Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

This supplement contains the following items:

1. Original Approved Study Protocol (v4.0)
2. Final Approved Study Protocol (v4.3)
3. Summary of changes
4. Statistical analysis plan (v1.0)
FLAIR

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Prospective, multi-center, double blind, randomised study to test the safety of deferral of stenting in physiological non-significant lesions in a clinical population of intermediate stenoses using iFR and FFR

Randomised Comparison of iFR to FFR

STUDY PROTOCOL
10 October 2013

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Sponsor:
Imperial College London is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder: Unrestricted grant from Volcano Corporation

This protocol describes the FLAIR study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

This protocol is strictly confidential and not for public distribution.
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1. Study overview

1.1. Study summary

**Design**
Patients with one or more coronary stenoses, in which the physiological severity from coronary angiography is in question, will be randomised 1:1 to use of the instantaneous wave free ratio (iFR) or fractional flow reserve (FFR) to guide the treatment strategy for percutaneous coronary intervention (PCI).

**Aims**
To assess whether the iFR is non-inferior to FFR when used to guide treatment of coronary stenosis with PCI.

**Outcome measures**
The primary endpoint will be major adverse cardiac event rate in the iFR and FFR groups at 30 days, 1, 2, and 5 years.

**Population**
This will be an international multi-centre study of 2500 patients. From population estimates, 35% of the total study population will present with stable angina and 65% will have acute coronary syndrome.

**Eligibility**
Patients will be eligible when the physiological severity of a stenosis within a vessel is in question. In the cases of stable angina this will be confined to the target vessel, or with acute coronary syndrome assessment this will be made in the non-culprit vessel.

**Duration**
Anticipated recruitment is 12 months. Follow-up will be performed at 30 days, 1, 2 and 5 years.
### 1.2. Glossary of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>BSR</td>
<td>Basal stenosis resistance index</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft surgery</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical events committee</td>
</tr>
<tr>
<td>CFR</td>
<td>Coronary flow reserve</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical research organisation</td>
</tr>
<tr>
<td>DES</td>
<td>Drug-eluting stent</td>
</tr>
<tr>
<td>FFR</td>
<td>Fractional flow reserve</td>
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<tr>
<td>HSR</td>
<td>Hyperaemic stenosis reserve index</td>
</tr>
<tr>
<td>ICTU</td>
<td>Imperial College Clinical Trials Unit</td>
</tr>
<tr>
<td>iFR</td>
<td>Instantaneous wave free ratio</td>
</tr>
<tr>
<td>iFR-ado</td>
<td>iFR with adenosine administration over entire cardiac cycle</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiac event rate</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RIND</td>
<td>Reversible ischaemic neurological deficit</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>SSA</td>
<td>Site specific assessment</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>TLR</td>
<td>Target lesion revascularisation</td>
</tr>
<tr>
<td>TVR</td>
<td>Target vessel revascularisation</td>
</tr>
</tbody>
</table>

### 1.3. Keywords

Instantaneous wave free ratio  
Fractional flow reserve  
Percutaneous coronary intervention
2. Introduction

2.1. Background
Decisions to perform or defer percutaneous coronary intervention (PCI) on the basis of physiological stenosis severity using fractional flow reserve (FFR) are safe and reduce stent implantation rates.\(^1\)\(^-\)\(^3\) Despite the evidence, this modality of ischemia driven revascularisation is applied only in a small proportion of patients undergoing PCI (6-10\%).\(^4\) The reasons for this are multifactorial, including partial or inadequate reimbursement, availability of suitable measurement equipment, or accessibility to pharmacological agents. Additionally, FFR adds on average 10 minutes to the procedure, which further discourages widespread adoption. This is particularly relevant in multi-vessel disease: multi-vessel assessment is rarely performed and when it is, takes considerably more time.

Recently a new technique for measuring physiological lesion severity, instantaneous wave-free ratio (iFR) was introduced.\(^5\) iFR, is very similar to the conventional measurement technique, but differs crucially as it does not require the administration of pharmacological vasodilators (such as adenosine).\(^6\)

To date, iFR has been assessed extensively over 18 months, being used in over 3000 lesions, principally in comparisons with FFR, which is commonly held as the reference standard for classifying stenoses according to haemodynamic severity.

The results of these studies suggest that iFR is a valid diagnostic tool in the catheterisation laboratory. Yet, widespread applicability of iFR in clinical practice will require studies investigating the equivalence of iFR to FFR in terms of patient outcomes when used as a clinical decision making tool in patients in whom PCI is considered as a potential treatment.

The FLAIR study is designed to thoroughly assess whether iFR-informed treatment decisions are non-inferior to FFR-informed decisions for the treatment or deferral of PCI. The following paragraphs are a discussion of the relevant aspects of iFR and FFR in order to explain the rationale for this study.
3. Study objectives

Diagnostic efficiency of iFR to characterise haemodynamic stenosis severity

1) Comparisons with FFR:
Since its introduction multiple studies using off-line analysis have been assessed the utility of iFR against FFR as a reference standard.\(^7\)\(^-\)\(^8\) This approach is intrinsically limited by the diagnostic efficiency of FFR, which in itself is a surrogate of non-invasive ischemia detection tests.\(^9\) Overall these studies have shown that iFR can be used to identify ischaemia-generating stenoses, as defined with FFR.\(^8\) Variations in the diagnostic efficiency of IFR appear related to the robustness of the identification algorithm used. When calculated using the proprietary Imperial College-Volcano algorithm, which among other features uses ECG for identification of the wave-free period within diastole, every study has reported a classification match between iFR and FFR of 80-90%. Recently, a large international analysis demonstrated similar levels of agreement with FFR when performed on-line using the commercially available console, in real-world catheter laboratory environments (ADVISE-in Practice, TCT 2013).

2) Head to head comparisons of iFR and FFR against other diagnostic modalities:
Direct comparisons with non-invasive ischemia detection tests (single-photon emission computed tomography, SPECT) or other physiological non-FFR indices (coronary flow reserve (CFR), hyperaemic stenosis resistance index (HSR)) have the advantage of overcoming the limitations of FFR as a comparator, and allow head-to-head comparison between both techniques. The number of reported direct iFR comparisons with these modalities at present is lower than studies using FFR as a comparator.

- **Comparison with HSR:** HSR assesses coronary stenoses according to their pressure-flow velocity relationships that form the foundation of all coronary physiology. Simply, HSR indexes pressure changes by flow changes, to provide a highly stenosis-specific assessment of coronary flow limitation. iFR has been assessed in the CLARIFY study, and in a larger independent dataset against hyperaemic stenosis resistance index (HSR). In both of these studies, iFR and FFR had a diagnostic classification match in excess of 90%, while both matched with HSR around 90%. No improvement in diagnostic accuracy was seen when adenosine was administered over the entire cardiac cycle (FFR) or over the wave-free period (iFR-adeno).

- **Comparison with SPECT:** iFR has been assessed against nuclear imaging in a study reported by Van de Hoef et al.\(^9\) This study reported that iFR, FFR, and a flow-based resting index, basal stenosis resistance index (BSR), all had similar diagnostic power. Again no improvement was observed following administration of adenosine.

- **Comparison with CFR:** A recent study by Petracco et al. (under review, TCT 2013) compared the classification match between FFR and iFR against CFR. In this multi-centre invasive study of 216 lesions measuring coronary pressure and flow in patients undergoing physiological assessment of the severity of coronary artery disease, it suggested that the discordance rates between pressure and flow based indices were significantly improved by using iFR as opposed to FFR. This improved
accuracy was independent of the CFR threshold used (i.e. 1.7, 2.0 or 2.5), or whether clinical or ischaemic cut-points for iFR or FFR were used.

**Ischaemia driven revascularisation and appropriateness of PCI**

Previous studies using physiological guidance have demonstrated the value of reserving revascularisation for lesions in which ischaemia is evident.\(^1\),\(^10\) Despite improvement in stent technology and pharmacological therapies, by reserving revascularisation for lesions demonstrating evidence of ischaemia leads to a reduction in acute, medium term and late complication rates. These include peri-procedural infarction, procedural related complications, in-stent re-stenosis, and stent thrombosis. Additionally, using physiology to guide revascularisation has been shown to be cost-effective.\(^11\) Pressure-wire based assessment of lesion severity provides a rapid, simple and lesion specific measure of ischaemia, guiding revascularisation decision making.

**DEFER and FAME studies linking outcomes to dichotomous cut points**

FFR-guided revascularisation has been tested using both the FFR 0.75 and 0.80 cut-points. The original small validation studies against other parameters of ischaemia found that FFR<0.75 best predicted the likelihood of ischaemia.\(^12\) The DEFER study subsequently demonstrated that stenoses with FFR≥0.75 are deferred, the event rate is extremely low (around 0.2 events/year). The FAME studies\(^1\),\(^2\) developed the concept of using FFR to indicate revascularisation, but used FFR≤0.80 as the threshold for decision making. This increase in FFR threshold from FFR <0.75 to ≤0.80 was to increase sensitivity, to avoid missing ischaemic lesions falling close to the threshold of ischaemia. This range of FFR 0.75-0.80 is referred to as “FFR grey zone”, as no significant difference in outcome has been identified using different treatment strategies within this zone. The FAME studies demonstrated reduction in MACE and stent implantation rates leading to widespread adoption of the FFR≤0.80 threshold as a dichotomous cut-point for guiding revascularisation. Whilst these clinical outcome studies provide a strong evidence base, the majority of stenoses were highly significant and FFR has never been tested in a population of truly intermediate clinical stenoses, which represent its main clinical application in the cardiac catheter laboratory.

In contrast, although iFR awaits formal clinical outcome studies, it has been extensively assessed in over 3500 lesions against FFR. This has allowed the iFR cut-point best matching the FFR clinical cut-point of ≤0.80 to be established. These studies include the ADVISE-Registry, the South Korean prospective single-blinded clinical study, RESOLVE (patient level meta-analysis), and ADVISE 2 a prospective double blinded core-lab multi-centre study.\(^7\),\(^13\) In all of these studies, the iFR cut-point best matching FFR ≤0.80 has consistently been found to be within a very narrow range between iFR 0.89-0.90. In this study we will use iFR≤0.90 as the dichotomous cut-point, equivalent to an FFR ≤0.80 as used in the FAME studies.
Rationale for FLAIR

1) The widespread application of iFR in clinical practice awaits studies showing the equivalence of iFR to FFR in terms of patient outcome when used as in clinical decision making in patients in whom PCI is considered as a potential treatment.

2) Although FFR has overcome the limitations of angiography as a tool to decide the appropriateness of coronary revascularisation, its overall benefit likely results from its ability to broadly differentiate between stenoses causing severe ischemia from those with negligible impact on coronary haemodynamics. This aspect is likely much more important that an extremely high diagnostic accuracy, and it is supported by the positive results of trials using either the <0.75 and ≤0.80 FFR cut-off for clinical decision-making.3,10

3) Since agreement of stenosis severity classification with iFR and FFR is extremely high outside of the FFR grey zone, it is foreseeable that iFR guided revascularisation is not inferior to that performed with FFR in terms of safety. It may have potential advantages by reducing procedural time and costs, increasing adoption of physiology-driven revascularisation.

Study hypotheses

In patients with coronary stenoses suitable for physiological assessment, the decision to perform coronary revascularisation based on iFR measurements is:

1. Non-inferior to FFR in terms of safety and efficacy
2. Superior to FFR in terms of cost-effectiveness.

Primary objective

The primary objective of the study is to assess the safety and efficacy of decision-making on coronary revascularisation based on iFR measurements of stenosis severity, compared with FFR.
4. Study design

4.1. Study review diagram

4.2. Study protocol:
Following enrolment in the study patients should undergo the following:

**Recommended optimization of medical therapy:**
1. Aspirin ≥75mg OD
2. Statin therapy to target LDL below 1.8mmol/L
3. Bisoprolol ≥5mg OD (or alternative β blocker at equivalent dose)
4. Amlodipine ≥5mg OD
5. Perindopril ≥4mg OD (or alternative ACE inhibitor at equivalent dose)
6. Alternative anti-anginal medication at physician’s discretion: nicorandil, ivabradine, ranolazine

**Pre-Angiography Testing**
- Biochemistry and Haematology
  - Serum Creatinine
  - Haemoglobin, white cell count, platelet count
  - Troponin
- Fasting lipid profile
- ECG
- Canadian quality of life questionnaire

**Post-PCI / Post-Angiography Testing**
- Troponin (>3 hours)
- ECG

**Invasive functional assessment**
The patient will be suitable for enrolment when the physiological significance of one or more stenosis is in doubt. For guidance this will typically be coronary stenosis in the range of 40-70% by visual estimation. Upon intubation of the guiding catheter, 300mcg of intracoronary nitrates will be administered to control coronary vasomotion. The pressure wire will then be inserted into the artery with the sensor at the ostium of the guiding catheter, and 5-10 beats of normalisation will be recorded.

The pressure wire will then be advanced to at least 3 vessel diameters beyond the most distal stenosis, and measurement of **either iFR or FFR** made according to standardised technique (see Appendix 1). After each distal measurement is made, the wire should be withdrawn with continuous recording, either under continued hyperaemia or at rest, over a 20 second period back to the ostium of the guiding catheter. A normalisation check for drift should be made and documented. Where drift is evident (Pd/Pa measured at the level of the catheter tip <0.98 or >1.02), measurements should be repeated.

**Randomisation**
Each patient will be randomised to either iFR or FFR guided therapy by the online FLAIR randomisation tool. Patients will be allocated to either iFR or FFR guided revascularisation or deferral. Balanced randomisation based on critical variables (diabetes, acute coronary syndrome) will be performed automatically by the randomisation algorithm.

To ensure study blinding, and to prevent moral conflict, in the iFR guided arm, **only iFR will be recorded** and in the FFR guided arm, **only FFR will be recorded**. This will be strictly mandated, and will be considered a serious breach of study protocol if this does not occur. A screenshot recording of the physiological measurement will be used to document the methodology used.

Treatment will be guided by the randomised methodology strategy, using the iFR ≤0.90 threshold, and FFR ≤0.80. Any cross-over of patients will be treated as a major study protocol violation.

**Vasodilatation**
Microcirculatory vasodilatation will be performed according to standard practice at that centre. High dose vasodilatation administration should be given *a priori* for all stenosis evaluation thereby removing the need for escalation of dosing. Depending on the agent used by the centre investigators will use one of the following regimes: IV adenosine...
(140mcg/kg/min), IC adenosine (200mcg for LCA and 150mcg for RCA), IV ATP (140mcg/kg/min) or IC papaverine (12mg LCA or 8mg for RCA) will be administered.

**Volcano S5/S5i haemodynamic settings**
Each patient should have the ECG attached to the console. The FFR averaging mode should be standardised according to the mode of administration. Intravenous vasodilators (IV adenosine and ATP) should be set to using a 3-beat moving Pd/Pa average. In the case of IC vasodilators (IC adenosine and papaverine) a 2-beat moving Pd/Pa average will be used. iFR settings will be fully automated, as performed by the console.

**Sedation, PCI**
Patient should be offered sedation and analgesia as required, and as normally offered by the laboratory in which the assessment is being made. PCI should be performed in accordance with the typical practice in the local centre. Wherever possible drug eluting stents should be used, a low threshold for post-stenting optimisation should be applied.

**Repeat invasive assessment**
iFR and FFR assessment will be repeated, according to the randomisation group in all coronary lesions post PCI.

**Angiographic visual assessment**
The severity of the stenosis, lesion length, characteristics of the lesion, will be documented by visual assessment by the operator. Where disease is present but minor with coronary stenosis severity <40%, this should be documented as atheroma.

**PCI**
The stent type, and size implanted should be documented on the e-CRF.

**4.3. Study outcome measures**

**Primary Endpoint**
Major adverse cardiac events (MACE) rate in the iFR and FFR groups at 30 days, 1, 2, and 5 years.

MACE is defined as a combined endpoint of death, non-fatal myocardial infarction (MI), or unplanned revascularisation.

**Secondary Endpoints:**
1) Death (all cause) at 30 days, 1, 2 and 5 years  
2) Death (cardiovascular) at 30 days, 1, 2 and 5 years  
3) MI at 30 days, 1, 2 and 5 years  
4) Repeat revascularisation by PCI or coronary artery bypass surgery (CABG) at 30 days, 1, 2 and 5 years  
5) Costs associated to iFR or FFR guidance.  
6) Quality of life (QOL) in patients included in the iFR or FFR guidance groups.  
7) Cost savings of removing secondary investigations, by assessing/treating non-culprit acute coronary syndrome (ACS) at the time of index presentation.
4.4. Relevance and implications of the trial results
1. If the primary endpoints are equivalent between the two randomised arms, it would confirm that iFR is non-inferior to FFR for physiological guidance of PCI. This would provide support for the use of iFR to decide on the appropriateness of revascularisation, based on coronary stenosis physiological severity, in a similar way to FFR.
2. To demonstrate the cost effectiveness of iFR/FFR guided strategy for ad hoc PCI to intermediate non-culprit ACS
3. To provide evidence to support guideline changes for use of iFR as a diagnostic tool.

4.5. Sample size/Power calculation
FLAIR event rates are based on conservative rates of stable coronary disease. However, in this study it is estimated that around 65% of patients enrolled would have non-culprit ACS. In this group of patients the event rate is significantly higher, and it is likely that we would be adequately powered to demonstrate our outcome objectives.

2494 are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group of more than 2%. Therefore, 2500 patients in total will be recruited on a 1:1 basis.
5. Participant entry

5.1. Pre-registration evaluation

Recruitment

Patients undergoing assessment of one or more coronary stenosis where the physiological significance is in doubt following visual assessment. For guidance this will typically be coronary stenosis in the range of 40-70% by visual estimation.

