Study Protocol

Physiologic assessment of coronary stenosis following PCI

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PROTOCOL APPROVAL PAGE

Study Title: DEFINE-PCI: Physiologic assessment of coronary stenosis following PCI

Version: 3.0

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I have received a copy of this version of the protocol, have read, understand the protocol, and agree the study will be conducted in compliance with the protocol, GCP, the Declaration of Helsinki, and the applicable regulatory requirement(s).

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Investigator Name

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Investigator Signature

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Date

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Philips Volcano

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Signature

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Date

Table of Contents

STUDY SUMMARY

Title	DEFINE-PCI
Study Chairman	Gregg Stone (CRF)
Study PIs	Allen Jeremias (CRF), Manesh Patel (Duke), Justin Davies (Imperial College London)
Background	Numerous studies of coronary stenting over the past decade have consistently demonstrated that recurrent episodes of angina within the first year post PCI are common, occurring in approximately 20% of patients. This may lead to a substantial increase in repeat invasive procedures and associated health care costs. Physiologic assessment of coronary stenoses prior to percutaneous coronary intervention (PCI) is superior to coronary angiography alone for lesion evaluation, reducing overall major cardiac events as well as cost. However, data on post PCI physiology is scarce and thus rarely used in clinical practice. Limited clinical data on post PCI Fractional Flow Reserve (FFR) and instantaneous wave-free ratio (iFR) indicate that a substantial number of patients (up to 20%) have impaired coronary physiology at the completion of the procedure despite an angiographically successful PCI. It is not known whether an abnormal post-PCI FFR or iFR is predictive of recurrent angina and whether the routine use of physiological indices of coronary function can predict future cardiovascular events. iFR safely and accurately quantifies stenosis severity in a wide range of lesions and may be helpful in assessing post PCI physiology. Compared with FFR, it allows rapid assessment of the lesion without induction of maximal hyperemia with adenosine. iFR pullback has the potential additional advantage of interrogating the entire coronary artery to identify culprit lesions with significant pressures gradients.
Hypothesis	This is a pilot study designed to assess the relationship between iFR pullback and the distribution of coronary atheroma/stenoses as assessed by Quantitative Coronary Angiography (QCA) post angiographically successful PCI. The hypotheses of this study are: 1. iFR is impaired in a substantial proportion of patients following operator-assessed angiographically successful PCI 2. Post-PCI iFR detects residual significant CAD that is not detected on QCA (defined by ≥50% stenosis) 3. Post PCI iFR is predictive of future adverse cardiovascular events
Objectives	1. Determine the range of post-PCI iFR and the rate of significant residual ischemia defined as iFR <0.90 following operator-assessed angiographically successful PCI 2. Determine the proportion of cases in which the iFR would become non-significant if a focal stenosis demonstrated by iFR pullback were treated with PCI. This will be the number or

	proportion used in the sample size calculation for the planned randomized trial. 3. Determine the relationship between post-PCI iFR pullback and QCA with respect to residual stenosis by QCA, residual stenoses and device success (i.e. optimal stent implantation). The goal is to correlate abnormal iFR measurements to their anatomic reason (i.e. device related complications, angiographically undetected residual lesions, or diffuse atherosclerotic disease). 4. Determine the relationship between post-PCI iFR and clinical outcomes, such as recurrent angina and MACE. 5. Establish the relationship between post-PCI iFR and objective assessment of quality of life.
Study Design and Methods	DEFINE-PCI is a multi-center, prospective study in up to 25 centers in USA and internationally. Consented subjects with CAD who undergo physiologic lesion assessment with iFR<0.90 in at least 1 coronary artery are eligible for participation. After successful PCI to all culprit lesions based on angiographic assessment of the treating physician, a blinded post-PCI iFR and iFR pullback will be performed. The proportion of patients with impaired post-PCI iFR will be assessed, and the number of patients in whom ischemia could theoretically be normalized with further PCI determined. Additionally, the association between the post-PCI iFR results and cardiovascular events and clinical symptoms will be assessed. Follow-up will be at 1, 6 and 12 months, including administration of quality of life questionnaires.
Number of subjects	An exact one sample binominal proportion test will be used for analysis of the primary endpoint. Assuming a 10% rate of residual ≥50% stenosis based on QCA versus a conservative 15% rate of iFR<0.90 with a two-sided type I error of 0.05, approximately 500 patients will be required to achieve 90% power.
Primary Endpoint	Rate of residual ischemia defined as iFR <0.90 after operator-assessed angiographically successful PCI (residual diameter stenosis <50% in any treated lesion in the target vessel)
Secondary Endpoint	**Secondary clinical endpoints (assessed in relation to post PCI iFR ([as dichotomous and continuous variable]):** 1. Composite of cardiac death, target vessel myocardial infarction, ischemia-driven target vessel revascularization or recurrent ischemia at one year (definition below) 2. Target vessel failure defined as cardiac death, target vessel myocardial infarction, ischemia-driven target vessel revascularization 3. Quality of life (assessed by the Seattle Angina Questionnaire) at baseline, 30-days, 6 months and 1year 4. All-cause and cardiac mortality at one year 5. Target vessel Myocardial infarction at one year 6. Ischemia-driven target vessel revascularization at one year

	7. Recurrent ischemia at one-year **Secondary physiology endpoints:** 8. Correlation between iFR <0.90 and coronary stenosis ≥50% assessed by visual interpretation 9. Proportion of cases in which the iFR would become non-significant if a focal stenosis demonstrated by iFR pullback were treated with PCI 10. Differentiation of the cause for impaired iFR (categorized as stent related, distant focal stenosis, or diffuse atherosclerosis) 11. Predictors of delta iFR before and after PCI
Inclusion Criteria	1. Subject must be ≥ 18 years old 2. Subjects presenting with stable angina, silent ischemia or non-ST-elevation ACS (unstable angina or biomarker positive) 3. Single vessel CAD with at least 2 separate lesions (≥10 mm apart) of ≥40% stenosis or a single long lesion of ≥20mm OR multi-vessel CAD, defined as at least 2 vessels with ≥40% stenosis 4. Pre-PCI iFR performed in all vessels intended for PCI 5. Pre-PCI iFR of <0.90 of at least 1 stenosis 6. Subjects are able and willing to comply with scheduled visits and tests and to provide informed consent.
Exclusion Criteria	1. Pregnant or planning to become pregnant for the duration of the study 2. Acute STEMI within the past 7 days 3. Cardiogenic shock (sustained (>10 min) systolic blood pressure < 90 mmHg in absence of inotropic support or the presence of an intra-aortic balloon pump). 4. Ionotropic or temporary pacing requirement 5. Sustained ventricular arrhythmias 6. Prior CABG 7. Known ejection fraction ≤30% 8. Chronic Total Occlusion (CTO) of study vessel 9. Known moderate to severe mitral or aortic disease. 10. Any known medical comorbidity resulting in life expectancy < 12 months. 11. Participation in any investigational study that has not yet reached its primary endpoint. 12. Known severe renal insufficiency (eGFR <30 ml/min/1.72 m2). 13. TIMI flow <3 at baseline of study vessel 14. Intra-coronary thrombus on baseline angiography
Sample size considerations	N=500 patients
Definition of recurrent ischemia	Recurrent ischemia is defined as ischemia meeting any of the criteria below: [1]

