How often can optimal post percutaneous coronary intervention (PCI) fractional flow reserve (FFR) results be achieved? - A randomised controlled trial of a physiology-guided PCI optimisation strategy (The Target FFR Study)

Statistical Analysis Plan (SAP)

Study Title:	**How often can optimal post percutaneous coronary intervention (PCI) fractional flow reserve (FFR) results be achieved? - A randomised controlled trial of a coronary physiology-guided optimisation strategy (The Target FFR Study)**
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		Signature	**Date**
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1. Introduction

1.1 Study Background

Post-Percutaneous Coronary Intervention (PCI) Fractional Flow Reserve (FFR) values ≥0.90 are associated with better clinical outcomes for patients but the available data suggest that, despite angiographically satisfactory results, this target is actually achieved in less than 40% of cases.

Using post-PCI FFR to guide further stent optimisation and/or additional stenting in the target vessel can increase the frequency with which optimal post-PCI FFR results are achieved. However, there are additional costs associated with the routine use of post-PCI FFR and it is not clear how often it is even possible to increase the initial post-PCI FFR result to ≥0.90. This uncertainty makes it currently difficult to either recommend the routine use of post-PCI FFR or justify its cost.

The Target FFR Study is a prospective, randomised controlled trial assessing the efficacy of an FFR-guided optimisation strategy in achieving optimal post-PCI FFR results in a series of consecutive patients undergoing standard PCI for stable angina and non-ST-segment elevation myocardial infarction (NSTEMI).

The study will also provide randomised, 'real-world' data on the incidence of suboptimal post-PCI FFR results and systematically elucidate the responsible mechanisms where these occur. The data from this developmental study could support a subsequent definitive phase 3 study of the impact of FFR-targeted PCI on clinical outcomes.

1.2 Study Objectives

Research Hypotheses:

> The null hypothesis is that there is no difference in the proportion of patients with final post-PCI Fractional Flow Reserve (FFR) results $\geqslant$0.90 between those receiving a coronary physiology-guided optimisation strategy and those receiving standard care. The alternative hypothesis is that there is a difference between the two treatment approaches.

Primary Objective:

> To determine the feasibility and efficacy of using a coronary physiology-guided optimisation strategy to achieve a final post-percutaneous intervention (PCI) Fractional Flow Reserve (FFR) result $\geqslant$0.90 compared to standard care.

Secondary Objectives:

> Further assessment using several alternative methods of measuring the efficacy of using a coronary physiology-guided optimisation strategy as defined below.

1.3 Study Design

A single centre, parallel group, randomised controlled clinical trial.
Patients are randomised in a 1:1 ratio to receive either a physiology-guided optimisation strategy (potentially undergoing additional stent post-dilation and/or further stenting in the target vessel as appropriate) or standard care.
The framework for the trial is testing the superiority of the extra treatment in terms of its efficacy.

1.4 Randomisation

Randomisation will be performed using a 1:1 variable block (2,4,6) randomisation method generated from within the study's electronic Case Report Form (eCRF) platform, Castor EDC.

1.5 Blinding

Patients will not be informed of their final coronary physiology results.
FFR results will not be displayed on the procedure-room monitor and the physiology interface will only be visible to research staff in the control room. These results will only be disclosed to the operator for patients with initial post-PCI FFR <0.90 who are randomized to receive the optimisation strategy. The rationale for maintaining operator-blinding for all other post-PCI physiology results is to try and minimise the potential Hawthorne effect ('observer effect') the study could have on local PCI practices.

1.6 Sample Size and Power

260 patients will be randomised.
Previous studies suggest that approximately 40% of patients in the control arm will have a post-PCI FFR $\geqslant$0.90.(1-5)
This is in keeping with pilot data from our own institution where, among 50 patients who underwent post-PCI FFR assessment, an initial result $\geqslant$0.90 was achieved in only 16 /50 (32%).
It is hypothesised that the proposed PIOS intervention will increase the proportion of patients with a final post-PCI FFR $\geqslant$0.90 by approximately 20% compared to the control group. (a relative improvement of at least 50%).
A sample size of 130 patients per group would be required to have 90% power to detect a 20% absolute difference between groups at the 5% significance level.