In the case of ACS physiological assessment should only take place in non-culprit vessels once the culprit vessel has been revascularised or if a non-culprit lesion has been identified. In the case of ST-elevation myocardial infarction (STEMI) at least 48 hours must have passed prior to study enrolment.

Population estimates are that approximately 35% of the total study population will have stable angina, and 65% will present with ACS. This is reflective of the current clinical population undergoing physiological assessment in the catheter lab. An interim demographic analysis will be performed at 30 days, 3, 6, 9, and 12 months to ensure that recruitment is not becoming skewed by overly high recruitment into either the stable or ACS arm. If this occurs, investigators will be informed and encouraged to adapt their recruitment patterns according to the expected ratios.

5.2. Inclusion criteria

1. Age > 18 years of age
2. Willing to participate and able to understand, read and sign the informed consent document before the planned procedure
3. Eligible for coronary angiography and/or percutaneous coronary intervention
4. Coronary artery disease in one or more native major epicardial vessels or their branches by coronary angiogram with visually assessed de novo coronary stenosis in which the physiological severity of the lesion is in question (typically 40-70% diameter stenosis).
5. Stable angina or ACS (non-culprit vessels only and outside of primary intervention during acute STEMI).

5.3. Exclusion criteria

1. Previous CABG with patent grafts to the interrogated vessel
2. Left main stenosis
3. Tandem stenoses separated by more than 10mm that require separate pressure guide wire interrogation or PCI (not to be interrogated or treated as a single stenosis)
4. Total coronary occlusions.
5. Restenotic lesions
6. Haemodynamic instability at the time of intervention (heart rate<50 beats per minute, systolic blood pressure <90mmHg), balloon pump
7. Significant contraindication to adenosine administration (e.g. heart block, severe asthma)
8. Contraindications to PCI or drug-eluting stent (DES) implantation
9. Heavily calcified or tortuous vessels
10. Significant hepatic or lung disease (chronic pulmonary obstructive disease), and/or malignant disease with unfavourable prognosis that may influence survival within the next 5 years.
11. Pregnancy
12. STEMI within 48 hours of procedure
13. Severe valvular heart disease
14. ACS patients in whom more than one target vessel is present.

5.4. Withdrawal criteria
Patients will be able to withdraw from the study at any time at their request.

5.5. Screening record
Any patient initially considered suitable, but then found inappropriate due to study exclusion criteria will be recorded into the screening record.
6. Clinical events

6.1. Definitions
The following clinical events will be adjudicated and will be defined as follows:

Death
All patient deaths will be documented on the case report form (CRF). The Sponsor or designee must be notified of a patient's death within 24 hours after the clinical site has knowledge of the event. The principal investigator's narrative summary of the circumstances of death is required. Autopsy results, when available, should be reported to the clinical research organization (CRO).

In the primary comparison of the two treatment strategies, all deaths will be examined. Death due to specific causes will be investigated and adjudicated by the clinical events committee (CEC). All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac Death
Any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death even in patients with co-existing and potentially fatal non cardiac disease (e.g. cancer or infection).

Vascular Cause death
Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-Cardiovascular death
Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

Myocardial Infarction

Spontaneous MI is considered an event after the first 48 hours after randomisation and after 7 days following CABG, which is unrelated to the procedure and is defined as either:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) Ischaemic symptoms; AND/OR
   b) Development of new pathologic Q-waves on the ECG; AND/OR
   c) ECG changes indicative of ischemia (ST segment elevation or depression);

   OR

2) Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.
OR

3) Pathological findings of an acute MI

Periprocedural MI is considered an event within the first 48 hours after randomisation and within 7 days following CABG:

- **Stable (Trop –ve population):**
  Peri-procedural MI in the setting of elective PCI is defined by a confirming cardiac specific biomarker (a positive value of CK-MB or Troponin I/T) on any one sample obtained after the procedure.
  - CKMB elevation >3 times upper limit of normal

  Or
  - Troponin elevation that is >5 times the 99th percentile of diagnostic value for the specific institution

- **ACS (Trop +ve population):**
  Peri-procedural MI in the setting of ACS PCI for evolving MI is defined as follows:

  When peak CK-MB or Troponin from the index infarction HAS been reached*:

  EITHER
  - If the biomarkers have returned to below the upper limit of normal. A new elevation in CK-MB > 3 times upper limit of normal or Troponin >5 times the 99 centile within 24 hours post index PCI

  OR
  - If the biomarkers have not returned to below the upper limit of normal A rise of >50% in CK-MB or Troponin above the previous nadir level

  AND the presence of:-
  - new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB
  - symptoms of ischemia with ECG changes indicative of new ischemia (new ST-T changes)
  - angiographic documentation of new coronary artery occlusion or dissection

- **Peri-procedural MI within the first 7 days following CABG**

  EITHER
- Enzyme changes defined as one plasma level of CKMB or troponin >5x upper limit for normal AND the development of new abnormal Q-waves not present on the patient’s baseline ECG

OR

- Enzyme changes defined as one plasma level of CKMB or troponin >10x upper limit for normal

* To allow for test-test reproducibility of the biomarker assay. A peak rise in biomarker is defined as when elevation in CK-MB or Troponin levels in successive measurements are not higher than 5% above the proceeding value within 24 hours post index PCI

For each MI adjudicated by the CEC, the type of MI will also be described as:

**ST-Elevation MI (STEMI)**
- Also categorise as:
  1. Q-wave (development of new Q waves in 2 or more contiguous leads)
  2. Non-Q-wave
  3. Unknown (no ECG or ECG not interpretable)

**Non-ST-Elevation MI (NSTEMI)**
- Also categorise as:
  1. Q-wave (development of new Q waves in 2 or more contiguous leads)
  2. Non-Q-wave
  3. Unknown (no ECG or ECG not interpretable)

If an angiogram is available for these events, this information should be provided to the CEC in order to help defining to which vessel the infarction is related. All infarcts that cannot be clearly attributed to a given vessel will be considered indeterminate.

**Revascularisation**

**Planned Revascularisation**
Revascularisation will be considered planned when it is decided at the time of the index procedure, based on the results of angiography and functional testing. Planned revascularisation could be performed at the time of the index procedure or within 60 days. Such revascularisation will be considered as “primary” revascularisation and will not be considered as an endpoint. The “planned” status of the revascularisation will be adjudicated.

**Unplanned Revascularisation**
Revascularisation will be considered “unplanned” when it was not performed as part of the care practice during the index procedure or identified at the time of the index procedure as a staged procedure to occur within 60 days. Additionally, unplanned revascularisation will require symptoms consistent ischemia leading to either PCI or CABG. PCI and CABG will be
reviewed as the revascularisation procedure, and both target lesion revascularisation and target vessel revascularisation will be assessed.

**Target lesion revascularisation (TLR)**

TLR is defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs will be classified prospectively as clinically indicated or not clinically indicated by the investigator.

A revascularisation is clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% and if one of the following occurs:

a) A positive history of recurrent angina pectoris presumably related to the target vessel.

b) Objective signs of ischemia at rest (ECG changes) or during stress/exercise test (or equivalent) presumably related to the target vessel.

c) Abnormal results of any invasive functional diagnostic test. The target lesion is defined as the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.

**Target vessel revascularisation (TVR)**

TVR is defined as any repeat PCI of any segment of the target vessel. All TVRs will be classified prospectively as clinically indicated or not clinically indicated by the investigator. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself.

**Revascularisation procedure**

Every subsequent revascularisation procedure and its indication will be reported and documented in the appropriate CRF.

**Cerebrovascular Event (stroke)**

Stroke is defined as a focal neurological deficit of central origin lasting more than 72 hours and resulting in irreversible brain damage or permanent body impairment. Type and severity of symptoms is dependent on the location and extent of brain tissue whose circulation has been involved. Strokes will be further classified as ischemic, hemorrhagic or undetermined based on imaging studies. When blood flow to the brain is interrupted because of rupture of a vessel causing bleeding into or around the brain, it is considered hemorrhagic. When a vessel that supplies the brain is blocked, the event is considered ischemic. If insufficient information is known to allow categorization, it will be considered as undetermined.

Reversible ischaemic neurological deficit (RIND) and transient ischaemic attack (TIA) events will be submitted to the CEC for final adjudication.

When events occur it is imperative to document the neurological deficit and neuroimaging results in the CRF form and send this information to the CEC.
6.2 Reporting procedures

Clinical Events Committee
The CEC is made up of interventional and non-interventional cardiologists who are not participants in the trial. The CEC is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial which are based on protocol.

The Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the treatment arm and the primary results of the trial.

The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is available. The Committee will also review and rule on all deaths that occur throughout the trial.

Reports of clinical events should be submitted within 15 days of the Chief Investigator becoming aware of the event.

Local investigators should report any clinical events as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting clinical events: TBC
Fax: TBC, attention TBC

Case report form
An online CRF form will be used throughout the study. This will be secure, and compatible with currently guidelines to ensure security of patient data. It will be managed via the Imperial College Clinical Trials Unit (ICTU), and data achieved securely.

7. Assessment and follow-up
Routine follow-up will be performed with a clinic visit at 30 days, 1, 2 and 5 years. The CRF should be completed, including the QOL assessment. A routine telephone call will also be made at 6 months to assess for any adverse clinical events during this period.

8. Statistics and data analysis
Data will be summarised as mean (SD) or median (interquartile range) for skewed data. Statistical comparisons will be undertaken using a paired Student’s t-test (after log transformation if necessary) or nonparametric alternative if data are not normalised by log transformation. Kaplan-Meier survival analysis curves will be used to assess clinical event timelines.
9. Regulatory issues

9.1. Ethics approval
The Chief Investigator has obtained approval from the TBC Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2. Consent
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3. Risks of procedure
Standard PCI techniques will be used in the evaluation and treatment of coronary artery stenosis. All operators are highly skilled in these techniques and in handling the standard clinical complications of PCI. Therefore the risk is similar in both arms of the study.

9.4. Confidentiality
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.5. Indemnity
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

9.6. Sponsor
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.7. Funding
Volcano Corporation is providing and unrestricted educational grant to fund this study

9.8. Audits
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).
10. Study management

The day-to-day management of the study will be co-ordinated through Imperial College London.

10.1. Study reporting
We anticipate that it will take 12 months to complete patient recruitment. We will aim to begin recruitment after Ethics review approval with first results available for presentation in 2016.

10.2. Study sites and enrolment
We anticipate the study enrolling patients through up to 40 large high volume PCI centres with experience in all of the physiological techniques proposed in this study. We envisage enrolment would take place within 12 months.

10.3. Documentation
All documentation will be collected electronically using ICTU. The ICTU has a track record for running large multi-centre international (e.g. ASCOT study). Clinical, and physiological records will be saved to DVD and then to a central server within ICTU in accordance with GCP guidelines.

11. Publication policy

Publication and future studies committee
A publication committee, consisting of member of the steering committee and study principal investigators will meet to formulate a publication plan to disseminate the principal findings of the study, and the primary and secondary endpoints.

Future studies, and sub-studies will be actively encouraged, by investigators and other interested parties. These will be assessed via the formal application process, and the committee will decide on the applicability and suitability of the study request. Sub-study proposals which aim to look at subset analyses of the primary and secondary endpoints will be underpowered and in general discouraged.
12. References


13. Park JJ, et al. Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis; results of an independent, blinded comparison with fractional flow reserve. *Int J Cardiol*. 2013
13. Appendices

Appendix 1
Standard Protocol for iFR/FFR assessment

1. Flush the guide wire with enough saline to fill the dispenser hoop early during pressure wire set-up.
2. Connect the ECG and BP cables from the s5 to the haemosystem (not applicable on s5i).
3. Enter patient information including randomisation number on imaging system.
4. Select FFR on the bottom right hand corner of the screen.
5. Select the Settings tab on the bottom of the screen.
   - Make sure the ECG Trace box is ON.
6. Select the Pressure tab on the s5 or s5i.
   - Make sure the s5 or s5i has the MAP reading at 3 beats.
7. Once the ECG trace is on and the MAP reading is at 3 beats, select the HOME tab on the bottom of the screen to go to the “LIVE” screen.
   - Make sure there is an ECG signal on the top of the HOME screen.
8. Plug the guide wire into the Volcano pimette and allow it to zero.
   - It will take 10 to 15 seconds for the wire to “zero”.
   - Once wire has zeroed, the machine will display a message at the bottom of the screen that states, “Wire Zeroed, ready to insert.”
   - The wire can now be taken out of the dispenser hoop.
9. Administer 300 mcg IC Nitro-glycerine through the guide catheter, per standard lab procedures.
10. Shape the guide wire (if needed), insert and advance transducer to the end of the guide catheter.
    - Flush catheter with saline.
    - Make sure guide catheter is coaxial with vessel and AO pressure is not damped.
    - If the AO pressure trace appears damped, ideally disengage the guide catheter to ensure an optimum AO pressure trace.
    - Remove wire introducer.
    - Tighten Tuohy manually, even if the Tuohy has a haemostatic valve.
11. Wait 10 seconds, then press NORMALISE on the s55 /s5i.
    - Make sure Pd/Pa equals 1.00.
    - If Pd/Pa does not equal 1.00, wait 10 seconds and then press NORMALISE again.
    - If the Pd/Pa ratio still does not equal 1.00, then check the height of the AO transducer to make sure it is midline to the patient and NORMALISE again.
    - If Pd/Pa ratio still will not equal 1.00, then open new wire and contact the Volcano study team member to obtain instructions on returning the guide wire to Volcano.
    - Press RECORD on the Volcano system to acquire 5-10 beats of normalisation.
12. Position the wire and pressure sensor at least 3 vessel diameters distal to the lesion to be evaluated.
    - Flush the guide catheter with saline (to prevent pressure damping).
    - Remove wire introducer.
    - Close Tuohy manually, even if it is a Tuohy with a haemostatic valve.
    - Turn transducer back on to pressure and make sure Pa pressure is not damped.
Randomisation to iFR arm
1. Switch to iFR mode.
2. Press RECORD on the Volcano system to make an iFR measurement.

Randomisation to FFR arm with IC administration
1. Select FFR on the bottom left hand corner of the screen.
2. Ensure that a 2 beat Pd/Pa average window is used to calculate FFR.
3. Press RECORD on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 10 seconds.
4. Intra-coronary adenosine bolus injection of 200mcg for LCA and 150mcg for RCA, intra-venous ATP at 140mcg/kg/min or intracoronary papaverine at 12mg for LCA and 8mg for RCA.
5. Repeat measurements of FFR twice. Escalation in dose of hyperaemic agent is not tolerated.

Randomisation to FFR arm with IV administration
1. Select FFR on the bottom left hand corner of the screen.
2. Ensure that a 3 beat Pd/Pa average window is used to calculate FFR.
3. Press RECORD on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 10 seconds.
- Continue recording and make an FFR assessment at the same location using hyperaemia for up to 3 minutes in duration or until stable hyperemia as determined by the physician using adenosine infusion through a central or peripheral vein at 140 mcg/kg/min.
- Make sure the recording is uninterrupted for the entire duration, no injection of contrast, or saline, or disruption to the aortic pressure transducer should be made during this recording phase.
- For patients greater than 100kg, but less than or equal to 220kg, please follow hospital protocol (found in pharmacy) for non-invasive cardiac stress testing using Adenosine and make note of it in the case log. Data from patients greater than 441 pounds (200 kg) will be excluded.
- Without interruption of adenosine infusion and without opening the Tuohy haemostatic valve, perform a manual pullback manoeuvre under fluoroscopic guidance at an estimated velocity of 0.5mm/sec until the guide wire sensor has reached the tip of the guide catheter. Once the guide wire is into the guide catheter, wait for 20 seconds to check normalization. Make sure the recording is uninterrupted for the entire duration of the pullback manoeuvre.
In all protocols (iFR, IC or IV hyperaemia administration)

Once FFR measurements are complete, pull the guide wire back to the guide catheter and assess for drift of the Pd/Pa recording. If this remains at 1.00 ± 0.02, continue to randomisation. If the Pd/Pa does not equal 1.00 ± 0.02, repeat the normalisation process until it equals 1.00, and repeat the appropriate steps above to obtain a drift-free comparison. Ensure that you record at least 5-10 beats of normalisation.

Once this is complete the values of iFR or FFR should be entered into the CRF.

Depending on the physiological value of either iFR or FFR, the patient will then be randomised to either iFR or FFR guided therapy.

In the case of being assigned to the PCI arm

1. Following PCI, operators will be encouraged to make repeat measures of iFR and FFR using the same modality (either iFR or FFR) as described above starting at bullet point 9 of Standard Protocol for iFR/FFR assessment. This will not be mandated and will be at the operator’s discretion.

2. Complete an entry on the Electronic Case Report System for each iFR/FFR run.

3. At the conclusion of the case, archive the case to DVD by selecting the Patient Tab, then the ARCHIVE button, the DVD location, and finally the SAVE button.

4. The site should then remove patient-specific identifiers and assign an ID number to the DVD that matches the Case Report Form).
Following PCI, operators will be encouraged to repeat physiological measurements according to the appropriate randomisation arm.
Appendix 2
Schedule of investigations

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<th>30 days (± 7 days)</th>
<th>6 months (± 30 days)</th>
<th>1 year (± 30 days)</th>
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Patient Information Leaflet

The FLAIR Study

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Prospective, multi-center, double blind, randomised study to test the safety of deferral of stenting in physiological non-significant lesions in a clinical population of intermediate stenoses using iFR and FFR

Chief Investigator: Dr Justin Davies & Dr Javier Escaned
Local Principal Investigator: Dr Iqbal Malik

Version 1.3 07.09.2013

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?
You are suffering from chest pain or shortness of breath. This may have occurred at rest or on exertion and may be due to a narrowing of one of your heart arteries. One way of treating these narrowings is with stents (small metal tubes that are inserted into the coronary artery during angiography to unblock the narrowing). This is why your doctor has recommended you undergo angiography.