	1. Recurrent ischemia with ECG changes: recurrent ischemic discomfort or equivalent at rest lasting ≥10 min associated with new ST or T-wave changes consistent with ischemia (ST elevation ≥0.1 mV or dynamic horizontal/down-sloping ST depression ≥0.05 mV or T-wave inversions ≥0.2 mV) or 2. Recurrent ischemia leading to hospitalization: recurrent ischemic discomfort or equivalent at rest lasting ≥10 min, repeated episodes at rest lasting ≥5 min, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration, and/or precipitated by less exertion) prompting re-hospitalization and considered to be myocardial ischemia upon final diagnosis or 3. Recurrent ischemia prompting revascularization, defined as: (a) During the index hospitalization: PCI or CABG prompted by recurrent ischemia with ECG changes or (b) After hospital discharge from index hospitalization: PCI or CABG prompted by increase in angina to a higher Canadian Cardiovascular Society Class, or evidence for ischemia on provocative testing or 4. Worsening angina/ischemia requiring additional medical therapy (a) An increase in angina to a higher Canadian Cardiovascular Society Class and (b) Requiring intensification of antianginal therapy with new or increasing doses of antianginal medications

	Baseline	During Procedure	Post-procedure (prior to D/C)	30 day follow-up	6 month follow-up	12 month follow-up
Physical assessment and Patient Interview						
Informed Consent	X					
Medical History	X					
Current antianginal Medications	X			X	X	X
Event assessment			X	X	X	X
Lab measurements						
CBC and platelet count*	X		X			
Troponin or CK-MB*	X		X			
Complete metabolic panel*	X		X			
Pregnancy test (for women of childbearing potential)**	X					
Non-invasive testing						
EKG	X		X			
Echocardiogram ^	X					
Ischemia assessment^ (TTE/nuclear/MRI/CCTA)	X					
Invasive Testing						
iFR +		X				
Angiography +		X				
IVUS/OCT ++		X				
Quality of Life measurement						
Seattle Angina Questionnaire	X			X	X	X

Table 1. Schedule of Events

***** Baseline and Post Procedure if Lab measurements are performed per local standard-of-care, data should be collected in the eCRF.
If performed as SOC, At least one biomarker level should be obtained post PCI at 4-8 hrs. Post procedure. CK-MB is preferred but Troponin I/T may be drawn if CK-MB not available. Subsequent biomarker levels are highly recommended if initial post PCI biomarker is elevated and should be followed per local standard of care

****** Pregnancy test must be negative within 7 days prior to enrollment

^ If Echo, TTE, Nuclear Scan, MRI or CCTA is performed per routine standard-of-care, data should be collected in the eCRF

+ Angiography and iFR tracings archived to DVD and submitted to the core lab

++ If IVUS or OCT are performed as standard of care- images should be archived to DVD and submitted to the core lab

ABBREVIATIONS

AE	Adverse event
ADE	Adverse Device Effect
CAD	Coronary artery disease
CBC	Complete blood count
CCTA	Coronary computed tomography angiography
CK-MB	Creatinine kinase – MB isoenzyme
EKG	Electrocardiogram
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
iFR	Instantaneous wave-free ratio
iFR PULLBACK	iFR Pressure wire pullback
IRB	Institutional Review Board
MACE	Major adverse cardiac events
MRI	Magnetic resonance imaging
NSTEMI	Non ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PHI	Personal Health Information
QCA	Quantitative Coronary Angiography
QoL	Quality of Life
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
TTE	Transthoracic echocardiogram
UADE	Unanticipated Adverse Device Effect

INTRODUCTION

Background

Although myocardial revascularization with percutaneous coronary intervention (PCI) has been demonstrated to provide symptomatic benefit in patients with myocardial ischemia, numerous studies have demonstrated that up to 20% of patients experience recurrent angina in the year following PCI, potentially leading to a substantial increase in invasive and/or noninvasive testing, as well as its attendant costs. To date, outside of traditional, guideline-recommended antianginal medical therapies, there are no techniques that have been demonstrated to reduce the likelihood of post-PCI recurrent angina.[2,3,4]

Among patients with stable angina, physiologic assessment of coronary stenoses for angiographically indeterminate lesions prior to PCI, typically with fractional flow reserve (FFR), has been demonstrated to be a superior strategy and has been shown to improve outcomes and reduce costs compared with coronary angiography alone.[5,6]

However, although routine assessment of intermediate coronary stenoses pre-PCI is common, data on FFR assessment post-PCI is sparse and ill-defined.[8] Prior studies have demonstrated that post-PCI lesion assessment is uncommon, and current expert consensus guidelines do not offer specific recommendations regarding its use. In a recent retrospective, single-center study of 574 patients (664 lesions), post-PCI FFR led to reclassification of about 20% of lesions, requiring additional intervention. Additionally, patients with a final FFR > 0.86 had significantly lower rates of major adverse cardiac events (MACE) compared with patients with a final FFR ≤ 0.86.[7] These data suggest a potential important role for the routine physiologic assessment of coronary arteries post-PCI, especially in situations where PCI may unmask a serial lesion or when additional post-stent deployment optimization may be necessary.

More recently, instantaneous wave-free ratio (iFR) measurement, which provides an instantaneous assessment of stenosis severity without the need for prolonged assessment or the administration of pharmacotherapies for maximal hyperemia, has emerged as a tool to provide rapid lesion assessment. iFR safely and accurately quantifies stenosis severity in a wide range of lesions and may be helpful in assessing post PCI physiology.[9] Compared with FFR, it allows rapid assessment of the lesion without induction of maximal hyperemia. iFR pullback has the potential additional advantage of interrogating the entire coronary artery to identify culprit lesions with significant pressures gradients as well as diffuse atherosclerosis.[10]

It is not known the frequency with which an abnormal iFR occurs post PCI, and to what extent that it is determined by a missed focal lesion, or extensive diffuse atherosclerosis along the length of the vessel. Additionally, it remains unknown whether an abnormal post-PCI iFR is predictive of recurrent angina and whether the routine use of physiological indices of coronary function can predict future cardiovascular events. This study will assess (a) the frequency of iFR significant

physiological lesions post PCI, (b) differentiation between focal and diffuse disease, (c) the proportion of cases in physiology that would normalize with additional PCI, and (d) the correlation between physiology and clinical outcomes.