1.7 Study Population

Consecutive patients with stable angina or Non-ST segment Elevation Myocardial Infarction (NSTEMI) referred to the cardiac catheterisation lab for invasive management who have been selected to undergo PCI based on either angiographic appearances or prior FFR assessment.

1.7.1 Inclusion Criteria

- Patients >18 years of age with coronary artery disease including stable angina and NSTEMI.
- Participants must be able to provide informed consent.

1.7.2 Exclusion Criteria

- PCI in a coronary artery bypass graft
- PCI to an in-stent restenosis (ISR) lesion
- PCI to a target artery providing Rentrop grade 2 or 3 collateral blood supply to another vessel
- Inability to receive adenosine (for example, severe reactive airway disease, marked hypotension, or advanced atrioventricular block without pacemaker).
- Recent (within 1 week prior to cardiac catheterization) ST-segment Elevation Myocardial Infarction (STEMI) in any arterial distribution (not specifically target lesion).
- Severe cardiomyopathy (ejection fraction <30%).
- Renal insufficiency such that an additional 20 to 30 mL of contrast would, in the opinion of the operator, pose unwarranted risk to the patient.

1.8 Statistical Analysis Plan (SAP)

1.8.1 SAP Objectives

The objective of the SAP is to describe the statistical analyses to be carried out for the Target FFR Study.

1.8.2 General Principles

All relevant study data will be summarised for the randomised population overall, and by randomised group.
The number of observations and number of missing values will be reported; continuous variables will be summarised using the mean, standard deviation (SD), median, quartiles and range; categorical variables will be summarised with frequencies and percentages.
Where relevant, changes from baseline will be summarised.

Efficacy analyses will be carried out according to the intention to treat principle, that is, in relation to randomised treatment allocation, rather than treatment received. Safety analyses will be carried out in relation to treatment received.

1.8.3 Current Protocol

The current protocol at the time of writing is version 1.0, dated 08 June 2017. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary

1.8.4 Deviations to Those Specified in Study Protocol

No deviations to the analyses specified in the study protocol are planned.

1.8.5 Additional Analyses to Those Specified in Study Protocol

Additional pre-specified analyses to the study protocol are outlined below in 2.7

1.8.6 Software

Analyses will be carried out using SPSS Statistics, version 25 and R, version 3.4 or above.

2. Analysis

All applicable analyses will be 2-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided.

2.1 Study Populations

The screened population will consist of all patients screened for inclusion in the study as recorded in the study screening logs.

The Full Analysis Set (FAS) will consist of all patients who were randomised. Analyses within the FAS will compare treatment groups as randomised, regardless of which (if any) treatment was received.

The Safety Set (SS) will consist of all patients who were randomised and received treatment. Analyses within the SS will compare treatment groups according to the treatment received.

The numbers of patients included in the SP and FAS will be reported as a whole and by age and by sex. Reasons for exclusion from the FAS will be summarised as a whole, by age and by sex.
The numbers of patients included in the FAS and SS will be reported as a whole and by treatment group. The numbers of patients in the FAS who did not receive treatment or received a different treatment to that allocated at randomisation, will be reported.

2.2 Baseline Characteristics

Baseline characteristics will be summarised in the FAS as a whole and by treatment group. The following baseline characteristics will be reported:

- Demographics: age (years), sex (male, female), height, weight, BMI, ethnicity (White or White British, Asian or Asian British: South Asian, Asian or Asian British: Chinese, Asian or Asian British: Other Asian, Black or Black British, Mixed or Multiple, Other)

- Lifestyle Factors: Smoking Status (No, Current, Ex-Smoker <12 months, Ex-Smoker >12 months)

- Vital Sign Observations: heart rate, blood pressure

- Pharmaceutical therapy (medications used for treatment of cardiovascular disorders including primary and secondary therapies)
    - Number of antianginal medications