However, not all heart artery narrowings need to be treated as they may not be the cause of your symptoms. To help doctors decide which narrowings need treatment and which can be left alone fine wires are passed into the arteries and pressure measurements are made during angiography. This is the recommended practice for treating patients with your condition because it has been shown to reduce the future need for repeat stents.
Currently during these measurements a drug needs to be given so that the measurements are accurate. As a result some patients who cannot be given the drug cannot benefit from this test. Furthermore the drug is simply not readily available in some countries. To increase the number of patients in which such vital technology can be used we have developed a new way of making these measurements that does not require an extra drug to be given. It has been demonstrated to be equivalent to the older technique in smaller studies. It has been awarded full regulatory approval in the European Union for use in patients like you. The purpose of this study is to compare our new technique – called iFR (instantaneous wave-free ratio) to the old technique called FFR (Fractional Flow Reserve). Therefore half the patients in this study will have their treatment guided by iFR and half the patients by FFR. If iFR is found to be equivalent to FFR it would enable more patients to benefit from such treatment.

**Why have I been chosen?**
You have been chosen because you are scheduled to have angioplasty and are not severely asthmatic. As a normal part of this procedure, a small tube will be inserted into the main artery in the groin or wrist. This means that at the time of your procedure, we can use this tube to pass our wires into your heart arteries and safely take measurements in your heart’s blood vessels. These measurements will guide the doctors’ treatment of your condition.

**Do I have to take part?**
No. Your decision whether to participate in this study is entirely voluntary. You have the right to refuse as well as to withdraw your participation at any time (even if you agree today) without giving a reason. If you decide not to participate or to withdraw, it will not affect the quality of your care or treatment, nor the relationship you have with your doctor and nursing team.

**What will happen to me if I take part?**
The coronary angiogram will occur as routinely performed. We will enter the artery at the top of your leg or via the wrist with a small tube, local anaesthetic will be used and this should not cause any discomfort. During the procedure the doctor may find a narrowing that needs closer inspection with a special pressure wire. This is a routine investigation that is performed commonly in patients with your condition. The wire will be passed into the heart arteries via the tube already in the wrist/leg. Measurements will be taken. During the measurements a drug to open up the small vessels may need to be infused. This may require a small tube to be placed at the top of the leg next to the first tube or the drug can be injected directly into the coronary artery via the existing tubes. In total the process will add 10 minutes to the procedure. The measurements will not prolong your recovery from the procedure. You will receive treatment according to the result of the pressure measurement either iFR or FFR. At the end of the procedure the wires and tubes will be removed.
Our clinical team will contact you via telephone 30 days and 6 months after the procedure. Over the next five years we will then be contacting you annually to find out how you have been keeping. Wherever possible this contact will be co-ordinated with your routine hospital visit.

**What are the possible side effects, risks and disadvantages of taking part?**

We do not expect you to experience any significant side effects as a result of participating in this study. During the measurements we will administering medications to open up the small blood vessels in the heart. These are routinely used every day in the cardiac catheter laboratory and maybe used in the clinical stages of your procedure. The risk of using such drugs are very low, but, in some patients it may cause a short lived chest discomfort which usually disappears within 3-5 seconds of stopping the drug. In order to administer the adenosine we will place a second tube at the top of the leg using local anaesthetic, which should not cause any discomfort. The measurements would have been necessary as part of the normal clinical process so will not extend the length of the procedure.

There is a very low risk (less than 1 in 1000) that the wire used to make the measurements will cause any damage to your blood vessels. The risk of death, heart attack or stroke is the same as your routine angiogram. This risk is minimised as the measurements are performed by an experienced senior Consultant Cardiologist. We will place the wires under x-ray guidance; the mean effective dose from this procedure is equivalent to 4.4 years of natural background radiation.

**What are the possible benefits of taking part?**

You will not directly benefit from this study, but the information we gain will give a much better understanding of whether there is a need to continue to give drugs to open the small blood vessels as part of the routine assessment of the diagnosis of coronary artery disease.

**What if something goes wrong?**

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone’s negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Justin Davies 020 7594 1264). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.
Will my taking part in this study be kept confidential?
If you agree to take part, data collected about you will be entered onto a computer. However, all data entered will be in an anonymous format and any information obtained from this investigation that can be identified will remain confidential. Relevant sections of your medical notes & data collected during the study may be looked at by individuals from Imperial College, from regulatory authorities or from Imperial NHS trust, where it is relevant to you taking part in this research. We will ask for your permission for these individuals to have access to your records. Your GP will be informed that you are participating in this study.

What will happen to the results of the research study?
Scientific data from this study may be presented at meetings and published so that the information can be used to help others, but your participation in the study will not be made known and will be kept strictly confidential. If you wish, we will give you a summary of the results.

Who is sponsoring the study?
The study will be sponsored by Imperial College London.

Who is funding the research?
The study will be funded by an unrestricted educational grant from Volcano Corporation to the Imperial College London.

Who has reviewed the study?
This study has been reviewed and given a favourable ethical opinion by the Outer London Research Ethics Committee.

If you have any further questions please do not hesitate to contact:
Dr Sayan Sen on 0207 594 1264, sayan.sen@imperial.ac.uk, or Dr Justin Davies on 0207 594 1264, justin.davies@imperial.ac.uk

Thank you for taking the time to consider participating in this study
Appendix 4
Participant consent form

CONSENT FORM

(Patients scheduled for pressure-flow wire measurements during coronary angiography/angioplasty)

The FLAIR Study

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Chief Investigator: Dr Justin Davies & Dr Javier Escaned
Local principal investigator: Dr Iqbal Malik

1. I have read the Patient Information Sheet (Version 1.3 Date 8/9/2013) for patients scheduled for the FLAIR Study

2. I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.

3. I have spoken to Dr..............................................................

4. I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care.

5. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the NHS Trust. I give permission for these individuals to access my records.

6. I agree to take part in this research study.

7. I agree to my GP being informed about my participation in this research study.

Signature.......................................................................................... Date............

Name (block capitals)............................................................................

Please initial

Yes ..... No .....
Signature of Study Investigator.................................................. Date.................
Name (block capitals).................................................................
General Practitioner Information Sheet

Dear Doctor

Re:

Name:
DOB:
Address:

Your patient has agreed to participate in the following research study at the Imperial College London:

Prospective, multi-center, double blind, randomised study to test the safety of deferral of stenting in physiological non-significant lesions in a clinical population of intermediate stenoses using iFR and FFR

Background and Aims

Physiologically guided revascularisation has been demonstrated to be superior to angiographically guided revascularisation for coronary artery disease. The most commonly used index to guide stenting currently is Fractional Flow Reserve.

Fractional Flow Reserve has been demonstrated to improve clinical outcomes and reduce healthcare costs when used to guide coronary artery revascularisation. As a result it has a Class 1A recommendation in European Guidelines. However adoption is poor. One of the reasons for this is the requirement for the administration of adenosine during its measurement. This adds time and cost...
to the procedure. Furthermore its administration is causes transient discomfort to patients and cannot be given to all patients due relative and absolute contra-indications to adenosine. It has been highlighted as one of the key reasons hindering adoption of FFR guided revascularisation.

We have developed a new way of assessing coronary stenoses called the instantaneous wave-free ratio (iFR). This uses existing pressure wire technology to assess stenosis severity without the need for drugs like adenosine. It has been demonstrated to have equivalent diagnostic agreement with FFR in terms of identifying ischaemia. The aim of this study is to determine if patients who have treatment guided by iFR have equivalent long term clinical outcomes as those whose treatment is guided by FFR. It is an outcome-based study that will follow patients at intervals for up to 5 years. Primary outcomes will be death, myocardial infarction, stroke and repeat revascularisation.

**What is involved for your patient**

The study protocol has been refined to minimise any inconvenience for your patient. During their planned angiographic procedure consenting patients will be randomised to either an iFR or FFR guided treatment strategy. Physiological measurements will be made with a pressure sensor tipped wires designed for such assessments. These are of the same calibre as normal angioplasty wires and will passed into the coronary artery.

All measurements will be made via the sheaths and guide catheters that are required for the routine angiographic procedure. It should be noted that the physiology of the coronary disease of the patient would have required such an assessment as routine clinical care and therefore the patient will not be exposed to any increased risk during the procedure.

Your patient will then be followed at 30 days, 6 months and one year. Thereafter they will be followed annually for a total of 5 years after the index procedure.

All of the information that we take will be fully anonymised.

The patients have been given an information sheet explaining the study further.

**Potential Benefits**

This study will not benefit your patient directly. We expect that the information that we gain from this study will however contribute to improvements in the adoption of physiologically guided revascularisation.

**Potential Side effects**

The side effects will be the same as that for a standard angioplasty procedure that is clinically required by your patient.
It is possible that one arm of the study has significantly better outcomes than the other. All events and interim analyses will be reviewed by an independent safety monitoring board and if necessary the trial will be halted. All patients and their GPs will be notified if this is the case.

**Adverse events and further information**

I would be grateful if you could report any adverse events to me on the address below.

Please do not hesitate to contact me for any further information on the following address:

Dr Sayan Sen  
FLAIR Medical Lead  
Clinical Lecturer  
Imperial College Healthcare NHS Trust  
Hammersmith Hospital  
Cardiology Dept.  
Du Cane Road  
W12 0HS

Telephone. 0207 594 1264  
E-mail. sayan.sen@imperial.ac.uk
FLAIR

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Prospective, multi-center, double blind, randomised study to test the safety of deferral of stenting in physiological non-significant lesions in a clinical population of intermediate stenoses using iFR and FFR

Randomised Comparison of iFR to FFR

STUDY PROTOCOL 4.3

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Imperial College London is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the FLAIR study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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1. Study overview

1.1. Study summary

Design
Patients with one or more coronary stenoses, in which the physiological severity from coronary angiography is in question, will be randomised 1:1 to use of the instantaneous wave free ratio (iFR) or fractional flow reserve (FFR) to guide the treatment strategy for percutaneous coronary intervention (PCI).

Aims
To assess whether the iFR is non-inferior to FFR when used to guide treatment of coronary stenosis with PCI.

Outcome measures
The primary endpoint will be major adverse cardiac event rate in the iFR and FFR groups at 30 days, 1, 2, and 5 years.

Population
This will be an international multi-centre study of 2500 patients. From population estimates, 35% of the total study population will present with stable angina and 65% will have acute coronary syndrome.

Eligibility
Patients will be eligible when the physiological severity of a stenosis within a vessel is in question. In the cases of stable angina this will be confined to the target vessel, or with acute coronary syndrome assessment this will be made in the non-culprit vessel.

Duration
Anticipated recruitment is 12 months. Follow-up will be performed at 30 days, 1, 2 and 5 years.
### 1.2 Glossary of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>BSR</td>
<td>Basal stenosis resistance index</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft surgery</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical events committee</td>
</tr>
<tr>
<td>CFR</td>
<td>Coronary flow reserve</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical research organisation</td>
</tr>
<tr>
<td>DES</td>
<td>Drug-eluting stent</td>
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<tr>
<td>FFR</td>
<td>Fractional flow reserve</td>
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<tr>
<td>HSR</td>
<td>Hyperaemic stenosis resistance index</td>
</tr>
<tr>
<td>ICTU</td>
<td>Imperial College Clinical Trials Unit</td>
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<tr>
<td>iFR</td>
<td>Instantaneous wave free ratio</td>
</tr>
<tr>
<td>iFR-adeno</td>
<td>iFR with adenosine administration over entire cardiac cycle</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiac event rate</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>SSA</td>
<td>Site specific assessment</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>TLR</td>
<td>Target lesion revascularisation</td>
</tr>
<tr>
<td>TVR</td>
<td>Target vessel revascularisation</td>
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### 1.3 Keywords

- Instantaneous wave free ratio
- Fractional flow reserve
- Percutaneous coronary intervention
2. Introduction

2.1. Background

Decisions to perform or defer percutaneous coronary intervention (PCI) on the basis of physiological stenosis severity using fractional flow reserve (FFR) are safe and reduce stent implantation rates.\(^1^\)\(^-\)\(^3^\) Despite the evidence, this modality of ischemia driven revascularisation is applied only in a small proportion of patients undergoing PCI (6-10\%).\(^4^\) The reasons for this are multifactorial, including partial or inadequate reimbursement, availability of suitable measurement equipment, or accessibility to pharmacological agents. Additionally, FFR adds on average 10 minutes to the procedure, which further discourages widespread adoption. This is particularly relevant in multi-vessel disease: multi-vessel assessment is rarely performed and when it is, takes considerably more time.

Recently a new technique for measuring physiological lesion severity, instantaneous wave-free ratio (iFR) was introduced.\(^5^\) iFR, is very similar to the conventional measurement technique, but differs crucially as it does not require the administration of pharmacological vasodilators (such as adenosine).\(^6^\)

To date, iFR has been assessed extensively over 18 months, being used in over 3000 lesions, principally in comparisons with FFR, which is commonly held as the reference standard for classifying stenoses according to haemodynamic severity.

The results of these studies suggest that iFR is a valid diagnostic tool in the catheterisation laboratory. Yet, widespread applicability of iFR in clinical practice will require studies investigating the equivalence of iFR to FFR in terms of patient outcomes when used as a clinical decision making tool in patients in whom PCI is considered as a potential treatment.

The FLAIR study is designed to thoroughly assess whether iFR-informed treatment decisions are non-inferior to FFR-informed decisions for the treatment or deferral of PCI. The following paragraphs are a discussion of the relevant aspects of iFR and FFR in order to explain the rationale for this study.
3. Study objectives

Diagnostic efficiency of iFR to characterise haemodynamic stenosis severity

1) Comparisons with FFR:
Since its introduction multiple studies using off-line analysis have assessed the utility of iFR against FFR as a reference standard. This approach is intrinsically limited by the diagnostic efficiency of FFR, which in itself is a surrogate of non-invasive ischemia detection tests. Overall these studies have shown that iFR can be used to identify ischaemia-generating stenoses, as defined with FFR. Variations in the diagnostic efficiency of iFR appear related to the robustness of the identification algorithm used. When calculated using the proprietary Imperial College-Volcano algorithm, which among other features uses ECG for identification of the wave-free period within diastole, every study has reported a classification match between iFR and FFR of 80-90%. Recently, a large international analysis demonstrated similar levels of agreement with FFR when performed on-line using the commercially available console, in real-world catheter laboratory environments (ADVISE-in Practice, TCT 2013).

2) Head to head comparisons of iFR and FFR against other diagnostic modalities:
Direct comparisons with non-invasive ischemia detection tests (single-photon emission computed tomography, SPECT) or other physiological non-FFR indices (coronary flow reserve (CFR), hyperaemic stenosis resistance index (HSR)) have the advantage of overcoming the limitations of FFR as a comparator, and allow head-to-head comparison between both techniques. The number of reported direct iFR comparisons with these modalities at present is lower than studies using FFR as a comparator.

- **Comparison with HSR**: HSR assesses coronary stenoses according to their pressure-flow velocity relationships that form the foundation of all coronary physiology. Simply, HSR indexes pressure changes by flow changes, to provide a highly stenosis-specific assessment of coronary flow limitation. iFR has been assessed in the CLARIFY study, and in a larger independent dataset against hyperaemic stenosis resistance index (HSR). In both of these studies, iFR and FFR had a diagnostic classification match in excess of 90%, while both matched with HSR around 90%. No improvement in diagnostic accuracy was seen when adenosine was administered over the entire cardiac cycle (FFR) or over the wave-free period (iFR-adeno).

- **Comparison with SPECT**: iFR has been assessed against nuclear imaging in a study reported by Van de Hoef et al. This study reported that iFR, FFR, and a flow-based resting index, basal stenosis resistance index (BSR), all had similar diagnostic power. Again no improvement was observed following administration of adenosine.

- **Comparison with CFR**: A recent study by Petracco et al. (under review, TCT 2013) compared the classification match between FFR and iFR against CFR. In this multi-centre invasive study of 216 lesions measuring coronary pressure and flow in patients undergoing physiological assessment of the severity of coronary artery disease, it suggested that the discordance rates between pressure and flow based indices were significantly improved by using iFR as opposed to FFR. This improved
accuracy was independent of the CFR threshold used (i.e. 1.7, 2.0 or 2.5), or whether clinical or ischaemic cut-points for iFR or FFR were used.

Ischaemia driven revascularisation and appropriateness of PCI

Previous studies using physiological guidance have demonstrated the value of reserving revascularisation for lesions in which ischaemia is evident.1,10 Despite improvement in stent technology and pharmacological therapies, by reserving revascularisation for lesions demonstrating evidence of ischaemia leads to a reduction in acute, medium term and late complication rates. These include peri-procedural infarction, procedural related complications, in-stent re-stenosis, and stent thrombosis. Additionally, using physiology to guide revascularisation has been shown to be cost-effective.11 Pressure-wire based assessment of lesion severity provides a rapid, simple and lesion specific measure of ischaemia, guiding revascularisation decision making.

DEFER and FAME studies linking outcomes to dichotomous cut points

FFR-guided revascularisation has been tested using both the FFR 0.75 and 0.80 cut-points. The original small validation studies against other parameters of ischaemia found that FFR<0.75 best predicted the likelihood of ischaemia.12 The DEFER study subsequently demonstrated that stenoses with FFR≥0.75 are deferred, the event rate is extremely low (around 0.2 events/year). The FAME studies1,2 developed the concept of using FFR to indicate revascularisation, but used FFR≤0.80 as the threshold for decision making. This increase in FFR threshold from FFR <0.75 to ≤0.80 was to increase sensitivity, to avoid missing ischaemic lesions falling close to the threshold of ischaemia. This range of FFR 0.75-0.80 is referred to as “FFR grey zone”, as no significant difference in outcome has been identified using different treatment strategies within this zone. The FAME studies demonstrated reduction in MACE and stent implantation rates leading to widespread adoption of the FFR≤0.80 threshold as a dichotomous cut-point for guiding revascularisation. Whilst these clinical outcome studies provide a strong evidence base, the majority of stenoses were highly significant and FFR has never been tested in a population of truly intermediate clinical stenoses, which represent its main clinical application in the cardiac catheter laboratory.