Clinical Experience with Device

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.[11] This approach is intrinsically limited by the diagnostic efficiency of FFR, which in itself is a surrogate of non-invasive ischemia detection tests.[13] Overall these studies have shown that iFR can be used to identify ischaemia-generating stenoses, as defined with FFR.[14] 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. [17]

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) [12,14] 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. HSR provides 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 had a diagnostic classification match in excess of 90% with HSR as the reference standard. 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 [13] 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 Petraco et al.[15] compared the classification match between FFR and iFR against CFR. In this multi-center 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 ischemic cut-points for iFR or FFR were used.

- **Comparison with PET:** Two recent studies have compared PET perfusion imaging with hyperaemic and rest invasive physiological measures. De Waard et al. showed no difference between classification of ischemia between iFR and FFR against PET as the reference standard. Classification agreement with PET hyperemic MBF was 76% for FFR and 77% for iFR. Hwang et al. also show similar findings with overall diagnostic accuracies of FFR and iFR of 69.6%, and 73.9% respectively. [12,16]

Study Rationale

Although iFR is increasingly used for physiologic assessment of coronary lesions prior to PCI, data on post-PCI iFR values is limited, and it is unclear how often coronary physiology remains abnormal after PCI, and whether PCI performance could be improved by routine use of iFR pullback. This study is designed to assess the relationship between iFR pullback and the distribution of coronary stenoses as assessed by Quantitative Coronary Angiography (QCA) following angiographically successful PCI. The hypotheses of this study are:

- iFR is impaired in a substantial proportion of patients following operator-assessed angiographically successful PCI.

- Post-PCI iFR detects residual significant CAD that is absent on QCA (defined by $\geq$50% stenosis)

    - This could be due to:-

        - The presence of stenosis which are not apparent on angiography

        - The presence of diffuse disease

        - Sub-optimal PCI result

- Post PCI iFR is predictive of future adverse cardiovascular events

STUDY OBJECTIVES

- Determine the range
- of post-PCI iFR and the rate of significant residual ischemia defined as iFR <0.90 following operator-assessed angiographically successful PCI
- Determine the proportion of cases in which the iFR would become non-significant if a focal stenosis demonstrated by iFR pullback were treated with PCI. This will be the used in the sample size calculation for a future randomized trial.
- Determine the relationship between post-PCI iFR pullback and QCA with respect to residual stenosis by QCA, residual stenoses and device success (i.e. optimal stent implantation). The goal is to correlate abnormal iFR measurements to their anatomic reason (i.e. device related complications, angiographically undetected residual lesions, or diffuse atherosclerotic disease).
- Determine the relationship between post-PCI iFR and clinical outcomes, such as recurrent angina and MACE.
- Establish the relationship between post-PCI iFR and objective assessment of quality of life.

STUDY Endpoints

Primary Endpoints

- Rate of residual ischemia defined as iFR <0.90 after operator-assessed angiographically successful PCI (residual diameter stenosis <50% in any treated lesion in the target vessel)

Secondary Endpoints

Secondary clinical endpoints (assessed in relation to post PCI iFR ([as dichotomous and continuous variable]) :

- Composite of cardiac death, target vessel myocardial infarction, ischemia-driven target vessel revascularization or recurrent ischemia at one year (definition below)
- Target vessel failure defined as cardiac death, target vessel myocardial infarction, ischemia-driven target vessel revascularization

- Quality of life (assessed by the Seattle Angina Questionnaire) at baseline, 30-days, 6 months and 1year
- All-cause and cardiac mortality at one year
- Target vessel Myocardial infarction at one year
- Ischemia-driven target vessel revascularization at one year
- Recurrent ischemia at one-year

Secondary physiology endpoints:

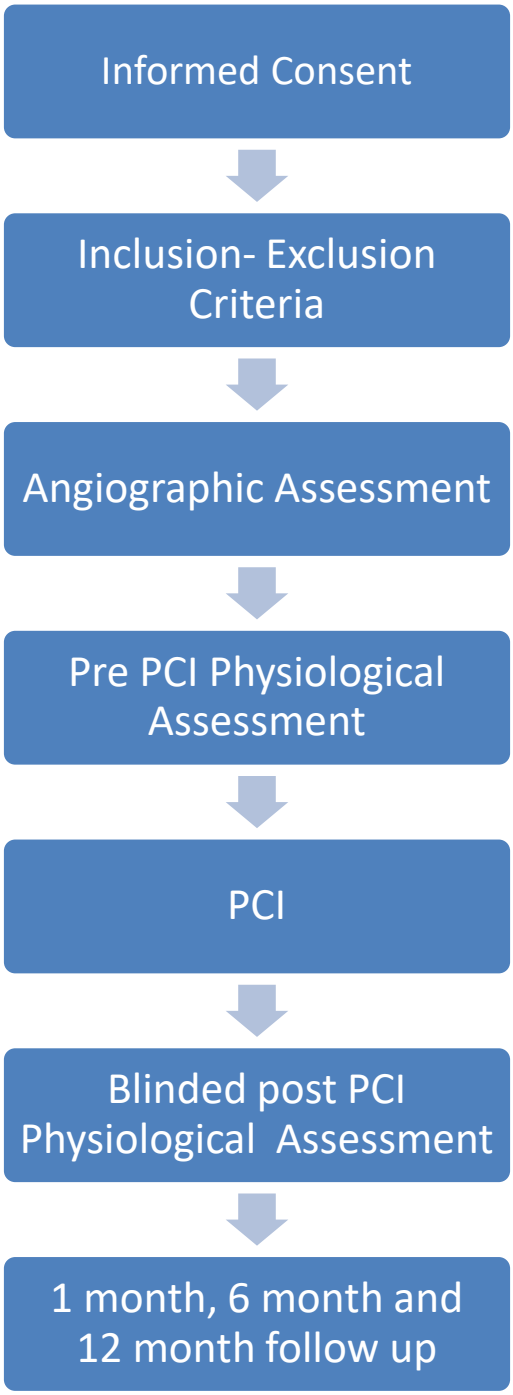
- Correlation between iFR <0.90 and coronary stenosis ≥50% assessed by visual interpretation
- Proportion of cases in which the iFR would become non-significant if a focal stenosis demonstrated by iFR pullback were treated with PCI
- Differentiation of the cause for impaired iFR (categorized as stent related, distant focal stenosis, or diffuse atherosclerosis)
- Predictors of delta iFR before and after PCI

Secondary clinical endpoints will be evaluated using iFR in a dichotomous fashion with a cut-point of iFR<0.90 as well as iFR as a continuous variable.