- Medical History including Risk Factors (yes/no unless otherwise stated)
    - Indication for Angiogram (Stable Angina, ACS-NSTEMI, ACS-Unstable Angina)
    - Time since NSTEMI
    - Troponin Assay Used and Peak Troponin Recorded if NSTEMI
    - Hypertension
    - Hypercholesterolaemia
    - Diabetes
    - TIA/Stroke
    - CKD
    - Thyroid Dysfunction
    - Pacemaker
    - ICD
    - Atrial Fibrillation
    - Heart Failure (No, HF-rEF, HF-pEF)
    - NYHA Class if Heart Failure (1-4)
    - Previous PCI
    - Previous MI
    - History of Previous MI in Target Vessel if Yes
    - CABG
    - Angina
    - Canadian Cardiovascular Society (CCS) Class if Angina (1-4)
    - Valvular Heart Disease
    - Valve Replacement/Repair
    - Family History of CAD

- Health Status questionnaire scores:
    - Seattle Angina Questionnaire
    - EQ-5D-5L

- Procedural Characteristics
    - Vascular Access (Radial, Femoral, Brachial)
    - Sheath Size

- Multivessel Procedure (Yes, No)
- Procedure Time
- Duration of Research Protocol
- Contrast Dose
- Dose Area Product
- Radiation Dose
- Total Duration of Adenosine Infusion
- Total Dose of Adenosine
- Total Number of Stents Deployed in Study Artery
- Total Length of Stents Used in Study Artery
- Diameter of Largest Balloon used for PCI
- Largest Stent Diameter

- Angiographic Characteristics
  - Target Coronary Artery Segment
  - Lesion Severity by Operator's Visual Assessment (Normal, Plaque Disease, <25%, 25-49%, 50-74%. 75-94%, >/= 95%, Subtotal Occlusion. Occluded)
  - AHA Lesion Type
  - Lesion APPROACH Score
  - Gensini Score
  - QCA Lesion Length
  - Pre- and Post-PCI QCA Diameter Stenosis
  - Pre- and Post-PCI QCA Area Stenosis

- Pre- and Post-PCI Coronary Physiology Test Results
  - Ratio of distal coronary to aortic pressure (Pd/Pa)
  - Diastolic Pressure Ratio (dPR)
  - Resting Full-cycle Ratio (RFR)
  - Mean Resting Transit Time
  - Fractional Flow Reserve (FFR)
  - Mean Hyperaemic Transit Time
  - Coronary Flow Reserve (CFR)
  - Index of Microcirculatory Resistance (IMR)
  - IMR corrected by Yong's Formula (IMRc)
  - Presence of 'Abrupt Drop' pattern on pressurewire pullback assessment
  - Time to Hyperaemia
  - Presence of Pressure Wire Drift >/=0.04 on pullback
  - Requirement for Repeat Assessment due to Drift
  - Chest Discomfort During Adenosine Infusion (None, Slight , Moderate, Severe)
  - Pre-PCI 'Grey Zone' FFR (0.75-0.80) Value (Yes/No)
  - Final FFR ≥0.90 (Yes/No)
  - Final FFR ≥0.80 (Yes/No)

2.3 Efficacy Outcomes

2.3.1 Primary Outcome

The proportion of patients with a physiologically optimal result post PCI (FFR $\geqslant$ 0.90). The primary outcome will be summarised in the FAS as a whole and by treatment group. A test and 95% CI for 2 proportions (adjusted Wald method) will be employed, together Fisher's exact test.

Additional secondary analyses on this outcome will use logistic regression to investigate whether any of the baseline characteristics affect the outcome. Given the sample size of 130 per group and the large number of baseline characteristics (since logistic regression is a large sample method), this will be performed by first investigating each characteristic on its own (together with the treatment group), Any variables that are significant here will be added to build a larger model, bearing in mind sample size limitations.