In contrast, although iFR awaits formal clinical outcome studies, it has been extensively assessed in over 3500 lesions against FFR. This has allowed the iFR cut-point best matching the FFR clinical cut-point of ≤0.80 to be established. These studies include the ADVISE-Registry, the South Korean prospective single-blinded clinical study, RESOLVE (patient level meta-analysis), and ADVISE 2 a prospective double blindered core-lab multi-centre study.7,13 In all of these studies, the iFR cut-point best matching FFR ≤0.80 has consistently been found to be within a very narrow range between iFR 0.89-0.90. In this study we will use iFR<0.90 as the dichotomous cut-point, equivalent to an FFR ≤0.80 as used in the FAME studies.
Rationale for FLAIR

1) The widespread application of iFR in clinical practice awaits studies showing the equivalence of iFR to FFR in terms of patient outcome when used as in clinical decision making in patients in whom PCI is considered as a potential treatment.

2) Although FFR has overcome the limitations of angiography as a tool to decide the appropriateness of coronary revascularisation, its overall benefit likely results from its ability to broadly differentiate between stenoses causing severe ischemia from those with negligible impact on coronary haemodynamics. This aspect is likely much more important that an extremely high diagnostic accuracy, and it is supported by the positive results of trials using either the <0.75 and ≤0.80 FFR cut-off for clinical decision-making.3,10

3) Since agreement of stenosis severity classification with iFR and FFR is extremely high outside of the FFR grey zone, it is foreseeable that iFR guided revascularisation is not inferior to that performed with FFR in terms of safety. It may have potential advantages by reducing procedural time and costs, increasing adoption of physiology-driven revascularisation.

Study hypotheses

In patients with coronary stenoses suitable for physiological assessment, the decision to perform coronary revascularisation based on iFR measurements is:

1. Non-inferior to FFR in terms of safety and efficacy
2. Superior to FFR in terms of cost-effectiveness.

Primary objective

The primary objective of the study is to assess the safety and efficacy of decision-making on coronary revascularisation based on iFR measurements of stenosis severity, compared with FFR.
4. Study design

4.1. Study review diagram

Intermediate lesion requiring physiological assessment
In ACS: intermediate non-culprit lesion

N=2500, 1:1 Randomisation

FFR guided PCI
- FFR>0.8
  - Defer PCI
- FFR≤0.8
  - Perform PCI

iFR guided PCI
- iFR≥0.9
  - Defer PCI
- iFR<0.9
  - Perform PCI

30 day, 1, 2 and 5yr follow-up

4.2 Study protocol

Following enrolment in the study patients should undergo the following:

**Recommended optimization of medical therapy:**

1. Aspirin ≥75mg OD
2. Statin therapy to target LDL below 1.8mmol/L
3. Bisoprolol ≥5mg OD (or alternative β blocker at equivalent dose)
4. Amlodipine ≥5mg OD
5. Perindopril ≥4mg OD (or alternative ACE inhibitor at equivalent dose)
6. Alternative anti-anginal medication at physician’s discretion: nicorandil, ivabradine, ranolazine

**Pre-Angiography Testing**

- Biochemistry and Haematology
  - Serum Creatinine
  - Haemoglobin,
  - Troponin (not required for patients with stable disease)
  - Fasting lipid profile
ECG

**Post-PCI / Post-Angiography Testing**

Troponin (>3 hours)

### Invasive functional assessment

The patient will be suitable for enrolment when the physiological significance of one or more stenosis is in doubt. For guidance this will typically be coronary stenosis in the range of 40-70% by visual estimation. Upon intubation of the guiding catheter, 300mcg of intracoronary nitrates will be administered to control coronary vasomotion. The pressure wire will then be inserted into the artery with the sensor at the ostium of the guiding catheter, and 5-10 beats of normalisation will be recorded.

The pressure wire will then be advanced to at least 3 vessel diameters beyond the most distal stenosis, and measurement of either iFR or FFR made according to standardised technique (see Appendix 1). After each distal measurement is made, the wire should be withdrawn with continuous recording, either under continued hyperaemia or at rest, over a 20 second period back to the ostium of the guiding catheter. A normalisation check for drift should be made and documented. Where drift is evident (Pd/Pa measured at the level of the catheter tip <0.98 or >1.02), measurements should be repeated.

### Randomisation

Each patient will be randomised to either iFR or FFR guided therapy by the online FLAIR randomisation tool. Patients will be allocated to either iFR or FFR guided revascularisation or deferral.

To ensure study blinding, and to prevent moral conflict, in the iFR guided arm, **only iFR will be recorded** and in the FFR guided arm, **only FFR will be recorded**. This will be strictly mandated, and will be considered a serious breach of study protocol if this does not occur. A screenshot recording of the physiological measurement will be used to document the methodology used.

Treatment will be guided by the randomised methodology strategy, using the iFR<0.90 threshold, and FFR ≤0.80. Any cross-over of patients will be treated as a major study protocol violation.

### Vasodilatation

Microcirculatory vasodilatation will be performed according to standard practice at that centre. High dose vasodilatation administration should be given *a priori* for all stenosis evaluation thereby removing the need for escalation of dosing. Depending on the agent used by the centre investigators will use one of the following regimes: IV adenosine (140mcg/kg/min), IC adenosine (200mcg for LCA and 150mcg for RCA), IV ATP (140mcg/kg/min) or IC papaverine (12mg LCA or 8mg for RCA) will be administered.

### Volcano S5/S5i haemodynamic settings
Each patient should have the ECG attached to the console. The FFR averaging mode should be standardised according to the mode of administration. Intravenous vasodilators (IV adenosine and ATP) should be set to using a 3-beat moving Pd/Pa average. In the case of IC vasodilators (IC adenosine and papaverine) a 2-beat moving Pd/Pa average will be used. iFR settings will be fully automated, as performed by the console.

**Sedation, PCI**

Patient should be offered sedation and analgesia as required, and as normally offered by the laboratory in which the assessment is being made. PCI should be performed in accordance with the typical practice in the local centre. Wherever possible drug eluting stents should be used, a low threshold for post-stenting optimisation should be applied.

**Repeat invasive assessment**

iFR and FFR assessment will be repeated, according to the randomisation group in all coronary lesions post PCI.

**Angiographic visual assessment**

The severity of the stenosis, lesion length, characteristics of the lesion, will be documented by visual assessment by the operator. Where disease is present but minor with coronary stenosis severity <40%, this should be documented as atheroma.

**PCI**

The stent type, and size implanted should be documented on the e-CRF.

### 4.3. Study outcome measures

**Primary Endpoint**

Major adverse cardiac events (MACE) rate in the iFR and FFR groups at 30 days, 1, 2, and 5 years.

MACE is defined as a combined endpoint of death, non-fatal myocardial infarction (MI), or unplanned revascularisation.

**Secondary Endpoints:**

1. Death (all cause) at 30 days, 1, 2 and 5 years
2. Death (cardiovascular) at 30 days, 1, 2 and 5 years
3. MI at 30 days, 1, 2 and 5 years
4. Repeat revascularisation by PCI or coronary artery bypass surgery (CABG) at 30 days, 1, 2 and 5 years
5. Costs associated to iFR or FFR guidance.
6. Quality of life (QOL) in patients included in the iFR or FFR guidance groups.
7. Cost savings of removing secondary investigations, by assessing/treating non-culprit acute coronary syndrome (ACS) at the time of index presentation.

### 4.4. Relevance and implications of the trial results

1. If the primary endpoints are equivalent between the two randomised arms, it would confirm that iFR is non-inferior to FFR for physiological guidance of PCI. This would
provide support for the use of iFR to decide on the appropriateness of revascularisation, based on coronary stenosis physiological severity, in a similar way to FFR.

2. To demonstrate the cost effectiveness of iFR/FFR guided strategy for ad hoc PCI to intermediate non-culprit ACS

3. To provide evidence to support guideline changes for use of iFR as a diagnostic tool.

4.5. Sample size/Power calculation

FLAIR event rates are based on conservative rates of stable coronary disease. However, in this study it is estimated that around 65% of patients enrolled would have non-culprit ACS. Based on current literature it is anticipated that the event rate will be around 8.5% in this group of patients, and it is likely that the study would be adequately powered to test our outcome objectives.

Using these assumptions and allowing for attrition, 2500 subjects will be recruited on a 1:1 basis to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group.

We do not expect the event rate to be different to that reported in previous studies; however, we will have >80% power to reject the null hypothesis if it is false with the current sample size for a wide range of assumptions including event rates in both arms up to 12%.

Full details of the analyses to be performed can be found in the FLAIR Statistical Analysis Plan.
5. Participant entry

5.1. Pre-registration evaluation
Recruitment
Patients undergoing assessment of one or more coronary stenosis where the physiological significance is in doubt following visual assessment. For guidance this will typically be coronary stenosis in the range of 40-70% by visual estimation.

In the case of ACS physiological assessment should only take place in non-culprit vessels once the culprit vessel has been revascularised or if a non-culprit lesion has been identified. In the case of ST-elevation myocardial infarction (STEMI) at least 48 hours must have passed prior to study enrolment.

Population estimates are that approximately 35% of the total study population will have stable angina, and 65% will present with ACS. This is reflective of the current clinical population undergoing physiological assessment in the catheter lab. An interim demographic analysis will be performed at 30 days, 3, 6, 9, and 12 months to ensure that recruitment is not becoming skewed by overly high recruitment into either the stable or ACS arm. If this occurs, investigators will be informed and encouraged to adapt their recruitment patterns according to the expected ratios.

5.2. Inclusion criteria
1. Age > 18 years of age
2. Willing to participate and able to understand, read and sign the informed consent document before the planned procedure
3. Eligible for coronary angiography and/or percutaneous coronary intervention
4. Coronary artery disease in one or more native major epicardial vessels or their branches by coronary angiogram with visually assessed de novo coronary stenosis in which the physiological severity of the lesion is in question (typically 40-70% diameter stenosis).
5. Stable angina or ACS (non-culprit vessels only and outside of primary intervention during acute STEMI).

5.3. Exclusion criteria
1. Previous CABG with patent grafts to the interrogated vessel
2. Significant left main stenosis (>50% narrowing).
3. Tandem stenoses separated by more than 10mm that require separate pressure guide wire interrogation or PCI (not to be interrogated or treated as a single stenosis)
4. Total coronary occlusions (CTOs). NOTE: Patients with CTOs can be included if i) treatment of the CTO is completed first ii) the CTO PCI is successful and iii) the physiological lesion is in another vessel.
5. Restenotic lesions
6. Haemodynamic instability at the time of intervention (heart rate < 50 beats per minute, systolic blood pressure < 90 mmHg), balloon pump
7. Significant contraindication to adenosine administration (e.g. heart block, severe asthma)
8. Contraindications to PCI or drug-eluting stent (DES) implantation
9. Heavily calcified or tortuous vessels
10. Significant hepatic or lung disease (chronic pulmonary obstructive disease), and/or malignant disease with unfavourable prognosis that may influence survival within the next 5 years.
11. Pregnancy
12. STEMI within 48 hours of procedure
13. Severe valvular heart disease
14. ACS patients in whom more than one target vessel is present.

5.4. Withdrawal criteria
Patients will be able to withdraw from the study at any time at their request.

5.5. Screening record
Any patient initially considered suitable, but then found inappropriate due to study exclusion criteria will be recorded into the screening record.
6. Clinical events

6.1. Definitions
The following clinical events will be adjudicated and will be defined as follows:

Death
All patient deaths will be documented on the case report form (CRF). The Sponsor or designee must be notified of a patient's death within 24 hours after the clinical site has knowledge of the event. The principal investigator's narrative summary of the circumstances of death is required. Autopsy results, when available, should be reported to the clinical research organization (CRO).

In the primary comparison of the two treatment strategies, all deaths will be examined. Death due to specific causes will be investigated and adjudicated by the clinical events committee (CEC). All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac Death
Any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death even in patients with co-existing and potentially fatal non cardiac disease (e.g. cancer or infection).

Vascular Cause death
Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-Cardiovascular death
Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

Myocardial Infarction

Spontaneous MI is considered an event after the first 48 hours after randomisation or PCI and after 7 days following CABG unrelated to the procedure and is defined as either:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) Ischaemic symptoms; AND/OR
   b) Development of new pathologic Q-waves on the ECG; AND/OR
   c) ECG changes indicative of ischemia (ST segment elevation or depression);

   OR

2) Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.
3) Pathological findings of an acute MI

*Periprocedural MI* is considered an event within the first 48 hours after randomisation or PCI and within 7 days following CABG:

- **Stable (Trop –ve population):**
  Peri-procedural MI in the setting of elective PCI is defined by a confirming cardiac specific biomarker (a positive value of CK-MB or Troponin I/T) on any one sample obtained after the procedure.
  - CKMB elevation >3 times upper limit of normal

  Or

  - Troponin elevation that is >5 times the 99th percentile of diagnostic value for the specific institution

- **ACS (Trop +ve population):**
  Peri-procedural MI in the setting of ACS PCI for evolving MI is defined as follows:

  When peak CK-MB or Troponin from the index infarction HAS been reached*:

  **EITHER**

  - If the biomarkers have returned to below the upper limit of normal. A new elevation in CK-MB > 3 times upper limit of normal or Troponin >5 times the 99 centile within 24 hours post index PCI

  **OR**

  - If the biomarkers have not returned to below the upper limit of normal A rise of >50% in CK-MB or Troponin above the previous nadir level

  **AND** the presence of:-

  - new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB
  - symptoms of ischemia  with ECG changes indicative of new ischemia (new ST-T changes)
  - angiographic documentation of new coronary artery occlusion or dissection

- **Peri-procedural MI within the first 7 days following CABG**

  **EITHER**
- Enzyme changes defined as one plasma level of CKMB or troponin >5x upper limit for normal AND the development of new abnormal Q-waves not present on the patient’s baseline ECG

OR

- Enzyme changes defined as one plasma level of CKMB or troponin >10x upper limit for normal

* To allow for test-test reproducibility of the biomarker assay. A peak rise in biomarker is defined as when elevation in CK-MB or Troponin levels in successive measurements are not higher than 5% above the preceding value within 24 hours post index PCI

For each MI adjudicated by the CEC, the type of MI will also be described as:

**ST-Elevation MI (STEMI)**
- Also categorise as:
  1. Q-wave (development of new Q waves in 2 or more contiguous leads)
  2. Non-Q-wave
  3. Unknown (no ECG or ECG not interpretable)

**Non-ST-Elevation MI (NSTEMI)**
- Also categorise as:
  1. Q-wave (development of new Q waves in 2 or more contiguous leads)
  2. Non-Q-wave
  3. Unknown (no ECG or ECG not interpretable)

If an angiogram is available for these events, this information should be provided to the CEC in order to help defining to which vessel the infarction is related. All infarcts that cannot be clearly attributed to a given vessel will be considered indeterminate.

**Revascularisation**

**Planned Revascularisation**
Revascularisation will be considered planned when it is decided at the time of the index procedure, based on the results of angiography and functional testing. Planned revascularisation could be performed at the time of the index procedure or within **60 days**, or within the timeline dictated by the local institution. Such revascularisation will be considered as “primary” revascularisation and will not be considered as an endpoint. The “planned” status of the revascularisation will be adjudicated.

**Unplanned Revascularisation**
Revascularisation will be considered “unplanned” when it was not performed as part of the care practice during the index procedure or identified at the time of the index procedure as a staged procedure to occur within 60 days or within the timeline dictated by the local institution. Additionally, unplanned revascularisation will require symptoms consistent
ischemia leading to either PCI or CABG. PCI and CABG will be reviewed as the revascularisation procedure, and both target lesion revascularisation and target vessel revascularisation will be assessed.

**Target lesion revascularisation (TLR)**
TLR is defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs will be classified prospectively as clinically indicated or not clinically indicated by the investigator.

A revascularisation is clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% and if one of the following occurs:

a) A positive history of recurrent angina pectoris presumably related to the target vessel.

b) Objective signs of ischemia at rest (ECG changes) or during stress/exercise test (or equivalent) presumably related to the target vessel.

c) Abnormal results of any invasive functional diagnostic test. The target lesion is defined as the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.

**Target vessel revascularisation (TVR)**
TVR is defined as any repeat PCI of any segment of the target vessel. All TVRs will be classified prospectively as clinically indicated or not clinically indicated by the investigator. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself.

**Revascularisation procedure**
Every subsequent revascularisation procedure and its indication will be reported and documented in the appropriate CRF.

**Cerebrovascular Event (stroke)**
Stroke is defined as a focal neurological deficit of central origin lasting more than 24 hours and resulting in irreversible brain damage or permanent body impairment. Type and severity of symptoms is dependent on the location and extent of brain tissue whose circulation has been involved. Strokes will be further classified as ischemic, hemorrhagic or undetermined based on imaging studies. When blood flow to the brain is interrupted because of rupture of a vessel causing bleeding into or around the brain, it is considered hemorrhagic. When a vessel that supplies the brain is blocked, the event is considered ischemic. If insufficient information is known to allow categorization, it will be considered as undetermined.

Transient ischaemic attack (TIA) events will be submitted to the CEC for final adjudication.