STUDY DESIGN

Overview

This is a prospective, single-arm, multi-center, pilot study to assess the relationship between iFR pullback and the distribution of coronary atheroma/stenoses as assessed by Quantitative Coronary Angiography (QCA) post angiographically successful PCI.



Methods

Consented subjects with CAD who undergo physiologic lesion assessment with iFR<0.90 in at least 1 coronary artery are eligible for participation. After successful PCI to all culprit lesions based on (visual) angiographic assessment of the treating physician, a blinded post-PCI iFR pullback will be performed. The proportion of patients with impaired post-PCI iFR will be assessed, and the number of patients in whom ischemia could theoretically be normalized with further PCI determined. Additionally, the association between the post-PCI iFR results and cardiovascular events and clinical symptoms will be assessed. Follow-up will be at 1, 6 and 12 months, including administration of quality of life questionnaires.

Treatment Arms

As this is a nonrandomized study, all patients will receive standard of care therapy. All patients will undergo iFR prior to PCI in order to provide physiologic assessment of each vessel. Following PCI, all patients will undergo blinded iFR pullback in order to determine the proportion of patients with impaired post-procedure physiology.

Study Population

Number of Subjects

This study will enroll approximately 500 subjects at approximately 25 centers globally. Enrollment is expected to last approximately 1 year.

Subject Enrollment and Length of Participation

Subjects are considered enrolled in this clinical study when the pre-interventional iFR measurement is abnormal (iFR<0.90) and with the intention to perform a PCI of at least 1 coronary stenosis. The expected duration of enrollment is approximately 12 months across all sites with each individual subject's participation lasting for 12 months after enrollment.

In the event that a post PCI iFR pullback is unable to be performed, the patient will remain in the study and continue to be followed during the follow up period.

Inclusion Criteria

To be eligible for this trial, subjects must meet all of the following criteria:

1. Subject must be ≥ 18 years old
2. Subjects presenting with stable angina, silent ischemia or non-ST-elevation ACS (unstable angina or biomarker positive)
3. Single vessel CAD with at least 2 separate lesions (≥10 mm apart) of ≥40% stenosis or a single long lesion of ≥20mm **OR** multi-vessel CAD, defined as at least 2 vessels with ≥40% stenosis
4. Pre-PCI iFR performed in all vessels intended for PCI
5. Pre-PCI iFR of <0.90 of at least 1 stenosis
6. Subjects are willing to comply with scheduled visits and tests and are able and willing to provide informed consent.

Exclusion Criteria

If subjects meet any of the following criteria, he or she may not be enrolled in the study:

1. Pregnant or planning to become pregnant for the duration of the study
2. Acute STEMI within the past 7 days
3. Cardiogenic shock (sustained (>10 min) systolic blood pressure < 90 mmHg in absence of inotropic support or the presence of an intra-aortic balloon pump).
4. Ionotropic or temporary pacing requirement
5. Sustained ventricular arrhythmias
6. Prior CABG
7. Known ejection fraction ≤ 30%
8. Chronic Total Occlusion (CTO) of study vessel
9. Known moderate to severe mitral or aortic disease
10. Any medical comorbidity resulting in life expectancy <12 months.
11. Participation in any investigational study that has not yet reached its primary endpoint.
12. Known severe renal insufficiency (eGFR <30 ml/min/1.72 m2).
13. TIMI flow <3 at baseline of study vessel
14. Intra-coronary thrombus on baseline angiography

Study Procedures

Baseline (up to 30 days prior to index procedure)

Prior to any study-specific procedures, the subject's written informed consent will be obtained. Basic demographic data will be collected, a targeted history and physical examination focused on the study limb. Female subjects of childbearing potential must have a negative pregnancy test within 7 days of the index procedure in order to participate. If the subject meets all Inclusion Criteria and none of the Exclusion Criteria, and provides written informed consent, he/she may be enrolled in the study.

- Informed Consent
- Medical History
- Current antianginal medications
- CBC and platelet count (if performed as SOC)
- Troponin or CK-MB (If performed as SOC)
- Complete metabolic panel (if performed as SOC)
- EKG
- Echocardiogram (if performed)
- Ischemia assessment (if performed) – TTE/nuclear/MRI/CCTA
- Seattle Angina Questionnaire