2.3.2 Secondary Outcomes

- Change from baseline in SAQ and EQ-5D-5L scores at 3 months
- The rate of target vessel failure and its components (cardiac death, myocardial infarction, stent thrombosis, unplanned rehospitalisation with target vessel revascularisation) will be analysed at 3 months
- The proportion of patients with final post-PCI FFR ≤0.80
- The proportion of patients with final post-PCI DPR ≥0.90
- The proportion of patients with final post-PCI RFR ≥0.90
- The proportion of patients with final post-PCI CFR ≥2.0
- The proportion of patients with final post-PCI IMR >25
- The proportion of patients with final post-PCI IMRc >25
- ΔFFR from pre-PCI to final post-PCI value
- ΔDPR from pre-PCI to final post-PCI value
- ΔRFR from pre-PCI to final post-PCI value
- ΔCFR from pre-PCI to final post-PCI value
- ΔResting transit time (TT_{rest}) from pre-PCI to final post-PCI value
- ΔHyperaemic transit time (TT_{hyp}) from pre-PCI to final post-PCI value
- ΔIMR from pre-PCI to final post-PCI value
- ΔIMRc from pre-PCI to final post-PCI value
- ΔFFR from pre-PCI to final post-PCI value
- Percent FFR change from pre-PCI to final post-PCI value
- Percent DPR change from pre-PCI to final post-PCI value
- Percent RFR change from pre-PCI to final post-PCI value
- Percent CFR change from pre-PCI to final post-PCI value
- Percent TT_{rest} change from pre-PCI to final post-PCI value
- Percent TT_{hyp} change from pre-PCI to final post-PCI value
- Percent IMR change from pre-PCI to final post-PCI value

- Percent IMRc change from pre-PCI to final post-PCI value
- Procedure Duration
- The cost of additional equipment employed in the experimental arm
- Fluoroscopy Dose
- Contrast Material Dose
- Incidence of procedural complications such as coronary artery dissection or perforation.
- An 'As Treated' analysis of the preceding primary and secondary outcome measures

For the binary categorical secondary outcomes, the same analysis approach will be used as with the primary outcome. For quantitative secondary outcomes, two sample t-tests and 95% CI will be used, as well as further analyses using regression to investigate whether any of the baseline characteristics affect the outcome. Given the sample size of 130 per group and large number of baseline characteristics, this will be performed by first investigating each characteristic on its own (together with the treatment group). Any variables that are significant here will be added to build a larger model, bearing in mind sample size limitations.

2.4 Feasibility Outcomes

- Completion of diagnostic protocol
- Blinding integrity and cross-over rates between groups

2.5 Safety Outcomes

2.5.1 Premature Withdrawal

The number and percentage of participants who complete follow-up assessment will be reported. The number and percentage of participants who actively withdraw from the study will be reported. Reasons for withdrawal will be summarised.

2.5.2 Adverse Outcomes During Coronary Function Tests

Information on adverse events related to the additional coronary function tests will be collected prospectively.

2.5.3 Serious Adverse Events

The characteristics of serious adverse events (SAEs) that occur on or before the date of the 3-month follow-up will be summarised as for the SS as a whole and

by randomisation group. SAEs will be summarised with respect to severity, relationship to study procedures, outcome and duration.

Separate summaries will be provided for fatal SAEs.

2.6 Angina Severity, Risk Factors and Coronary Function Parameters

The relationship between angina questionnaire scores, cardiovascular risk factors and parameters of post-PCI coronary function listed below will be summarised between the randomised groups and overall:

- Pd/Pa
- dPR
- RFR
- TT_{rest}
- FFR
- TT_{hyp}
- CFR
- IMR
- IMRc

2.7 Subgroup Analyses

The following subgroup variables will be considered:

- Age
- Sex
- Acute Coronary Syndrome
- Smoking Status
- Diabetes
- Target Vessel

2.8 Additional Analyses

Other analyses that are planned but not covered by this SAP include:

- Clinical Predictors of post-PCI FFR ≥0.90
- Clinical Predictors of post-PCI FFR ≤0.80
- Clinical Predictors of post-PCI dPR <0.90
- Clinical Predictors of post-PCI RFR <0.90
- Clinical Predictors of post-PCI CFR <2.0
- Clinical Predictors of Target Vessel Failure at 3 months and 1 year

3. References

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4. Document History

This is version 1.0 of the SAP for the Target FFR Study, dated 23/07/2019. This is the original version of this document.