When events occur it is imperative to document the neurological deficit and neuroimaging results in the CRF form and send this information to the CEC.
6.2 Reporting procedures
Clinical Events Committee
The CEC is made up of interventional and non-interventional cardiologists who are not participants in the trial. The CEC is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial which are based on protocol.

The Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the treatment arm and the primary results of the trial.

The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is available. The Committee will also review and rule on all deaths that occur throughout the trial.

Reports of clinical events should be submitted within 15 days of the Chief Investigator becoming aware of the event. Serious Adverse Events will be reported if they are “Related” – that is, it resulted from administration of any of the research procedures, and “unexpected” – that is, the type of event is not an expected occurrence of the treatment processes described in this protocol. The reporting requirements for these events as described in the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be followed.

Local investigators should report any clinical events as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting clinical events: Dr Sayan Sen sayan.sen@imperial.ac.uk

Case report form
An online CRF form will be used throughout the study. This will be secure, and compatible with currently guidelines to ensure security of patient data. It will be managed via the Imperial College Clinical Trials Unit (ICTU), and data achieved securely.
7. Assessment and follow-up
Routine follow-up will be performed with a clinic visit at 30 days, 1, 2 and 5 years. The CRF should be completed, including the QOL assessment (EQ-5D-5L and Seattle Angina Questionnaire). A routine telephone call will also be made at 6 months to assess for any adverse clinical events during this period. A Schedule of Investigations can be found in Appendix 2.

8. Statistics and data analysis
Data will be summarised as mean (SD) or median (interquartile range) for skewed data. Statistical comparisons will be undertaken using a paired Student’s t-test (after log transformation if necessary) or nonparametric alternative if data are not normalised by log transformation. Kaplan-Meier survival analysis curves will be used to assess clinical event timelines.
9. Regulatory issues

9.1. Ethics approval
The Chief Investigator has obtained approval from the NRES Committee London - Hampstead Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2. Consent
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3. Risks of procedure
Standard PCI techniques will be used in the evaluation and treatment of coronary artery stenosis. All operators are highly skilled in these techniques and in handling the standard clinical complications of PCI. Therefore the risk is similar in both arms of the study.

9.4. Confidentiality
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.5. Indemnity
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

9.6. Sponsor
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.7. Funding
Volcano Corporation is providing an unrestricted educational grant to fund this study.

9.8. Audits
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).
10. Study management

The day-to-day management of the study will be co-ordinated through Imperial College London.

10.1. Study reporting
We anticipate that it will take 12 months to complete patient recruitment. We will aim to begin recruitment after Ethics review approval with first results available for presentation in 2016.

10.2. Study sites and enrolment
We anticipate the study enrolling patients through up to 40 large high volume PCI centres with experience in all of the physiological techniques proposed in this study. We envisage enrolment would take place within 12 months.

10.3. Documentation
All documentation will be collected electronically using ICTU. The ICTU has a track record for running large multi-centre international trials (e.g. ASCOT study). Clinical, and physiological records will be saved to DVD and then to a central server within ICTU in accordance with GCP guidelines.
11. Publication policy

Publication and future studies committee

A publication committee, consisting of member of the steering committee and study principal investigators will meet to formulate a publication plan to disseminate the principal findings of the study, and the primary and secondary endpoints.

Future studies, and sub-studies will be actively encouraged, by investigators and other interested parties. These will be assessed via the formal application process, and the committee will decide on the applicability and suitability of the study request. Sub-study proposals which aim to look at subset analyses of the primary and secondary endpoints will be underpowered and in general discouraged.
12. References


13. Park JJ, et al. Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis; results of an independent, blinded comparison with fractional flow reserve. *Int J Cardiol*. 2013
13. Appendices

Appendix 1 - Standard Protocol for iFR/FFR assessment

1. Flush the guide wire with enough saline to fill the dispenser hoop early during pressure wire set-up.
2. Connect the ECG and BP cables from the s5 to the haemosystem (not applicable on s5i).
3. Enter patient information including randomisation number on imaging system.
4. Select FFR on the bottom right hand corner of the screen.
5. Select the **Settings** tab on the bottom of the screen.
   - Make sure the **ECG Trace** box is **ON**.
6. Select the **Pressure** tab on the s5 or s5i.
   - Make sure the s5 or s5i has the MAP reading at 3 beats.
7. Once the ECG trace is on and the MAP reading is at 3 beats, select the **HOME** tab on the bottom of the screen to go to the “LIVE” screen.
   - Make sure there is an ECG signal on the top of the **HOME** screen.
8. Plug the guide wire into the Volcano pimette and allow it to zero.
   - It will take 10 to 15 seconds for the wire to “zero”.
   - Once wire has zeroed, the machine will display a message at the bottom of the screen that states, “Wire Zeroed, ready to insert.”
   - The wire can now be taken out of the dispenser hoop.
9. Administer 300 mcg IC Nitro-glycerine through the guide catheter, per standard lab procedures.
10. Shape the guide wire (if needed), insert and advance transducer to the end of the guide catheter.
    - Flush catheter with saline.
    - Make sure guide catheter is coaxial with vessel and AO pressure is not damped.
    - If the AO pressure trace appears damped, ideally disengage the guide catheter to ensure an optimum AO pressure trace.
    - Remove wire introducer.
    - Tighten Tuohy manually, even if the Tuohy has a haemostatic valve.
11. Wait 10 seconds, then press **NORMALISE** on the s5/S5i.
    - Make sure Pd/Pa equals 1.00.
    - If Pd/Pa does not equal 1.00, wait 10 seconds and then press NORMALISE again.
    - If the Pd/Pa ratio still does not equal 1.00, then check the height of the AO transducer to make sure it is midline to the patient and NORMALISE again.
    - If Pd/Pa ratio still will not equal 1.00, then open new wire and contact the Volcano study team member to obtain instructions on returning the guide wire to Volcano.
    - Press RECORD on the Volcano system to acquire 5-10 beats of normalisation.
12. Position the wire and pressure sensor at least 3 vessel diameters distal to the lesion to be evaluated.
    - Flush the guide catheter with saline (to prevent pressure damping).
    - Remove wire introducer.
    - Close Tuohy manually, even if it is a Tuohy with a haemostatic valve.
    - Turn transducer back on to pressure and make sure Pa pressure is not damped.
Randomisation to iFR arm
1. Switch to iFR mode.
2. Press RECORD on the Volcano system to make an iFR measurement.

Randomisation to FFR arm with IC administration
1. Select FFR on the bottom left hand corner of the screen.
2. Ensure that a 2 beat Pd/Pa average window is used to calculate FFR.
3. Press RECORD on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 10 seconds.
4. Intra-coronary adenosine bolus injection of 200mcg for LCA and 150mcg for RCA, intra-venous ATP at 140mcg/kg/min or intracoronary papaverine at 12mg for LCA and 8mg for RCA.
5. Repeat measurements of FFR twice. Escalation in dose of hyperaemic agent is not tolerated.

Randomisation to FFR arm with IV administration
1. Select FFR on the bottom left hand corner of the screen.
2. Ensure that a 3 beat Pd/Pa average window is used to calculate FFR.
3. Press RECORD on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 10 seconds.
   - Continue recording and make an FFR assessment at the same location using hyperaemia for up to 3 minutes in duration or until stable hyperemia as determined by the physician using adenosine infusion through a central or peripheral vein at 140 mcg/kg/min.

- Make sure the recording is uninterrupted for the entire duration, no injection of contrast, or saline, or disruption to the aortic pressure transducer should be made during this recording phase.
- For patients greater than 100kg, but less than or equal to 220kg, please follow hospital protocol (found in pharmacy) for non-invasive cardiac stress testing using Adenosine and make note of it in the case log. Data from patients greater than 441 pounds (200 kg) will be excluded.
- Without interruption of adenosine infusion and without opening the Tuohy haemostatic valve, perform a manual pullback manoeuvre under fluoroscopic guidance at an estimated velocity of 0.5mm/sec until the guide wire sensor has reached the tip of the guide catheter. Once the guide wire is into the guide catheter, wait for 20 seconds to check normalization. Make sure the recording is uninterrupted for the entire duration of the pullback manoeuvre.
In all protocols (iFR, IC or IV hyperaemia administration)
Once FFR measurements are complete, pull the guide wire back to the guide catheter and assess for drift of the Pd/Pa recording. If this remains at 1.00 ± 0.02, continue to randomisation. If the Pd/Pa does not equal 1.00 ± 0.02, repeat the normalisation process until it equals 1.00, and repeat the appropriate steps above to obtain a drift-free comparison. Ensure that you record at least 5-10 beats of normalisation.

Once this is complete the values of iFR or FFR should be entered into the CRF.

Depending on the physiological value of either iFR or FFR, the patient will then be randomised to either iFR or FFR guided therapy.

In the case of being assigned to the PCI arm
1. Following PCI, operators will be encouraged to make repeat measures of iFR and FFR using the same modality (either iFR or FFR) as described above starting at bullet point 9 of Standard Protocol for iFR/FFR assessment. This will not be mandated and will be at the operator’s discretion.
2. Complete an entry on the Electronic Case Report System for each iFR/FFR run.
3. At the conclusion of the case, archive the case to DVD by selecting the Patient Tab, then the ARCHIVE button, the DVD location, and finally the SAVE button.
4. The site should then remove patient-specific identifiers and assign an ID number to the DVD that matches the Case Report Form).
Catheterisation lab flowchart for iFR/FFR assessment

*Following PCI, operators will be encouraged to repeat physiological measurements according to the appropriate randomisation arm*
## Appendix 2 - Schedule of investigations

<table>
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<tr>
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FLAIR

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Prospective, multi-center, double blind, randomised study to test the safety of deferral of stenting in physiological non-significant lesions in a clinical population of intermediate stenoses using iFR and FFR

Randomised Comparison of iFR to FFR

STUDY PROTOCOL 4.3

Approval Date: 13th June 2016

Main sponsor: Imperial College London
Funders: Unrestricted Educational grant from Volcano Corporation
Study coordination centre: Imperial College London
NRES reference: 13/LO/1725
Principal Investigators: Justin Davies & Javier Escaned

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1
Sponsor:
Imperial College London is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
SL10C, 5th Floor Lab Block
Charing Cross Hospital, Fulham Palace Road London W6 8RF
Tel: 0203 311 0204
Fax: 0203 311 0203

This protocol describes the FLAIR study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

THIS PROTOCOL IS STRICTLY CONFIDENTIAL AND NOT FOR PUBLIC DISTRIBUTION.
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1. Study overview

1.1. Study summary

**Design**
Patients with one or more coronary stenoses, in which the physiological severity from coronary angiography is in question, will be randomised 1:1 to use of the instantaneous wave free ratio (iFR) or fractional flow reserve (FFR) to guide the treatment strategy for percutaneous coronary intervention (PCI).

**Aims**
To assess whether the iFR is non-inferior to FFR when used to guide treatment of coronary stenosis with PCI.

**Outcome measures**
The primary endpoint will be major adverse cardiac event rate in the iFR and FFR groups at 30 days, 1, 2, and 5 years.

**Population**
This will be an international multi-centre study of 2500 patients. From population estimates, 35% of the total study population will present with stable angina and 65% will have acute coronary syndrome.

**Eligibility**
Patients will be eligible when the physiological severity of a stenosis within a vessel is in question. In the cases of stable angina this will be confined to the target vessel, or with acute coronary syndrome assessment this will be made in the non-culprit vessel.

**Duration**
Anticipated recruitment is 12 months. Follow-up will be performed at 30 days, 1, 2 and 5 years.
1.2 Glossary of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>BSR</td>
<td>Basal stenosis resistance index</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass graft surgery</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical events committee</td>
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<tr>
<td>CFR</td>
<td>Coronary flow reserve</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CRO</td>
<td>Clinical research organisation</td>
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<tr>
<td>DES</td>
<td>Drug-eluting stent</td>
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<tr>
<td>FFR</td>
<td>Fractional flow reserve</td>
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<tr>
<td>HSR</td>
<td>Hyperaemic stenosis resistance index</td>
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<tr>
<td>ICTU</td>
<td>Imperial College Clinical Trials Unit</td>
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<tr>
<td>iFR</td>
<td>Instantaneous wave free ratio</td>
</tr>
<tr>
<td>iFR-adeno</td>
<td>iFR with adenosine administration over entire cardiac cycle</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiac event rate</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
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<tr>
<td>SSA</td>
<td>Site specific assessment</td>
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<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>TLR</td>
<td>Target lesion revascularisation</td>
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<tr>
<td>TVR</td>
<td>Target vessel revascularisation</td>
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</table>

1.3 Keywords

- Instantaneous wave free ratio
- Fractional flow reserve
- Percutaneous coronary intervention
2. Introduction

2.1. Background

Decisions to perform or defer percutaneous coronary intervention (PCI) on the basis of physiological stenosis severity using fractional flow reserve (FFR) are safe and reduce stent implantation rates.\textsuperscript{1-3} Despite the evidence, this modality of ischemia driven revascularisation is applied only in a small proportion of patients undergoing PCI (6-10%).\textsuperscript{4} The reasons for this are multifactorial, including partial or inadequate reimbursement, availability of suitable measurement equipment, or accessibility to pharmacological agents. Additionally, FFR adds on average 10 minutes to the procedure, which further discourages widespread adoption. This is particularly relevant in multi-vessel disease: multi-vessel assessment is rarely performed and when it is, takes considerably more time.

Recently a new technique for measuring physiological lesion severity, instantaneous wave-free ratio (iFR) was introduced.\textsuperscript{5} iFR, is very similar to the conventional measurement technique, but differs crucially as it does not require the administration of pharmacological vasodilators (such as adenosine).\textsuperscript{6}

To date, iFR has been assessed extensively over 18 months, being used in over 3000 lesions, principally in comparisons with FFR, which is commonly held as the reference standard for classifying stenoses according to haemodynamic severity.

The results of these studies suggest that iFR is a valid diagnostic tool in the catheterisation laboratory. Yet, widespread applicability of iFR in clinical practice will require studies investigating the equivalence of iFR to FFR in terms of patient outcomes when used as a clinical decision making tool in patients in whom PCI is considered as a potential treatment.

The FLAIR study is designed to thoroughly assess whether iFR-informed treatment decisions are non-inferior to FFR-informed decisions for the treatment or deferral of PCI. The following paragraphs are a discussion of the relevant aspects of iFR and FFR in order to explain the rationale for this study.
3. Study objectives

Diagnostic efficiency of iFR to characterise haemodynamic stenosis severity

1) Comparisons with FFR:
Since its introduction multiple studies using off-line analysis have assessed the utility of iFR against FFR as a reference standard. This approach is intrinsically limited by the diagnostic efficiency of FFR, which is itself a surrogate of non-invasive ischemia detection tests. Overall these studies have shown that iFR can be used to identify ischaemia-generating stenoses, as defined with FFR. Variations in the diagnostic efficiency of iFR appear related to the robustness of the identification algorithm used. When calculated using the proprietary Imperial College-Volcano algorithm, which among other features uses ECG for identification of the wave-free period within diastole, every study has reported a classification match between iFR and FFR of 80-90%. Recently, a large international analysis demonstrated similar levels of agreement with FFR when performed on-line using the commercially available console, in real-world catheter laboratory environments (ADVISE-in Practice, TCT 2013).

2) Head to head comparisons of iFR and FFR against other diagnostic modalities:
Direct comparisons with non-invasive ischemia detection tests (single-photon emission computed tomography, SPECT) or other physiological non-FFR indices (coronary flow reserve (CFR), hyperaemic stenosis resistance index (HSR)) have the advantage of overcoming the limitations of FFR as a comparator, and allow head-to-head comparison between both techniques. The number of reported direct iFR comparisons with these modalities at present is lower than studies using FFR as a comparator.

- **Comparison with HSR:** HSR assesses coronary stenoses according to their pressure-flow velocity relationships that form the foundation of all coronary physiology. Simply, HSR indexes pressure changes by flow changes, to provide a highly stenosis-specific assessment of coronary flow limitation. iFR has been assessed in the CLARIFY study, and in a larger independent dataset against hyperaemic stenosis resistance index (HSR). In both of these studies, iFR and FFR had a diagnostic classification match in excess of 90%, while both matched with HSR around 90%. No improvement in diagnostic accuracy was seen when adenosine was administered over the entire cardiac cycle (FFR) or over the wave-free period (iFR-adeno).

- **Comparison with SPECT:** iFR has been assessed against nuclear imaging in a study reported by Van de Hoef et al. This study reported that iFR, FFR, and a flow-based resting index, basal stenosis resistance index (BSR), all had similar diagnostic power. Again no improvement was observed following administration of adenosine.

- **Comparison with CFR:** A recent study by Petracco et al. (under review, TCT 2013) compared the classification match between FFR and iFR against CFR. In this multi-centre invasive study of 216 lesions measuring coronary pressure and flow in patients undergoing physiological assessment of the severity of coronary artery disease, it suggested that the discordance rates between pressure and flow based indices were significantly improved by using iFR as opposed to FFR. This improved accuracy was
independent of the CFR threshold used (i.e. 1.7, 2.0 or 2.5), or whether clinical or ischaemic cut-points for iFR or FFR were used.

**Ischaemia driven revascularisation and appropriateness of PCI**

Previous studies using physiological guidance have demonstrated the value of reserving revascularisation for lesions in which ischaemia is evident.\(^1\)\(^-\)\(^10\) Despite improvement in stent technology and pharmacological therapies, by reserving revascularisation for lesions demonstrating evidence of ischaemia leads to a reduction in acute, medium term and late complication rates. These include peri-procedural infarction, procedural related complications, in-stent re-stenosis, and stent thrombosis. Additionally, using physiology to guide revascularisation has been shown to be cost-effective.\(^11\) Pressure-wire based assessment of lesion severity provides a rapid, simple and lesion specific measure of ischaemia, guiding revascularisation decision making.