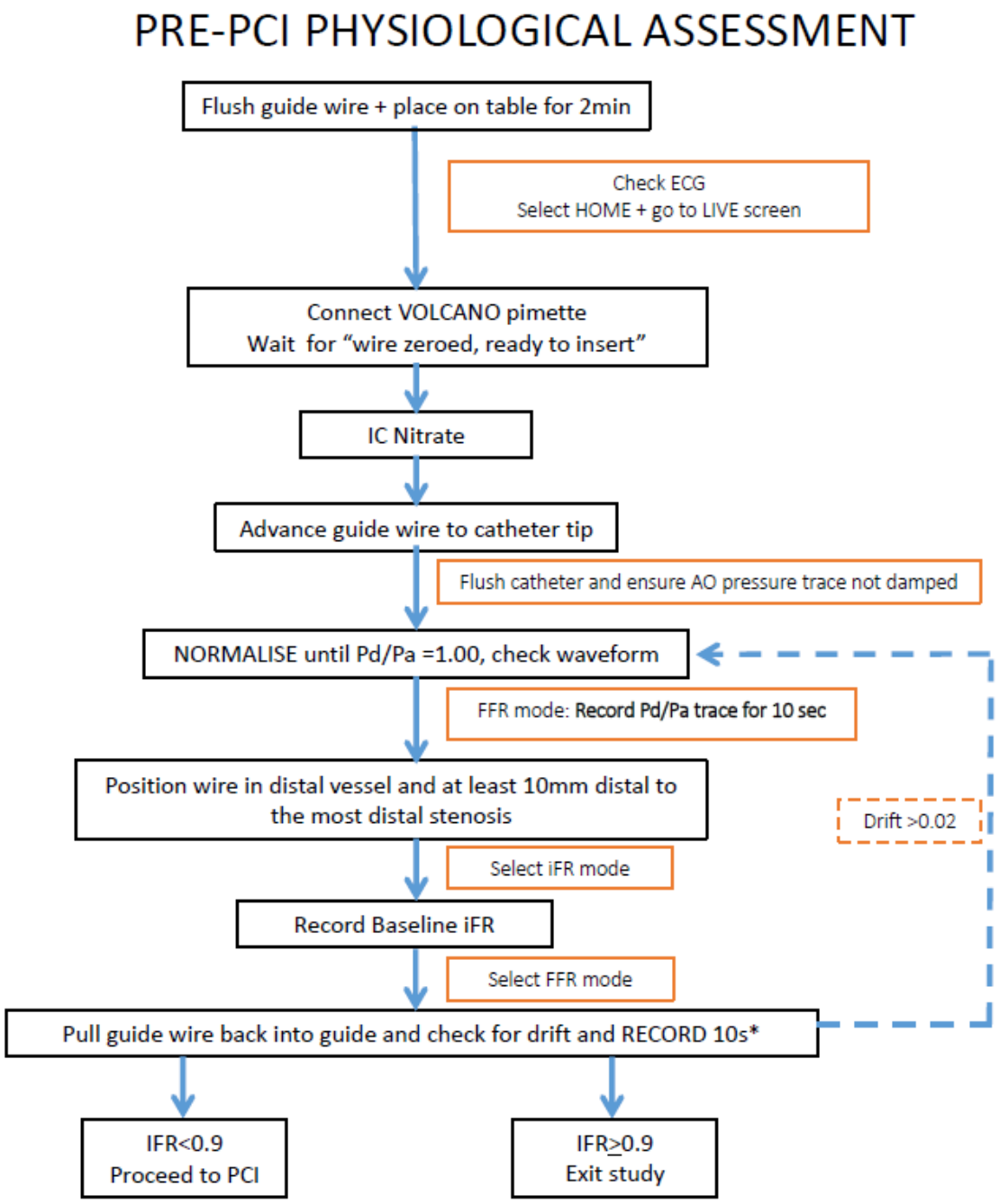
Pre PCI Procedure

Subjects are taken to the procedure room and appropriate anesthesia is administered per institutional standards. Assessments:

- Angiography
- Baseline iFR of each vessel intended for PCI
- Drift Check after each vessel assessment
- UADE assessment
- IVUS/OCT (if performed as SOC)
- iFR Pullback should not be performed during pre pci assessment. This is a major protocol deviation.

Angiographic Assessment

- Intracoronary Nitrates
- Orthogonal views of any potential target vessel in which 1 or more stenosis is at least 40% by visual assessment.



*When pulling the wire back to check for drift, it is a MAJOR protocol deviation to perform this under the iFR pullback mode.

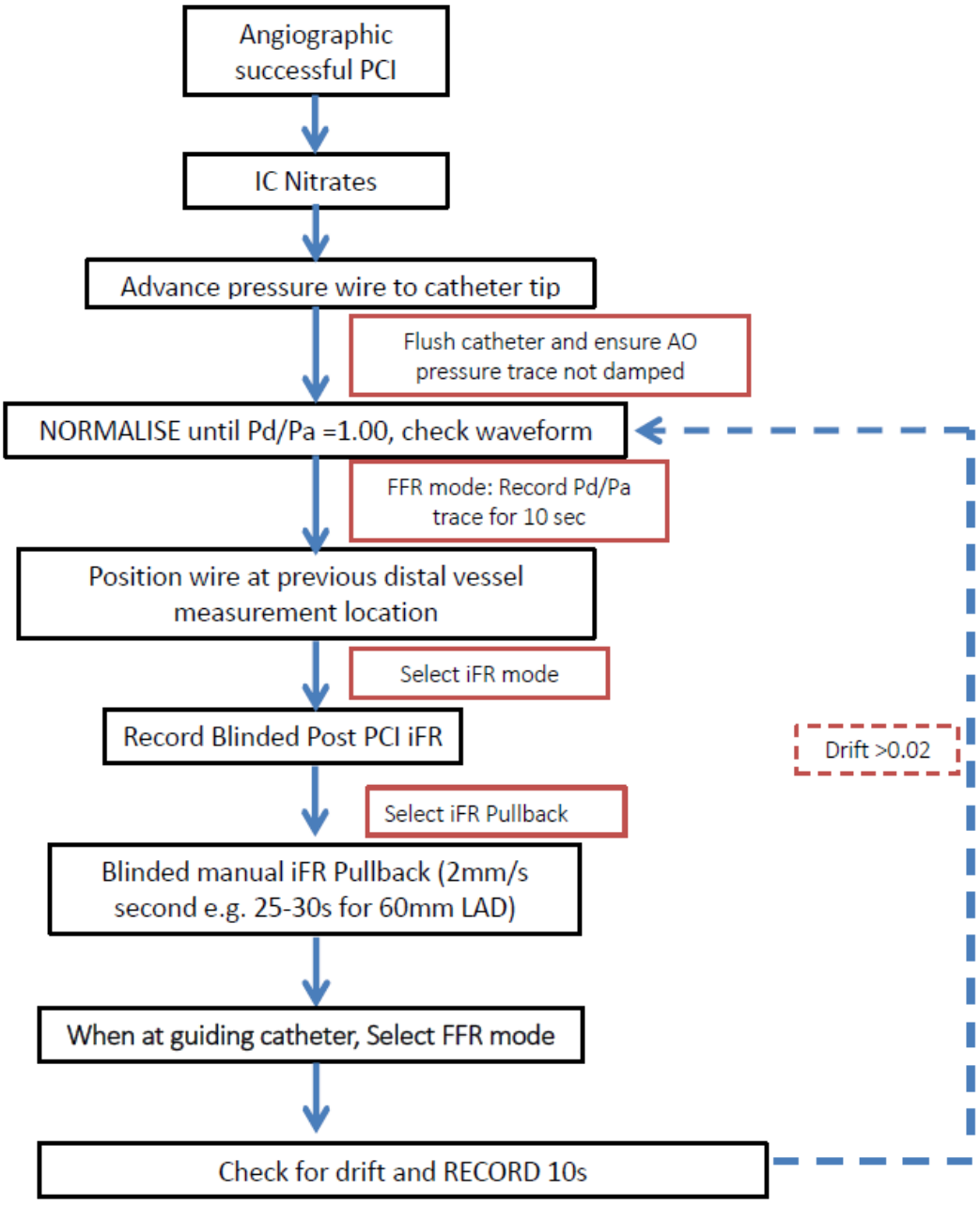
PCI Procedure

- Create a second case in the Volcano system for the blinded data
- If Verrata wire is used for the PCI, it must be renormalized prior re-crossing the lesion
- Any coronary guidewire can be used
- Perform PCI in accordance with the local PCI guideline and protocols
- IVUS/OCT (if performed as SOC)
- Visual assessment of final angiographic results documented

Post PCI Procedure (Blinded Data)

- If re-inserting Verrata wire, it must be renormalized.
- Perform Post PCI iFR measurements of each vessel treated
- Perform Post PCI iFR Pullback measurements of each vessel treated
- Drift Check should occur after each vessel iFR pullback
- No additional IVUS/OCT imaging after final iFR measurements
- No additional treatment after final iFR measurements, unless urgent/emergent needs arise.

