PCI procedure is negligible considering the average low radiation dose and the short fluoroscopy time used.

When compared with the PCI protocol currently used in our centre, the current clinical trial protocol differs only with respect to routine use of cardiac physiological measurements and the routine use of intravascular imaging (OCT) according to a dedicated algorithm after stenting. Optimisation of the PCI result will be carried out only if clinically indicated by FFR or OCT findings, which is in line with current routine practise. Final assessment of IMR and CFR after stenting are not part of routine practice and special attention will be paid to minimize radiation and use of contrast agent.

8.1.2 Cardiac physiological measurements

Coronary pressure wire studies are routinely performed during PCI procedures. Based on local audit data, the average radiation exposure for a patient during routine angiography is 5 mSv. The additional IMR/CFR measurement adds on average only 1.6 mSv to the procedure. Wire associated adverse effects (e.g. coronary dissection) are to be expected in 1 in 500 to 1000 cases. This is in the range of the expected rate of adverse events using a standard guide wire.

8.1.3 Intravascular imaging

Intravascular imaging using OCT is often performed during PCI to assist in the procedure. This current study will use OCT as indicated by the study specific algorithm. The OCT procedure itself is done in standard manner. The utilization of these modalities typically adds up to 5 minutes to the procedure duration. Use of any intra-coronary device such as OCT device can cause ischaemia, chest discomfort or, rarely, other local coronary complications during the PCI (1 in 500 cases). 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.

8.2 Study benefits

Optimisation of the PCI according to a dedicated algorithm gaining information from coronary pressure/flow measurements and intravascular imaging is useful to the interventional cardiologist in optimising the PCI strategy. Based on current literature potential benefits include a reduction in repeated myocardial infarction and target lesion revascularisation.

9. PARTICIPANT IDENTIFICATION

9.1 Study Participants

Participants aged 30-90 referred for either non-emergency or emergency diagnostic coronary angiography (except for ST elevation myocardial infarction) on the basis of known or suspected coronary artery disease, with the intention to proceed to PCI where clinically indicated.

9.2 Inclusion Criteria

Participants must satisfy the following conditions:

- Participant is willing and able to give informed consent for participation in the study
- Male or Female, aged 30 to 90 years,
- angiogram shows haemodynamically relevant lesion suitable for PCI and suitable for the use of intravascular imaging (OCT)

9.3 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.
- ST elevation myocardial infarction
- Anaemia (Hb <9)
- pregnancy, trying for a baby or breast feeding
- Revascularization by mean of balloon angioplasty without stenting
- Known severe renal failure (eGFR < 30 ml/min/1.73m2) or history of dialysis or renal transplant
- Presentation with cardiogenic shock
- Unconscious on presentation
- Contraindications to adenosine

10. STUDY PROCEDURES

10.1 Study timeline (see "Integrated flowchart for OXOPT-PCI study" as in Appendix 1)

10.2 Recruitment

Participants will be identified by the clinical care team from pre-angiogram clinic or angiogram procedure waiting lists. They will be posted or given an invitation letter and information leaflet with reply slip, either with their appointment letter or whilst awaiting the PCI procedure as an inpatient. If patients are willing to participate, they may return the reply slip and/or inform the clinical care team at their consultation who will then inform study investigators. Inpatients will have a minimum of 24 hours to consider their participation in this study.

Based on the annual audit data ~1500 PCI are performed at the JR Hospital (~30 per week). Of these 30 cases at least > 50% would fulfil the inclusion criteria of the present study. These numbers justify the feasibility of the suggested 100 participants over the time of 1 year.

10.3 Consent

10.3.1 Screening and Final Eligibility Assessment

The following details will be addressed taking into account the patients' medical history and screening the patients' medical notes:

a. demographics;
b. exclusion of exclusion criteria
c. detailed collection of any relevant medical history
d. list of current medications

10.3.2 Informed Consent

Informed consent (IC) will be obtained by a qualified and experienced investigator who is familiar with the study protocol and procedures. This may be the Chief Investigator (CI), a Key Investigator, the research fellow or a research nurse. The list of eligible individuals will be specified in the delegation log.

Written versions of the Participant Information and Informed Consent (IC) will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the study and the benefits and risks

involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time without giving a reason or any prejudice to future care and rights.

Written IC will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the IC. This will be undertaken before the baseline visit commences. A copy of the signed ICF will be given to the participants and one copy will be added to the patients' medical notes. The original signed form will be retained at the study site. The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

10.4 Baseline Visit

In addition to the screening and final eligibility assessment before the consent the patients' medical notes and medical history will be taken on the day of the study visit.

10.5 Study visit - Intervention: Coronary angiogram and PCI

All PCI procedures, coronary imaging and coronary physiology measurements will be performed in a standard fashion. A specific treatment algorithm incorporating parameters of coronary imaging and coronary physiology will dictate further optimisation of the stent result (Figure 2).