**DEFER and FAME studies linking outcomes to dichotomous cut points**

FFR-guided revascularisation has been tested using both the FFR 0.75 and 0.80 cut-points. The original small validation studies against other parameters of ischaemia found that FFR<0.75 best predicted the likelihood of ischaemia.\(^12\) The DEFER study subsequently demonstrated that stenoses with FFR≥0.75 are deferred, the event rate is extremely low (around 0.2 events/year). The FAME studies\(^1\)\(^-\)\(^2\) developed the concept of using FFR to indicate revascularisation, but used FFR≥0.80 as the threshold for decision making. This increase in FFR threshold from FFR <0.75 to ≤0.80 was to increase sensitivity, to avoid missing ischaemic lesions falling close to the threshold of ischaemia. This range of FFR 0.75-0.80 is referred to as “FFR grey zone”, as no significant difference in outcome has been identified using different treatment strategies within this zone. The FAME studies demonstrated reduction in MACE and stent implantation rates leading to widespread adoption of the FFR≤0.80 threshold as a dichotomous cut-point for guiding revascularisation. Whilst these clinical outcome studies provide a strong evidence base, the majority of stenoses were highly significant and FFR has never been tested in a population of truly intermediate clinical stenoses, which represent its main clinical application in the cardiac catheter laboratory.

In contrast, although iFR awaits formal clinical outcome studies, it has been extensively assessed in over 3500 lesions against FFR. This has allowed the iFR cut-point best matching the FFR clinical cut-point of ≤0.80 to be established. These studies include the ADVISE-Registry, the South Korean prospective single-blinded clinical study, RESOLVE (patient level meta-analysis), and ADVISE 2 a prospective double blinded core-lab multi-centre study.\(^7\)\(^\)\(^13\) In all of these studies, the iFR cut-point best matching FFR ≤0.80 has consistently been found to be within a very narrow range between iFR 0.89-0.90. In this study we will use iFR<0.90 as the dichotomous cut-point, equivalent to an FFR ≤0.80 as used in the FAME studies.
Rationale for FLAIR

1) The widespread application of iFR in clinical practice awaits studies showing the equivalence of iFR to FFR in terms of patient outcome when used as in clinical decision making in patients in whom PCI is considered as a potential treatment.

2) Although FFR has overcome the limitations of angiography as a tool to decide the appropriateness of coronary revascularisation, its overall benefit likely results from its ability to broadly differentiate between stenoses causing severe ischemia from those with negligible impact on coronary haemodynamics. This aspect is likely much more important than an extremely high diagnostic accuracy, and it is supported by the positive results of trials using either the <0.75 and ≤0.80 FFR cut-off for clinical decision-making.

3) Since agreement of stenosis severity classification with iFR and FFR is extremely high outside of the FFR grey zone, it is foreseeable that iFR guided revascularisation is not inferior to that performed with FFR in terms of safety. It may have potential advantages by reducing procedural time and costs, increasing adoption of physiology-driven revascularisation.

Study hypotheses

In patients with coronary stenoses suitable for physiological assessment, the decision to perform coronary revascularisation based on iFR measurements is:

1. Non-inferior to FFR in terms of safety and efficacy
2. Superior to FFR in terms of cost-effectiveness.

Primary objective

The primary objective of the study is to assess the safety and efficacy of decision-making on coronary revascularisation based on iFR measurements of stenosis severity, compared with FFR.
4. Study design

4.1. Study review diagram

Intermediate lesion requiring physiological assessment
In ACS : intermediate non-culprit lesion

N=2500, 1:1 Randomisation

FFR guided PCI

- FFR>0.8
  - Defer PCI

- FFR≤0.8
  - Perform PCI

iFR guided PCI

- iFR>0.9
  - Defer PCI

- iFR<0.9
  - Perform PCI

30 day, 1, 2 and 5yr follow-up

4.2 Study protocol

Following enrolment in the study patients should undergo the following:

**Recommended optimization of medical therapy:**

1. Aspirin ≥75mg OD
2. Statin therapy to target LDL below 1.8mmol/L
3. Bisoprolol ≥5mg OD (or alternative β blocker at equivalent dose)
4. Amlodipine ≥5mg OD
5. Perindopril ≥4mg OD (or alternative ACE inhibitor at equivalent dose)
6. Alternative anti-anginal medication at physician’s discretion: nicorandil, ivabradine, ranolazine

**Pre-Angiography Testing**

Biochemistry and Haematology
- Serum Creatinine
- Haemoglobin
- Troponin (not required for patients with stable disease)
- Fasting lipid profile

**Exclusion criteria**

- TIMI within previous 48 hours
- Previous CABG
- Contraindications to PCI/CABG
- Haemodynamic instability during PCI

30 day, 1, 2 and 5yr follow-up
Invasive functional assessment

The patient will be suitable for enrolment when the physiological significance of one or more stenosis is in doubt. For guidance this will typically be coronary stenosis in the range of 40-70% by visual estimation. Upon intubation of the guiding catheter, 300mcg of intra-coronary nitrates will be administered to control coronary vasomotion. The pressure wire will then be inserted into the artery with the sensor at the ostium of the guiding catheter, and 5-10 beats of normalisation will be recorded.

The pressure wire will then be advanced to at least 3 vessel diameters beyond the most distal stenosis, and measurement of either iFR or FFR made according to standardised technique (see Appendix 1). After each distal measurement is made, the wire should be withdrawn with continuous recording, either under continued hyperaemia or at rest, over a 20 second period back to the ostium of the guiding catheter. A normalisation check for drift should be made and documented. Where drift is evident (Pd/Pa measured at the level of the catheter tip <0.98 or >1.02), measurements should be repeated.

Randomisation

Each patient will be randomised to either iFR or FFR guided therapy by the online FLAIR randomisation tool. Patients will be allocated to either iFR or FFR guided revascularisation or deferral.

To ensure study blinding, and to prevent moral conflict, in the iFR guided arm, only iFR will be recorded and in the FFR guided arm, only FFR will be recorded. This will be strictly mandated, and will be considered a serious breach of study protocol if this does not occur. A screenshot recording of the physiological measurement will be used to document the methodology used.

Treatment will be guided by the randomised methodology strategy, using the iFR<0.90 threshold, and FFR ≤0.80. Any cross-over of patients will be treated as a major study protocol violation.

Vasodilatation

Microcirculatory vasodilatation will be performed according to standard practice at that centre. High dose vasodilatation administration should be given a priori for all stenosis evaluation thereby removing the need for escalation of dosing. Depending on the agent used by the centre investigators will use one of the following regimes: IV adenosine (140mcg/kg/min), IC adenosine (200mcg for LCA and 150mcg for RCA), IV ATP (140mcg/kg/min) or IC papaverine (12mg LCA or 8mg for RCA) will be administered.

Volcano S5/S5i haemodynamic settings
Each patient should have the ECG attached to the console. The FFR averaging mode should be standardised according to the mode of administration. Intravenous vasodilators (IV adenosine and ATP) should be set to using a 3-beat moving Pd/Pa average. In the case of IC vasodilators (IC adenosine and papaverine) a 2-beat moving Pd/Pa average will be used. iFR settings will be fully automated, as performed by the console.

**Sedation, PCI**
Patient should be offered sedation and analgesia as required, and as normally offered by the laboratory in which the assessment is being made. PCI should be performed in accordance with the typical practice in the local centre. Wherever possible drug eluting stents should be used, a low threshold for post-stenting optimisation should be applied.

**Repeat invasive assessment**
iFR and FFR assessment will be repeated, according to the randomisation group in all coronary lesions post PCI.

**Angiographic visual assessment**
The severity of the stenosis, lesion length, characteristics of the lesion, will be documented by visual assessment by the operator. Where disease is present but minor with coronary stenosis severity <40%, this should be documented as atheroma.

**PCI**
The stent type, and size implanted should be documented on the e-CRF.

### 4.3. Study outcome measures

**Primary Endpoint**
Major adverse cardiac events (MACE) rate in the iFR and FFR groups at 30 days, 1, 2, and 5 years.

MACE is defined as a combined endpoint of death, non-fatal myocardial infarction (MI), or unplanned revascularisation.

**Secondary Endpoints:**
1) Death (all cause) at 30 days, 1, 2 and 5 years
2) Death (cardiovascular) at 30 days, 1, 2 and 5 years
3) MI at 30 days, 1, 2 and 5 years
4) Repeat revascularisation by PCI or coronary artery bypass surgery (CABG) at 30 days, 1, 2 and 5 years
5) Costs associated to iFR or FFR guidance.
6) Quality of life (QOL) in patients included in the iFR or FFR guidance groups.
7) Cost savings of removing secondary investigations, by assessing/treating non-culprit acute coronary syndrome (ACS) at the time of index presentation.

### 4.4. Relevance and implications of the trial results

1. If the primary endpoints are equivalent between the two randomised arms, it would confirm that iFR is non-inferior to FFR for physiological guidance of PCI. This would...
provide support for the use of iFR to decide on the appropriateness of revascularisation, based on coronary stenosis physiological severity, in a similar way to FFR.

2. To demonstrate the cost effectiveness of iFR/FFR guided strategy for ad hoc PCI to intermediate non-culprit ACS

3. To provide evidence to support guideline changes for use of iFR as a diagnostic tool.

4.5. Sample size/Power calculation

FLAIR event rates are based on conservative rates of stable coronary disease. However, in this study it is estimated that around 65% of patients enrolled would have non-culprit ACS. Based on current literature it is anticipated that the event rate will be around 6.5% in this group of patients, and it is likely that the study would be adequately powered to test our outcome objectives.

Using these assumptions and allowing for attrition, 2500 subjects will be recruited on a 1:1 basis to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group.

We do not expect the event rate to be different to that reported in previous studies; however, we will have >80% power to reject the null hypothesis if it is false with the current sample size for a wide range of assumptions including event rates in both arms up to 12%.

Full details of the analyses to be performed can be found in the FLAIR Statistical Analysis Plan.
5. Participant entry

5.1. Pre-registration evaluation

Recruitment

Patients undergoing assessment of one or more coronary stenosis where the physiological significance is in doubt following visual assessment. For guidance this will typically be coronary stenosis in the range of 40-70% by visual estimation.

In the case of ACS physiological assessment should only take place in non-culprit vessels once the culprit vessel has been revascularised or if a non-culprit lesion has been identified. In the case of ST-elevation myocardial infarction (STEMI) at least 48 hours must have passed prior to study enrolment.

Population estimates are that approximately 35% of the total study population will have stable angina, and 65% will present with ACS. This is reflective of the current clinical population undergoing physiological assessment in the catheter lab. An interim demographic analysis will be performed at 30 days, 3, 6, 9, and 12 months to ensure that recruitment is not becoming skewed by overly high recruitment into either the stable or ACS arm. If this occurs, investigators will be informed and encouraged to adapt their recruitment patterns according to the expected ratios.

5.2. Inclusion criteria

1. Age > 18 years of age
2. Willing to participate and able to understand, read and sign the informed consent document before the planned procedure
3. Eligible for coronary angiography and/or percutaneous coronary intervention
4. Coronary artery disease in one or more native major epicardial vessels or their branches by coronary angiogram with visually assessed de novo coronary stenosis in which the physiological severity of the lesion is in question (typically 40-70% diameter stenosis).
5. Stable angina or ACS (non-culprit vessels only and outside of primary intervention during acute STEMI).

5.3. Exclusion criteria

1. Previous CABG with patent grafts to the interrogated vessel
2. Significant left main stenosis (>50% narrowing).
3. Tandem stenoses separated by more than 10mm that require separate pressure guide wire interrogation or PCI (not to be interrogated or treated as a single stenosis)
4. Total coronary occlusions (CTOs). NOTE: Patients with CTOs can be included if i) treatment of the CTO is completed first ii) the CTO PCI is successful and iii) the physiological lesion is in another vessel.
5. Restenotic lesions
6. Haemodynamic instability at the time of intervention (heart rate<50 beats per minute, systolic blood pressure <90mmHg), balloon pump
7. Significant contraindication to adenosine administration (e.g. heart block, severe asthma)
8. Contraindications to PCI or drug-eluting stent (DES) implantation
9. Heavily calcified or tortuous vessels
10. Significant hepatic or lung disease (chronic pulmonary obstructive disease), and/or malignant disease with unfavourable prognosis that may influence survival within the next 5 years.
11. Pregnancy
12. STEMI within 48 hours of procedure
13. Severe valvular heart disease
14. ACS patients in whom more than one target vessel is present.

5.4. Withdrawal criteria
Patients will be able to withdraw from the study at any time at their request.

5.5. Screening record
Any patient initially considered suitable, but then found inappropriate due to study exclusion criteria will be recorded into the screening record.
6. Clinical events

6.1. Definitions
The following clinical events will be adjudicated and will be defined as follows:

Death
All patient deaths will be documented on the case report form (CRF). The Sponsor or designee must be notified of a patient’s death within 24 hours after the clinical site has knowledge of the event. The principal investigator's narrative summary of the circumstances of death is required. Autopsy results, when available, should be reported to the clinical research organization (CRO).

In the primary comparison of the two treatment strategies, all deaths will be examined. Death due to specific causes will be investigated and adjudicated by the clinical events committee (CEC). All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac Death
Any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death even in patients with co-existing and potentially fatal non-cardiac disease (e.g. cancer or infection).

Vascular Cause death
Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-Cardiovascular death
Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

Myocardial Infarction

Spontaneous MI is considered an event after the first 48 hours after randomisation or PCI and after 7 days following CABG unrelated to the procedure and is defined as either:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) Ischaemic symptoms; AND/OR
   b) Development of new pathologic Q-waves on the ECG; AND/OR
   c) ECG changes indicative of ischemia (ST segment elevation or depression);
   OR

2) Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.

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3) Pathological findings of an acute MI

_Periprocedural MI is considered an event within the first 48 hours after randomisation or PCI and within 7 days following CABG:_

- **Stable (Trop –ve population):**
  Peri-procedural MI in the setting of elective PCI is defined by a confirming cardiac specific biomarker (a positive value of CK-MB or Troponin I/T) on any one sample obtained after the procedure.
  - CKMB elevation >3 times upper limit of normal

  Or

  - Troponin elevation that is >5 times the 99th percentile of diagnostic value for the specific institution

- **ACS (Trop +ve population):**
  Peri-procedural MI in the setting of ACS PCI for evolving MI is defined as follows:

  When peak CK-MB or Troponin from the index infarction **HAS** been reached:

  _EITHER_

  - If the biomarkers have returned to below the upper limit of normal. A new elevation in CK-MB > 3 times upper limit of normal or Troponin >5 times the 99 centile within 24 hours post index PCI

  _OR_

  - If the biomarkers have not returned to below the upper limit of normal A rise of >50% in CK-MB or Troponin above the previous nadir level

  _AND_ the presence of:-

  - new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB
  - symptoms of ischemia with ECG changes indicative of new ischemia (new ST-T changes)
  - angiographic documentation of new coronary artery occlusion or dissection

- **Peri-procedural MI within the first 7 days following CABG**

  _EITHER_
- Enzyme changes defined as one plasma level of CKMB or troponin >5x upper limit for normal AND the development of new abnormal Q-waves not present on the patient’s baseline ECG

OR

- Enzyme changes defined as one plasma level of CKMB or troponin >10x upper limit for normal

* To allow for test-test reproducibility of the biomarker assay. A peak rise in biomarker is defined as when elevation in CK-MB or Troponin levels in successive measurements are not higher than 5% above the previous value within 24 hours post index PCI.

For each MI adjudicated by the CEC, the type of MI will also be described as:

**ST-Elevation MI (STEMI)**

- Also categorise as:
  1. Q-wave (development of new Q waves in 2 or more contiguous leads)
  2. Non-Q-wave
  3. Unknown (no ECG or ECG not interpretable)

**Non-ST-Elevation MI (NSTEMI)**

- Also categorise as:
  1. Q-wave (development of new Q waves in 2 or more contiguous leads)
  2. Non-Q-wave
  3. Unknown (no ECG or ECG not interpretable)

If an angiogram is available for these events, this information should be provided to the CEC in order to help defining to which vessel the infarction is related. All infarcts that cannot be clearly attributed to a given vessel will be considered indeterminate.

**Revascularisation**

*Planned Revascularisation*

Revascularisation will be considered planned when it is decided at the time of the index procedure, based on the results of angiography and functional testing. Planned revascularisation could be performed at the time of the index procedure or within 60 days, *or within the timeline dictated by the local institution*. Such revascularisation will be considered as “primary” revascularisation and will not be considered as an endpoint. The “planned” status of the revascularisation will be adjudicated.

*Unplanned Revascularisation*

Revascularisation will be considered “unplanned” when it was not performed as part of the care practice during the index procedure or identified at the time of the index procedure as a staged procedure to occur within 60 days, *or within the timeline dictated by the local institution*. Additionally, unplanned revascularisation will require symptoms consistent
ischemia leading to either PCI or CABG. PCI and CABG will be reviewed as the revascularisation procedure, and both target lesion revascularisation and target vessel revascularisation will be assessed.

**Target lesion revascularisation (TLR)**
TLR is defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs will be classified prospectively as clinically indicated or not clinically indicated by the investigator.

A revascularisation is clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% and if one of the following occurs:

- a) A positive history of recurrent angina pectoris presumably related to the target vessel.
- b) Objective signs of ischemia at rest (ECG changes) or during stress/exercise test (or equivalent) presumably related to the target vessel.
- c) Abnormal results of any invasive functional diagnostic test. The target lesion is defined as the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.

**Target vessel revascularisation (TVR)**
TVR is defined as any repeat PCI of any segment of the target vessel. All TVRs will be classified prospectively as clinically indicated or not clinically indicated by the investigator. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself.