BLINDED POST PCI PHYSIOLOGICAL ASSESSMENT



Blinding Procedure

During the post-PCI iFR pullback, and the remainder of the study, these steps should be taken when possible to ensure Investigator and other Blinded research staff continue to be blinded to the results.

Index Procedure Post PCI iFR Pullback

- Monitors (with integrated systems) will be turned off in the catheter laboratory procedure room. With a mobile unit, the screen will be turned away from the Investigator. Investigator will perform blinded iFR pullback under fluoroscopy.
- A second case will be created in the Volcano system for the Blinded portion of the study. This case will not contain patient identifiers and it will not be archived to the hospital archiving system.
- The blinded data (case #2) will be closed out immediately after the PCI, so the operator does not have visibility of the blinded data.
- Un-blinded catheter laboratory staff and/or research staff will burn the blinded data to a DVD, and will then be deleted from the Volcano system once confirmation the data is on the disk. Blinded data will not be documented in catheter laboratory procedure notes or patients chart.
- For sites where the cases are automatically pushed to an archiving system (i.e. PACS, Heart lab), it will be necessary to ensure the post-PCI iFR pullback (blinded data) does not get archived with the patients procedural images and data.
- The catheter laboratory staff will be educated on the importance of the blinded data; to ensure they do not share the information with the Investigators or blinded research staff.

Immediately after the index procedure:

- The un-blinded research staff will secure the blinded data. There is no written blinded data- only the data on the disk. The data will be transferered electronically to the core lab and will then be secured in a sealed envelope in the subject binder in the research office. . Only to be opened by monitors for source document verification, then resealed.

Follow up Phone Calls/Visits

- A blinded research staff member will be assigned to perform the follow up phone calls/visits with the subject.

Post Procedure to Discharge

- CBC and platelet count (if performed as SOC)
- Troponin or CK-MB: If performed as SOC, at least one biomarker level should be obtained post PCI at 4-8 hrs. Post procedure. CK-MB is preferred but Troponin I/T may be drawn if CK-MB not available. Subsequent biomarker levels are highly recommended if initial post PCI biomarker is elevated and should be followed per local standard of care.
- Complete metabolic panel (if performed as SOC)
- EKG
- Event Assessment

Follow Up Procedures

1 month follow up (day 30 +14 days), 6 month follow up (day 180 +30 days) and 12 month follow up (day 365 +30 days)

Follow up can be done via telephone conversation.

- Current Anti-anginal medications
- Event Assessment
- Seattle Angina Questionnaire

Note: Event Assessment will be conducted at every encounter (scheduled and unscheduled) with the subject to specifically collect possible endpoints for CEC adjudication. Specifically, the subject should be asked regarding any cardiac hospitalization, myocardial infarction, repeat coronary angiography, repeat PCI, or recurrent angina.

Discontinued Subjects

Subjects have the right to withdraw from this study at any time and for any reason. Data that is collected prior to the subject's withdrawal from the study will be analyzed. The Principal Investigator has the right to discontinue a subject's participation in the study in the event of an underlying illness, adverse event, or protocol violation. Philips Volcano has the right to discontinue the study at any time. A complete final evaluation at the time of the subject's discontinuation should be made. The cause for subject withdrawal will be recorded in the appropriate case

report form (CRF). Discontinued subjects will not be replaced; i.e., overall study enrollment will not exceed 500 subjects.

Adverse Event Reporting

For the purposes of this study, because the Verrata pressure guide wire is commercially available, adverse event reporting for this study will be limited to ADEs, SADEs, and UADEs (per the below definitions).

Definitions

Adverse Event (AE)
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or medical device and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product or device, whether or not related to the medicinal (investigational) product or device.

Serious Adverse Event (SAE)
A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the subject and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

Note that adverse events requiring hospitalization are SAEs but elective hospitalizations related to non-study-emergent conditions do not constitute SAEs.

Adverse Device Effect (ADE)
For the purposes of this protocol, an ADE is defined as an adverse event that is related to or associated with Veratta pressure wire use, or an adverse event for which a causal relationship by iFR cannot be ruled out.

Serious Adverse Device Effect (SADE)

An SADE is defined as an adverse device effect that has resulted in any of the consequences or characteristics of a serious adverse event.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the protocol (including documents such as the protocol, informed consent form, or other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of subjects.

Anticipated potential Adverse Events (per device IFU) are described below in Description of Device.

Reporting of Clinical Events

All clinical events observed during the course of this study will be recorded by the investigator on the appropriate e-CRF. All MACE will be evaluated by the CEC after review of original study records, ECGs, and angiograms. Additional events may be triggered by review of lab data, monitoring, and by CEC review of other events (these additional possible events will be referred to as "triggered events".)

Device Malfunctions or Use Errors

Device malfunctions or use errors will be recorded and evaluated for possible untoward effects on the subject. For the purposes of this study, a device malfunction is defined as a failure of the device to perform its intended function when used in accordance with the Instructions for Use (IFU). If a VERRATA® PRESSURE GUIDE WIRE or any subsequent next generation Philips Volcano pressure wires device malfunction results in an adverse experience for the subject, this adverse experience should be considered an adverse device effect and recorded on the appropriate CRF. A device malfunction by itself should not be reported as ADE unless it leads to the new medical condition or worsening of pre-existing condition. If a VERRATA® PRESSURE GUIDE WIRE device malfunction occurs in this study, the site should follow standard commercial procedures as described in the Precautions section of the VERRATA® PRESSURE GUIDE WIRE IFU.

Reporting Requirements

The VERRATA ® PRESSURE GUIDE WIRE or any subsequent next generation Philips Volcano pressure wires used in this study are cleared by the FDA and CE marked for use in coronary vessels. Information related to contraindications, adverse effects, warnings, and precautions are included in the device Instructions for Use.

For these reasons, adverse event reporting for this study will be limited to ADEs, SADEs, and UADEs (per the above definitions). These events will be recorded on the corresponding case report forms. Complaints should be reported to the Study Medical Monitor and Customer_Inquiry@volcanocorp.com (see below). All serious adverse device effects (SADEs) must be reported to Philips Volcano as soon as possible after first awareness of the event; every attempt must be made to report such events to Philips Volcano within 24 hours of first awareness.