**Revascularisation procedure**
Every subsequent revascularisation procedure and its indication will be reported and documented in the appropriate CRF.

**Cerebrovascular Event (stroke)**
Stroke is defined as a focal neurological deficit of central origin lasting more than 24 hours and resulting in irreversible brain damage or permanent body impairment. Type and severity of symptoms is dependent on the location and extent of brain tissue whose circulation has been involved. Strokes will be further classified as ischemic, hemorrhagic or undetermined based on imaging studies. When blood flow to the brain is interrupted because of rupture of a vessel causing bleeding into or around the brain, it is considered hemorrhagic. When a vessel that supplies the brain is blocked, the event is considered ischemic. If insufficient information is known to allow categorization, it will be considered as undetermined.

**Transit** ischaemic attack (TIA) events will be submitted to the CEC for final adjudication.

When events occur it is imperative to document the neurological deficit and neuroimaging results in the CRF form and send this information to the CEC.
6.2 Reporting procedures

Clinical Events Committee

The CEC is made up of interventional and non-interventional cardiologists who are not participants in the trial. The CEC is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial which are based on protocol.

The Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the treatment arm and the primary results of the trial.

The Clinical Events Committee will meet regularly to review and adjudicate all clinical events in which the required minimum data is available. The Committee will also review and rule on all deaths that occur throughout the trial.

Reports of clinical events should be submitted within 15 days of the Chief Investigator becoming aware of the event.

Serious Adverse Events will be reported if they are “related” – that is, it resulted from administration of any of the research procedures, and “unexpected” – that is, the type of event is not an expected occurrence of the treatment processes described in this protocol. The reporting requirements for these events as described in the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be followed.

Local investigators should report any clinical events as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting clinical events: Dr Sayan Sen sayan.sen@imperial.ac.uk

Case report form

An online CRF form will be used throughout the study. This will be secure, and compatible with currently guidelines to ensure security of patient data. It will be managed via the Imperial College Clinical Trials Unit (ICTU), and data achieved securely.
7. Assessment and follow-up
Routine follow-up will be performed with a clinic visit at 30 days, 1, 2 and 5 years. The CRF should be completed, including the QOL assessment (EQ-5D-5L and Seattle Angina Questionnaire). A routine telephone call will also be made at 6 months to assess for any adverse clinical events during this period. A Schedule of Investigations can be found in Appendix 2.

8. Statistics and data analysis
Data will be summarised as mean (SD) or median (interquartile range) for skewed data. Statistical comparisons will be undertaken using a paired Student’s t-test (after log transformation if necessary) or nonparametric alternative if data are not normalised by log transformation. Kaplan-Meier survival analysis curves will be used to assess clinical event timelines.
9. Regulatory issues

9.1. Ethics approval
The Chief Investigator has obtained approval from the NRES Committee London - Hampstead Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2. Consent
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3. Risks of procedure
Standard PCI techniques will be used in the evaluation and treatment of coronary artery stenosis. All operators are highly skilled in these techniques and in handling the standard clinical complications of PCI. Therefore the risk is similar in both arms of the study.

9.4. Confidentiality
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

9.5. Indemnity
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

9.6. Sponsor
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.7. Funding
Volcano Corporation is providing an unrestricted educational grant to fund this study.

9.8. Audits
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).
10. Study management

The day-to-day management of the study will be co-ordinated through Imperial College London.

10.1. Study reporting

We anticipate that it will take 12 months to complete patient recruitment. We will aim to begin recruitment after Ethics review approval with first results available for presentation in 2016.

10.2. Study sites and enrolment

We anticipate the study enrolling patients through up to 40 large high volume PCI centres with experience in all of the physiological techniques proposed in this study. We envisage enrolment would take place within 12 months.

10.3. Documentation

All documentation will be collected electronically using ICTU. The ICTU has a track record for running large multi-centre international trials (e.g. ASCOT study). Clinical, and physiological records will be saved to DVD and then to a central server within ICTU in accordance with GCP guidelines.
11. Publication policy

Publication and future studies committee
A publication committee, consisting of members of the steering committee and study principal investigators will meet to formulate a publication plan to disseminate the principal findings of the study, and the primary and secondary endpoints.

Future studies, and sub-studies will be actively encouraged, by investigators and other interested parties. These will be assessed via the formal application process, and the committee will decide on the applicability and suitability of the study request. Sub-study proposals which aim to look at subset analyses of the primary and secondary endpoints will be underpowered and in general discouraged.
12. References

13. Park JJ, et al. Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis; results of an independent, blinded comparison with fractional flow reserve. *Int J Cardiol.* 2013
13. Appendices

Appendix 1 - Standard Protocol for iFR/FFR assessment

1. Flush the guide wire with enough saline to fill the dispenser hoop early during pressure wire set-up.
2. Connect the ECG and BP cables from the s5 to the haemosystem (not applicable on s5i).
3. Enter patient information including randomisation number on imaging system.
4. Select FFR on the bottom right hand corner of the screen.
5. Select the Settings tab on the bottom of the screen.
   - Make sure the ECG Trace box is ON.
6. Select the Pressure tab on the s5 or s5i.
   - Make sure the s5 or s5i has the MAP reading at 3 beats.
7. Once the ECG trace is on and the MAP reading is at 3 beats, select the HOME tab on the bottom of the screen to go to the “LIVE” screen.
   - Make sure there is an ECG signal on the top of the HOME screen.
8. Plug the guide wire into the Volcano pinmete and allow it to zero.
   - It will take 10 to 15 seconds for the wire to “zero”.
   - Once wire has zeroed, the machine will display a message at the bottom of the screen that states, “Wire Zeroed, ready to insert.”
   - The wire can now be taken out of the dispenser hoop.
9. Administer 300 mcg IC Nitro-glycerine through the guide catheter, per standard lab procedures.
10. Shape the guide wire (if needed), insert and advance transducer to the end of the guide catheter.
    - Flush catheter with saline.
    - Make sure guide catheter is coaxial with vessel and AO pressure is not damped.
    - If the AO pressure trace appears damped, ideally disengage the guide catheter to ensure an optimum AO pressure trace.
    - Remove wire introducer.
    - Tighten Tuohy manually, even if the Tuohy has a haemostatic valve.
11. Wait 10 seconds, then press NORMALISE on the s5/S5i.
    - Make sure Pd/Pa equals 1.00.
    - If Pd/Pa does not equal 1.00, wait 10 seconds and then press NORMALISE again.
    - If the Pd/Pa ratio still does not equal 1.00, then check the height of the AO transducer to make sure it is midline to the patient and NORMALISE again.
    - If Pd/Pa ratio still will not equal 1.00, then open new wire and contact the Volcano study team member to obtain instructions on returning the guide wire to Volcano.
    - Press RECORD on the Volcano system to acquire 5-10 beats of normalisation.
12. Position the wire and pressure sensor at least 3 vessel diameters distal to the lesion to be evaluated.
    - Flush the guide catheter with saline (to prevent pressure damping).
    - Remove wire introducer.
    - Close Tuohy manually, even if it is a Tuohy with a haemostatic valve.
    - Turn transducer back on to pressure and make sure Pa pressure is not damped.
**Randomisation to iFR arm**
1. Switch to iFR mode.
2. Press **RECORD** on the Volcano system to make an iFR measurement.

**Randomisation to FFR arm with IC administration**
1. Select FFR on the bottom left hand corner of the screen.
2. Ensure that a 2 beat Pd/Pa average window is used to calculate FFR.
3. Press **RECORD** on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 10 seconds.
4. **Intra-coronary adenosine bolus injection of 200mcg for LCA and 150mcg for RCA, intra-venous ATP at 140mcg/kg/min or intracoronary papaverine at 12mg for LCA and 8mg for RCA.**
5. Repeat measurements of **FFR** twice. Escalation in dose of hyperaemic agent is not tolerated.

**Randomisation to FFR arm with IV administration**
1. Select FFR on the bottom left hand corner of the screen.
2. Ensure that a 3 beat Pd/Pa average window is used to calculate FFR.
3. Press **RECORD** on the Volcano system and make a Baseline assessment of the stenosis (without adenosine) for 10 seconds.
   - Continue recording and make an FFR assessment at the same location using hyperaemia for up to 3 minutes in duration or until stable hyperemia as determined by the physician using adenosine infusion through a central or peripheral vein at 140 mcg/kg/min.
   - Make sure the recording is uninterrupted for the entire duration, no injection of contrast, or saline, or disruption to the aortic pressure transducer should be made during this recording phase.
   - For patients greater than 100kg, but less than or equal to 220kg, please follow hospital protocol (found in pharmacy) for non-invasive cardiac stress testing using Adenosine and make note of it in the case log. Data from patients greater than 441 pounds (200 kg) will be excluded.
   - Without interruption of adenosine infusion and without opening the Tuohy haemostatic valve, perform a manual pullback manoeuvre under fluoroscopic guidance at an estimated velocity of 0.5mm/sec until the guide wire sensor has reached the tip of the guide catheter. Once the guide wire is into the guide catheter, wait for 20 seconds to check normalization. **Make sure the recording is uninterrupted for the entire duration of the pullback manoeuvre.**
In all protocols (iFR, IC or IV hyperaemia administration)

Once FFR measurements are complete, pull the guide wire back to the guide catheter and assess for drift of the Pd/Pa recording. If this remains at 1.00 ± 0.02, continue to randomisation. If the Pd/Pa does not equal 1.00 ± 0.02, repeat the normalisation process until it equals 1.00, and repeat the appropriate steps above to obtain a drift-free comparison. Ensure that you record at least 5-10 beats of normalisation.

Once this is complete the values of iFR or FFR should be entered into the CRF.

Depending on the physiological value of either iFR or FFR, the patient will then be randomised to either iFR or FFR guided therapy.

In the case of being assigned to the PCI arm

1. Following PCI, operators will be encouraged to make repeat measures of iFR and FFR using the same modality (either iFR or FFR) as described above starting at bullet point 9 of Standard Protocol for iFR/FFR assessment. This will not be mandated and will be at the operator’s discretion.

2. Complete an entry on the Electronic Case Report System for each iFR/FFR run.

3. At the conclusion of the case, archive the case to DVD by selecting the Patient Tab, then the ARCHIVE button, the DVD location, and finally the SAVE button.

4. The site should then remove patient-specific identifiers and assign an ID number to the DVD that matches the Case Report Form).
* Following PCI, operators will be encouraged to repeat physiological measurements according to the appropriate randomisation arm
## Appendix 2 - Schedule of investigations

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- We will administer medications to open up the small blood vessels in the heart. These are routinely used every day in the cardiac catheter laboratory and maybe used in the clinical stages of your procedure. The risk of using such drugs are very low, but, in some patients it may cause a short lived chest discomfort which usually disappears within 3-5 seconds of stopping the drug. In order to administer the adenosine we will place a second tube at the top of the leg using local anaesthetic, which should not cause any discomfort. The measurements would have been necessary as part of the normal clinical process so will not extend the length of the procedure.
10 October 2013

Study Chairman: Manesh Patel
Medical Lead: Sayan Sen
Steering Committee: Eric Van Belle, Farrel Hellig, Raj Kharbanda, Martin Mates, Hitoshi Matsuo, and Nob Tanaka

Column Break

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Clinical Events Committee: TBC

Head of Trial monitoring oversight: Neil Poulter, Imperial College Clinical Trials Unit

Study coordination centre: Imperial College London

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Fax: 02075941706
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Clinical Queries:
Clinical queries should be directed to Emma Coady (e.coady@imperial.ac.uk) or Sayan Sen (sayan.sen@imperial.ac.uk) who will direct the query to the appropriate person.
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You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?
You are suffering from chest pain or shortness of breath. This may have occurred at rest or on exertion and may be due to a narrowing of one of your heart arteries. One way of treating these narrowing is with stents (small metal tubes that are inserted into the coronary artery during angiography to unblock the narrowing). This is why your doctor has recommended you undergo angiography.

However, not all heart artery narrowings need to be treated as they may not be the cause of your symptoms. To help doctors decide which narrowings need treatment and which can be
left alone fine wires are passed into the arteries and pressure measurements are made during angiography. This is the recommended practice for treating patients with your condition because it has been shown to reduce the future need for repeat stents. Currently during these measurements a drug needs to be given so that the measurements are accurate. As a result some patients who cannot be given the drug cannot benefit from this test. Furthermore the drug is simply not readily available in some countries. To increase the number of patients in which such vital technology can be used we have developed a new way of making these measurements that does not require an extra drug to be given. It has been demonstrated to be equivalent to the older technique in smaller studies. It has been awarded full regulatory approval in the European Union for use in patients like you. The purpose of this study is to compare our new technique – called iFR (instantaneous wave-free ratio) to the old technique called FFR (Fractional Flow Reserve). Therefore half the patients in this study will have their treatment guided by iFR and half the patients by FFR. If iFR is found to be equivalent to FFR it would enable more patients to benefit from such treatment.

**Why have I been chosen?**
You have been chosen because you are scheduled to have angioplasty and are not severely asthmatic. As a normal part of this procedure, a small tube will be inserted into the main artery in the groin or wrist. This means that at the time of your procedure, we can use this tube to pass our wires into your heart arteries and safely take measurements in your heart’s blood vessels. These measurements will guide the doctors’ treatment of your condition.

**Do I have to take part?**
No. Your decision whether to participate in this study is entirely voluntary. You have the right to refuse as well as to withdraw your participation at any time (even if you agree today) without giving a reason. If you decide not to participate or to withdraw, it will not affect the quality of your care or treatment, nor the relationship you have with your doctor and nursing team.

**What will happen to me if I take part?**
The coronary angiogram will occur as routinely performed. We will enter the artery at the top of your leg or via the wrist with a small tube, local anaesthetic will be used and this should not cause any discomfort. During the procedure the doctor may find a narrowing that needs closer inspection with a special pressure wire. This is a routine investigation that is performed commonly in patients with your condition. The wire will be passed into the heart arteries via the tube already in the wrist/leg. Measurements will be taken. During the measurements a drug to open up the small vessels may need to be infused. This may require a small tube to be placed at the top of the leg next to the first tube or the drug can be injected directly into the coronary artery via the existing tubes. In total the process will add 10 minutes to the procedure. The measurements will not prolong your recovery from the procedure. You will
receive treatment according to the result of the pressure measurement either iFR or FFR. At the end of the procedure the wires and tubes will be removed.

Our clinical team will contact you via telephone 30 days and 6 months after the procedure. Over the next five years we will then be contacting you annually to find out how you have been keeping. Wherever possible this contact will be co-ordinated with your routine hospital visit.

What are the possible side effects, risks and disadvantages of taking part?

We do not expect you to experience any significant side effects as a result of participating in this study. During the measurements we will administering medications to open up the small blood vessels in the heart. These are routinely used every day in the cardiac catheter laboratory and maybe used in the clinical stages of your procedure. The risk of using such drugs are very low, but, in some patients it may cause a short lived chest discomfort which usually disappears within 3-5 seconds of stopping the drug. In order to administer the adenosine we will place a second tube at the top of the leg using local anaesthetic, which should not cause any discomfort. The measurements would have been necessary as part of the normal clinical process so will not extend the length of the procedure.

There is a very low risk (less than 1 in 1000) that the wire used to make the measurements will cause any damage to your blood vessels. The risk of death, heart attack or stroke is the same as your routine angiogram. This risk is minimised as the measurements are performed by an experienced senior Consultant Cardiologist. We will place the wires under x-ray guidance; the mean effective dose from this procedure is equivalent to 4.4 years of natural background radiation.

What are the possible benefits of taking part?
You will not directly benefit from this study, but the information we gain will give a much better understanding of whether there is a need to continue to give drugs to open the small blood vessels as part of the routine assessment of the diagnosis of coronary artery disease.

What if something goes wrong?
Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible
to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation. If you are harmed due to someone’s negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Justin Davies 020 7594 1264). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

**Will my taking part in this study be kept confidential?**

If you agree to take part, data collected about you will be entered onto a computer. However, all data entered will be in an anonymous format and any information obtained from this investigation that can be identified will remain confidential. Relevant sections of your medical notes & data collected during the study may be looked at by individuals from Imperial College, from regulatory authorities or from Imperial NHS trust, where it is relevant to you taking part in this research. We will ask for your permission for these individuals to have access to your records. Your GP will be informed that you are participating in this study.

**What will happen to the results of the research study?**

Scientific data from this study may be presented at meetings and published so that the information can be used to help others, but your participation in the study will not be made known and will be kept strictly confidential. If you wish, we will give you a summary of the results.

**Who is sponsoring the study?**

The study will be sponsored by Imperial College London.

**Who is funding the research?**

The study will be funded by an unrestricted educational grant from Volcano Corporation to the Imperial College London.

**Who has reviewed the study?**

This study has been reviewed and given a favourable ethical opinion by the Outer London Research Ethics Committee.

If you have any further questions please do not hesitate to contact:
Dr Sayan Sen on 0207 594 1264, sayan.sen@imperial.ac.uk, or Dr Justin Davies on 0207 594 1264, justin.davies@imperial.ac.uk

Thank you for taking the time to consider participating in this study
CONSENT FORM

(Patients scheduled for pressure-flow wire measurements during coronary angiography/ angioplasty)

The FLAIR Study

Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation

Chief Investigator: Dr Justin Davies & Dr Javier Escaned
Local principal investigator: Dr Iqbal Malik

1. I have read the Patient Information Sheet (Version 1.3 Date 8/9/2013) for patients scheduled for the FLAIR Study
   Yes ..... No ..... 

2. I have received enough information about this study, had the opportunity to ask questions and I am satisfied with the answers to my questions.
   Yes ..... No ..... 