Contact information for SADE reporting:

Brad Matsubara, MD
Study Medical Monitor
Philips Volcano
Office: (858) 720-4045
Mobile: (858) 568-8946
Fax: (858) 720-0325
Email: bmatsubara@volcanocorp.com and Customer_Inquiry@volcanocorp.com

Protocol Deviations and Waivers

A protocol deviation is defined as an event where the clinical Investigator or site personnel deviate from the study protocol or study procedures. It is the Investigator's responsibility to ensure that there are no deviations from the protocol without prior notification and approval of the Sponsor or Sponsor's designee and in full compliance with all established procedures and conditions of the reviewing IRB/IEC.

The Investigator may deviate from the protocol without prior written approval from the Sponsor or Sponsor's designee in cases of medical emergencies, when the deviation is necessary to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify the Sponsor or Sponsor's designee immediately by phone or electronic communication, notify the reviewing IRB/IEC and confirm notification to the Sponsor or designee in writing. Prior deviation approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, for example, the subject was not available for a scheduled follow-up office visit. These events, although outside the Investigator's control, are still required to be reported on the appropriate protocol deviation form in order to ensure that all deviations from the standard subject population are adequately documented and reported. The Investigator will inform the Sponsor or

Sponsor's designee of all deviations, and the reviewing IRB/IEC of all protocol deviations as per the IRB/IEC requirements for this study.

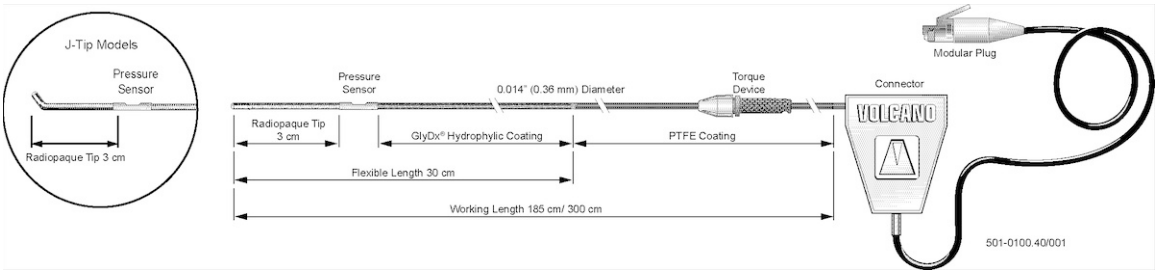
The occurrence of protocol deviations will be monitored by the Sponsor or Sponsor's designee for evaluation of Investigator compliance to the Protocol, Good Clinical Practices, and regulatory requirements.

Gross non-compliance with the protocol at an individual site that may jeopardize the outcomes or the integrity of the trial may result in termination of enrollment at such non-compliant sites.

Description of the Device

The Verrata pressure guide wire (hereafter referred to as the "pressure guide wire") is a steerable guide wire with a pressure transducer mounted 3 cm proximal to the tip. The Verrata guide wire measures pressure when used with the SmartMap, ComboMap, s5 Series, and CORE Series of systems. The pressure guide wire has a diameter of 0.014" (0.36 mm) and is available in lengths of 185 cm or 300 cm* and also in straight or preshaped tips. The pressure guide wire is packaged attached to the connector with a torque device to facilitate navigation through the vasculature. It is possible that future iterations of the Verrata wire may be used in the study which will offer improved performance and reliability.

CONTRAINDICATIONS:
This pressure guide wire is not intended for use in crossing a total vessel occlusion.



Please review IFU attached.

Ethical Considerations

This protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

Benefits

No direct benefits to the patient are expected. However, information gained during this study may lead to improved treatment workflows for patients with coronary artery disease in the future.

Risks

The Philips Volcano pressure guide wires used in this study are cleared for commercial use by the FDA and CE marked for commercial distribution in Europe for use in the coronary vessels as described in this protocol. Information related to contraindications, adverse effects, warnings, and precautions are included in the device Instructions for Use.

Risks associated with the use of pressure guide wires in patients with coronary artery disease are well understood, and incidence rates are very low. An extensive review of the safety of using pressure wires in 14 studies covering 1,284 patients revealed just 2 reports of arterial dissection (0.16%) and a single report of device entrapment (0.8%). The largest of these studies[1] (N=648) is that which reported the 2 dissections. Both were successfully managed and represented only 0.3% of the adverse events for this single study. A widely reported event was chest discomfort associated with the administration of adenosine in 86% of patients. Notably, the DEFINE PCI protocol will be using the instantaneous free-wave ration (iFR) which does not require the administration of adenosine.

[1] Ahmed N, Layland J, Carrick D, et al. Safety of guidewire-based measurement of fractional flow reserve and the index of microvascular resistance using intravenous adenosine in patients with acute or recent myocardial infarction. *International Journal of Cardiology.* 2016;202:305-310.

The single report of device entrapment occurred when a pressure guide wire was extended across a mechanical aortic valve[2] and was not used in the native coronary anatomy. The incidence of pressure guide wire entrapment or breakage in the Volcano complaints record is 0.0056% and 0.0048 (less than one chance in more than 17,000-20,000 uses), respectively.

Patients deciding to participate in this study are thus expected to bear standard risk associated with advancing and pulling back the pressure guide wire through the vasculature more times than would be typical in a standard PCI procedure. Site personnel are well-practiced in the use of pressure guide wires in the coronary anatomy, and are advised to use discretion in repeating a pressure reading in cases where this presents elevated patient risk due to any specific anatomical or physiological factor. Hence, the risk associated with the additional pressure wire procedures is considered standard.

Mitigation of Risks

The study site investigators will be selected for their experience and skill in Coronary interventions and familiarity with the use iFR and iFR pullback. Appropriate subjects will be selected using clearly defined inclusion/exclusion criteria to ensure that subject treatment is consistent with current medical standards and practices.

Risk – Benefit Analysis

. In terms of complexity, the Verrata Wire does not have moving or expandable parts, nor is any portion of the device implanted within the subject. Finally, the Verrata Wire is cleared by the FDA and CE marked for use in coronary arteries, and the device does not emit ionizing radiation. Patient participation is expected to provide insight for better managing ischemic coronary artery disease despite not experiencing any direct benefit. Hence, the overall benefits to the body of knowledge for treating coronary artery disease outweighs the risk associated with the additional pressure wire steps.

Data Handling and Record Keeping

[2] Marmagkiolis K, Cilingiroglu M. Radi pressurewire rupture and embolization to the right common carotid artery after crossing a Bjork-Shiley mechanical aortic valve. *Journal of Invasive Cardiology.* 2013;25(10):E191-E193.

Case Report Forms

This study will be performed using an electronic data capture (EDC) system. The Investigator and study site staff will receive training and support on the use of the EDC system. All eCRF data are to be completed by the Investigator, study coordinator, or other designated site personnel.