3. I have spoken to Dr.................................
   Yes ..... No ..... 

4. I understand that I am free to withdraw from the study at any time without giving a reason and without affecting my future care.
   Yes ..... No ..... 

5. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from Imperial College, from regulatory authorities or from the NHS Trust. I give permission for these individuals to access my records.
   Yes ..... No ..... 

6. I agree to take part in this research study.
   Yes ..... No ..... 

7. I agree to my GP being informed about my participation in this research study.
   Yes ..... No ..... 

Signature.................................................. ..............................................

Date..........................
Name (block capitals).................................................................

Signature of Study Investigator.................................................... Date.............

Name (block capitals).................................................................
Dear Doctor

Re:

Name:
DOB:
Address:

Your patient has agreed to participate in the following research study at the Imperial College London:

Prospective, multi-center, double blind, randomised study to test the safety of deferral of stenting in physiological non-significant lesions in a clinical population of intermediate stenoses using iFR and FFR

Background and Aims

Physiologically guided revascularisation has been demonstrated to be superior to angiographically guided revascularisation for coronary artery disease. The most commonly used index to guide stenting currently is Fractional Flow Reserve.
Fractional Flow Reserve has been demonstrated to improve clinical outcomes and reduce healthcare costs when used to guide coronary artery revascularisation. As a result it has a Class 1A recommendation in European Guidelines. However adoption is poor. One of the reasons for this is the requirement for the administration of adenosine during its measurement. This adds time and cost to the procedure. Furthermore its administration causes transient discomfort to patients and cannot be given to all patients due relative and absolute contra-indications to adenosine. It has been highlighted as one of the key reasons hindering adoption of FFR guided revascularisation.

We have developed a new way of assessing coronary stenoses called the instantaneous wave-free ratio (iFR). This uses existing pressure wire technology to assess stenosis severity without the need for drugs like adenosine. It has been demonstrated to have equivalent diagnostic agreement with FFR in terms of identifying ischaemia. The aim of this study is to determine if patients who have treatment guided by iFR have equivalent long term clinical outcomes as those whose treatment is guided by FFR. It is an outcome-based study that will follow patients at intervals for up to 5 years. Primary outcomes will be death, myocardial infarction, stroke and repeat revascularisation.

**What is involved for your patient**

The study protocol has been refined to minimise any inconvenience for your patient. During their planned angiographic procedure consenting patients will be randomised to either an iFR or FFR guided treatment strategy. Physiological measurements will be made with a pressure sensor tipped wires designed for such assessments. These are of the same calibre as normal angioplasty wires and will passed into the coronary artery. All measurements will be made via the sheaths and guide catheters that are required for the routine angiographic procedure. It should be noted that the physiology of the coronary disease of the patient would have required such an assessment as routine clinical care and therefore the patient will not be exposed to any increased risk during the procedure.

Your patient will then be followed at 30 days, 6 months and one year. Thereafter they will be followed annually for a total of 5 years after the index procedure. All of the information that we take will be fully anonymised. The patients have been given an information sheet explaining the study further.

**Potential Benefits**

This study will not benefit your patient directly. We expect that the information that we gain from this study will however contribute to improvements in the adoption of physiologically guided revascularisation.

**Potential Side effects**
The side effects will be the same as that for a standard angioplasty procedure that is clinically required by your patient.

It is possible that one arm of the study has significantly better outcomes than the other. All events and interim analyses will be reviewed by an independent safety monitoring board and if necessary the trial will be halted. All patients and their GPs will be notified if this is the case.

**Adverse events and further information**

I would be grateful if you could report any adverse events to me on the address below.

Please do not hesitate to contact me for any further information on the following address:

Dr Sayan Sen  
FLAIR Medical Lead  
Clinical Lecturer  
Imperial College Healthcare NHS Trust  
Hammersmith Hospital  
Cardiology Dept.  
Du Cane Road  
W12 0HS

Telephone. 0207 594 1264  
E-mail. sayan.sen@imperial.ac.uk
Statistical Analysis Plan (SAP)

FLAIR

Study Investigators:
Justin Davies & Javier Escaned
Patrick Serruys & Manesh Patel

SAP Working Group:
Trial statistician: Hakim-Moulay Dehbi
Trial manager: Elisa Voros

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<td>Hakim-Moulay Dehbi</td>
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1. Introduction

The purpose of this Statistical Analysis Plan is to provide a detailed statement of the intended statistical analyses that will be performed on data collected in the FLAIR trial.

This document is intended to be stand-alone from the protocol and adhere to the main points in the analysis summary specified in the protocol. However, the Statistical Analysis Plan can undergo revision outside of the protocol. It is not anticipated that revisions to the Statistical Analysis Plan that are in the spirit of the specified protocol analysis would require review by an ethics committee.

1.1 Study rationale

Fractional flow reserve (FFR) is commonly held as the reference standard for classifying stenoses according to haemodynamic severity. FFR overcomes the limitations of angiography as a tool to decide the appropriateness of coronary revascularization. The overall benefit of FFR likely results from its ability to broadly differentiate between stenoses causing severe ischemia from those with negligible impact on coronary haemodynamics. FFR is used only in a small proportion of patients undergoing PCI (6% to 10%) (Pijls NH, 2013). The reasons for this are multifactorial, including partial or inadequate reimbursement, availability of suitable measurement equipment, or accessibility to pharmacological agents. Additionally, FFR adds on average 10 minutes to the procedure, which further discourages widespread adoption.

A new technique for measuring physiological lesion severity, instantaneous wave-free ratio (iFR) was introduced recently (Sen S, 2012). iFR, is very similar to the conventional measurement technique, but differs crucially as it does not require the administration of pharmacological vasodilators, such as adenosine (Ntalianis A, 2010). iFR may therefore have potential advantages by reducing procedural time and costs, increasing adoption of physiology-driven revascularization.

To date, iFR has been assessed extensively over 18 months, being used in over 3000 lesions, principally in comparisons with FFR. The results of these studies suggest that iFR is a valid diagnostic tool in the catheterisation laboratory. Yet, widespread applicability of iFR in clinical practice will require studies investigating the equivalence of iFR to FFR in terms of patient outcomes when used as a clinical decision making tool in patients in whom percutaneous coronary intervention (PCI) is considered as a potential treatment.

1.2 Study hypothesis

In patients with coronary stenoses suitable for physiological assessment, the decision to perform coronary revascularisation based on iFR measurements is:

1. Non-inferior to FFR in terms of efficacy.
2. Superior to FFR in terms of cost-effectiveness.

1.3 Study objectives

1.3.1 Primary objective: efficacy

To assess whether the instantaneous wave-free ratio (iFR) is non-inferior to fractional flow reserve (FFR) when used to guide treatment of coronary stenosis with PCI.
1.3.2 Secondary objective: cost-effectiveness
To assess whether iFR has potential advantages over FFR in reducing procedural time and costs.

1.4 Study endpoints

1.4.1 Primary endpoint
The primary endpoint is related to the primary objective of the study, i.e. to assess the efficacy of iFR compared to FFR as measured by major adverse cardiac events (MACE) at 1 year. MACE is defined as a combined endpoint of death from all causes, non-fatal myocardial infarction (MI), or unplanned revascularization.

For the avoidance of doubt, the 1-year time point is the principal time point. The other time points at which MACE rates will compared between the iFR and FFR groups are 30 days, 2 and 5 years.

1.4.2 Secondary endpoints
The secondary endpoints are related to the primary and secondary objectives of the study.

- Efficacy:

  1) Death (all cause) at 30 days, 1, 2 and 5 years; 2) Death (cardiovascular) at 30 days, 1, 2 and 5 years; 3) MI at 30 days, 1, 2 and 5 years; 4) Repeat revascularization by PCI or coronary artery bypass surgery (CABG) at 30 days, 1, 2 and 5 years. A distinction will be made between those revascularized based on an assessment of ischemia and all revascularizations.

- Cost-effectiveness:

  1) Costs associated to iFR or FFR guidance; 2) Quality of life (QOL) in patients included in the iFR or FFR groups; 3) Cost savings of removing secondary investigations, by assessing/treating non-culprit acute coronary syndrome (ACS) at the time of index presentation.

1.5 Study population
The study population is composed of patients with one or more coronary stenoses, in which the physiological severity from coronary angiography is in question.

1.6 Study design
The study is a prospective international multi-centre randomized controlled trial (RCT).

1.7 Sample size
The sample size is based on an assumed annual event rate in a predominate ACS population of 8.5%. Allowing for attrition, the sample size is 2500 patients. This sample size provides 90% power, at a significance level of 5%, that the upper limit of a one-sided 95% confidence interval (or equivalently a two-sided 90% confidence interval) will exclude a difference in MACE at 1 year in favor of FFR of more than 3.4 percentage points. These powering assumptions and statistical tests are in keeping with other pivotal studies in the field such as iFR-SwedeHeart (NCT:NCT02166736).
1.8 Randomization

1:1 to iFR or FFR to guide the treatment strategy for PCI using the online FLAIR randomization tool (see document called “FLAIR AND SRUB Final Version December 2014.doc”). There is no stratification variables.

1.9 Schedule of time

Routine follow-up will be performed with a clinic visit at 30 days, 1, 2 and 5 years. The CRF should be completed, including the QOL assessment (EQ-5D-5L and Seattle Angina Questionnaire). A routine telephone call will also be made at 6 months to assess for any adverse clinical events during this period.

2. General considerations

2.1 Definition of population for analysis
The study population will comprise all participants who were randomized.

2.2 Data management

OpenClinica online web based software was used for data capture, extraction and visualisation. This software package provides built in tools for audit, validation and log of changes. OpenClinica is a 21 CFR Part 11 compliant system. More details are available in the Data Management Plan.

2.3 Losses to follow-up and withdrawals

All randomized participants will be followed-up, regardless of whether or not they underwent allocated treatment.

Subjects who withdraw their consent for follow-up status to be collected will be censored at that point. Subjects who are lost to follow-up will be censored in the Kaplan Meier and Cox regression analyses at last follow-up visit.

2.4 Protocol violations

Any cross-over of patients will be treated as a major protocol violation. The summary of protocol violations will be reported in both arms. Protocol violations include cross-over from one arm to another, violating decision making form physiological measurement, inclusion of non-eligible patients, or non-performance of physiological assessment following randomization.

2.5 Interim analysis

No formal interim analyses are planned. Informal interim analyses will be performed if requested by the Data Monitoring Committee (DMC) but findings will be made available to member of the DMC only. Unless advised by the DMC in response to clear evidence of benefit or hazard, the Steering Committee, collaborators, participants and all clinical staff (except those who provide the confidential...
analyses to the DMC) will remain blind to the allocation until the end of the study unless a decision to unblind is made by the DMC.

2.6 Deviations from the statistical analysis plan
All the deviation from the SAP will be reported in the final analysis report. If problems or fundamental issues become apparent in the on-going checking that forms part of the statistical analysis, the trial statistician will raise these with a senior statistician and will consult with other appropriate individuals if necessary. Any such action and subsequent decisions will be documented in the final statistical analysis report.

2.7 Presentation of results
Early presentation of results at conferences may be done in keeping with the endpoints timeline. The main analyses (see sections 3.5 and 3.6) will be reported in clinical journals.

3. Statistical plan

3.1 General methodology
All statistical tests will be one-tailed and a 5% significance level maintained throughout the analyses.

The following strategy will apply in terms of testing order:

1. IFR will be compared to FFR for MACE at 1 year for non-inferiority;

2. If non-inferiority is met: IFR will be tested against FFR for superiority of MACE, with standard 2-sided testing with p<0.05 as significant;

3. If superiority is met: a closed testing procedure will be carried out to test for secondary efficacy endpoints (in the order of endpoints as described above).

4. If superiority is not met: the cost-effectiveness of the two tested arms (IFR vs. FFR) will be evaluated. A closed testing procedure will be carried out to test for secondary efficacy endpoints (in the order of endpoints as described above).

No subgroup analysis and no exploratory analysis are foreseen.

The Stata software version 14 will be employed to perform all analyses, possibly complemented by R if required.

3.2 Baseline demographics
Summaries of continuous variables will be presented as means and standard deviations (or medians and inter-quartiles for skewed data). Categorical variables will be presented as frequencies and percentages.
3.3 Population of analysis sets
All treatment evaluations will be performed on the principles of intention to treat (ITT) and per-protocol (PP).

ITT analysis implies that the FLAIR participants will be analyzed according to their randomization groups regardless of the actual assessment method (iFR or FFR) used.

PP analysis implies that protocol compliant FLAIR participants will be analyzed according to the actual assessment method employed.

3.4 Treatment of missing data
Complete case analyses will be performed. There will be no data imputation for missing data in the primary endpoint and the secondary endpoints. However, the level and pattern of the missing data in the baseline variables and outcomes will be reported. The potential causes of any absent data will be investigated and documented as far as possible.

3.5 Primary endpoint analysis
The primary endpoint will be analyzed based on relative risk of MACE at 1 year in the two arms, using Pearson’s chi-squared test. The non-inferiority margin is defined as 3.4 percentage points in favor of FFR.

An adjusted analysis for center effects will be considered, using: a) a hierarchical model and, b) an adjustment using a categorical variable in the non-hierarchical model.

An additional analysis will be based on a landmark point of 7 days after randomization.

Once longer term follow-up is available, time-to-event analysis will be by the Kaplan-Meier method. The log-rank test would be employed for the between-group comparison of the primary efficacy endpoint. Cox survival models would be used to derive hazard ratios (HR) and 95% confidence intervals. Testing of validity of proportional hazard assumption would be done using Schoenfeld residuals. Additionally, flexible parametric survival models might be used to model the primary endpoint. Hazard rates, hazard ratios and corresponding 95% confidence intervals will be derived from the flexible parametric survival models.

3.6 Secondary endpoints analysis
- Efficacy endpoints:

Exactly the same statistical methods as for the primary endpoint will be employed.

- Cost-effectiveness endpoints:

Costs:
We will use ANOVA (or the non-parametric version) to compare iFR vs FFR in terms of costs.
Additionally, deferred patients will be compared to treated patients. Within the group of treated patients, groups based on the number of vessels treated will be compared.

QoL:
QoL will be assessed by the Seattle Angina questionnaire and the EQ-5D-5L. During the cathlab admission episode, patients will assess the quality of the experience by a graded score. The arms will be compared using non-parametric tests.
### Table 1*: patient characteristics

<table>
<thead>
<tr>
<th>Table 1*: patient characteristics</th>
<th>iFR (N=)</th>
<th>FFR (N=)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of vessels affected:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
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<tr>
<td>Disease type</td>
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<td>Diabetes</td>
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<td>Smoking</td>
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<td>Hypertension</td>
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<tr>
<td>hypercholesterolaemia</td>
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<td>Previous MI</td>
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<td></td>
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<tr>
<td>Previous PCI</td>
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<td>1</td>
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<td>2</td>
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<td>BMI</td>
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*: Summaries of continuous variables will be presented as means and standard deviations or medians and inter-quartiles for skewed data, and categorical variables as frequencies and percentages.

Table 2a) Number of events, in absolute terms and percentages, for the primary endpoint and its individual components (i.e. secondary efficacy endpoints 1-4) by treatment group, and p-value.

<table>
<thead>
<tr>
<th>Table 2a: clinical events</th>
<th>IFR</th>
<th>FFR</th>
<th>Relative risk</th>
<th>P-value</th>
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<tbody>
<tr>
<td>MACE</td>
<td>x (%)</td>
<td>y (%)</td>
<td>RR (95% CI)</td>
<td>x.xx</td>
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<tr>
<td>All-cause death</td>
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<td></td>
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<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
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<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unplanned revascularization</td>
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</tbody>
</table>
Table 2b) Landmark analysis at 7 days: number of events, in absolute terms and percentages, for the primary endpoint and its individual components (i.e. secondary efficacy endpoints 1-4) by treatment group, and p-value.

<table>
<thead>
<tr>
<th>Table 2b: landmark analysis for clinical events</th>
<th>IFR</th>
<th>FFR</th>
<th>Relative risk</th>
<th>P-value</th>
<th>P-value for interaction</th>
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</thead>
<tbody>
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<td>MACE</td>
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<tr>
<td>Up to 7 days</td>
<td>x (%)</td>
<td>y (%)</td>
<td>RR (95% CI)</td>
<td>x.xx</td>
<td></td>
</tr>
<tr>
<td>After 7 days</td>
<td>x (%)</td>
<td>y (%)</td>
<td>RR (95% CI)</td>
<td>x.xx</td>
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</tr>
<tr>
<td>All-cause death</td>
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<td></td>
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<tr>
<td>Up to 7 days</td>
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<tr>
<td>After 7 days</td>
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<tr>
<td>Cardiovascular death</td>
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<td>Up to 7 days</td>
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<td>After 7 days</td>
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<td>MI</td>
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<tr>
<td>After 7 days</td>
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<tr>
<td>Unplanned revascularization</td>
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<td>Up to 7 days</td>
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<td>After 7 days</td>
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</table>
Table 3) QoL, including Seattle Angina, EQ-5D-5L and the cathlab patient experience score, will be compared between the two arms.

<table>
<thead>
<tr>
<th>Table 3: QoL</th>
<th>IFR</th>
<th>FFR</th>
<th>Treatment effect</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Seattle Angina questions</td>
<td>x (sd)</td>
<td>y (sd)</td>
<td>Treatment effect (95% CI)</td>
<td>x.xx</td>
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<tr>
<td>(multiple raws)</td>
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<td>EQ-5D-5L questions</td>
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<td>(multiple raws)</td>
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<tr>
<td>score</td>
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</tbody>
</table>

3.8 Figures to present

Figure 1) CONSORT diagram of study population.

Figure 2) Cumulative event rates by treatment groups, for the primary endpoint and its individual components.
Bibliography