Source Documents

Investigators are required to maintain information in the study subject's medical records to corroborate data collected on the eCRF. Shadow charts are not appropriate or adequate for source documentation. Source data includes all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of source documents are: hospital medical records, clinical and office medical charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, print-outs of ECG, CDs/DVDs of angiograms and IVUS images, subject files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments involved in the clinical study.

Data Queries

During the review of source documents and eCRF, any discrepancies will be queried by the monitor or its designee and must be resolved by the investigational site staff and Investigator in a timely manner. In addition, the monitor or its designee may also generate data queries during routine or remote review of the data. These queries will be sent to the site and must also be resolved in a timely manner by the Investigator and/or the study site staff.

Record Retention

All source documents (i.e., laboratory reports, progress notes, medical histories, physical and diagnostic findings, fluoroscopic and IVUS images and tracings, diagnoses and procedure dates, device disposition records, etc.) that support the CRFs of each subject must be retained in the files of the responsible Investigator for a minimum of two years following notification by Philips Volcano that all investigations of the device have been completed or discontinued.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to

a person who will accept the responsibility. Philips Volcano must be notified in writing of the name and address of the new custodian.

Monitoring and Oversight

This study will be monitored according to the applicable requirements in the US Code of Federal Regulations (21 CFR Part 812, 50, 56), the guidelines in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the standards in the International Organization for Standardization (ISO) 14155:2011, and of the Declaration of Helsinki (2013).

Selection of Investigators

Study Investigators will be selected for their experience and skill in cardiovascular interventions and familiarity with the use of iFR physiology assessment. The Sponsor or designee may conduct a site visit to verify the qualifications of each Investigator, tour the site facilities, and evaluate the suitability of the site for participation in this study.

Individual Investigators will be evaluated by the Sponsor based on experience with the intended procedure, and ability to conduct the study according to the study protocol. Prior to enrolling subjects, each potential investigator must submit current, signed and dated curriculum vitae. Additional criteria may be applied to site and/or Investigator selection including:

- Adequate patient population to meet requirements of the study
- Adequate time to be personally involved in the conduct of the study
- Adequate research staff and resources to support the study
- Experience conducting clinical trials research
- Facility must be associated with an IRB/IEC that satisfies all applicable regulatory requirements, or be able to use a Central IRB/IEC that satisfies these requirements

Site Initiation Visits

Training of appropriate clinical site personnel will be the responsibility of the Sponsor. To ensure uniform data collection and protocol compliance, the Sponsor will review the

Protocol, techniques for identification of eligible subjects, instructions on data collection, and methods for scheduling follow-up visits in the defined follow-up window.

Interim Monitoring Visits

Routine monitoring visits will be made to ensure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities are acceptable, the protocol is being followed, and the IRB has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to Philips Volcano and/or its designees and the IRB, and the Investigator is carrying out all agreed activities.

During monitoring visits, the monitor will perform, at a minimum, a review of source data for key variables for all enrolled subjects at each site (including but not limited to, inclusion/exclusion criteria, informed consents, endpoints, and safety) from the eCRFs compared against each subject's source documents. All available source documentation for monitored subjects will be reviewed for potential adverse device effects. Any discrepancies will be noted and resolved.

Study Close-out Visits

Upon completion of the study at a site, a close-out visit (remote or on-site) will be conducted. The monitor will ensure that the study related files at the investigational site are up to date and complete and that any outstanding issues from previous visits have been resolved. The monitor will ensure that the clinical trial materials and subject data are properly documented and stored for a minimum of two years following study completion. The Sponsor or designee will notify each site during the closeout visit of the current data storage requirements. Other topics that will be reviewed at this visit include: possibility of site audits, publication policy, notifying the IRB/EC of study closure, etc.

Direct Access to Source Data / Documents

The Investigator will permit study-related monitoring, audits, and inspections by the IEC/IRB, the Sponsor, government regulatory bodies, and compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

Amendments to the Protocol

To alter the protocol, amendments must be written, receive approval from the appropriate Sponsor personnel, and receive IRB/IEC approval prior to implementation (if appropriate). All amendments will be distributed to all protocol recipients, with appropriate instructions.

Device Accountability

No device will be supplied to sites for this study.

Administrative Responsibilities

Independent Ethics Committee/ Institutional Review Board Information

The study will not be initiated before the protocol, informed consent, and any applicable subject information forms have been reviewed and received approval/favorable opinion from the local or regional Independent Ethics Committee/ Institutional Review Board. Should a protocol amendment be made that needs IEC/IRB approval and Authority notification/approval, the changes in the protocol will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and have received approval/favorable opinion form the local IEC/IRB.

The constitution of the IEC/IRB must meet the requirements of the participating country/countries. A list of the IEC/IRB members must be provided. The Investigator (for EU: The Sponsor) must provide to the regulatory authorities, if applicable, the name and address of the IEC/IRB along with a statement from the IEC/IRB that is organized according to Good Clinical Practice and the applicable laws and regulations. The IRB/IEC must perform all duties outlined by the requirements of the participating country/countries.

Informed Consent and Subject Information

Prior to participation in the study, written informed consent must be obtained from each subject according to the regulatory and legal requirements of the participating site/country. Each signature must be dated by each signatory and the informed consent and any additional subject information forms retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

The subject must be informed that his/her personal trial-related data will be used by Philips Volcano in accordance with the local data protection law. The subject must be informed that his/her medical records may be examined by authorized sponsor personnel, quality assurance auditors appointed by Philips Volcano, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

Should a trial protocol amendment be necessary, the subject informed consent form may need to be revised to reflect the changes to the protocol. It is the responsibility of the Investigator to ensure that an amended consent form is reviewed and he has received

approval/favorable opinion from the IRB/IEC, and that it is signed by all subjects subsequently entered in the trial, and those currently in the trial affected by the amendment.

Investigator Responsibilities

Participating Investigators are required to accept the following responsibilities according to 21 CFR Part 812, and the ICH/ISO guidelines:

- Ensure that the investigation is conducted according to the Investigators agreement.
- Protect the rights, safety, and welfare of subjects.
- Obtain informed consent from each subject.
- Retain specific records and issue specific reports.
- Assure that an IEC/IRB is provided information for initial and continuing review of the study.
- Ensure that all work and services described within this protocol are conducted in accordance with the highest standards of medical practice and Good Clinical Practice.
- Ensure that all associated clinical and support staff members conduct the study in accordance with the protocol and amendments.
- Ensure that complete and accurate study data is collected and submitted to the sponsor.
- Ensure that the study regulatory binder, and study files containing CRFs, consent information, source documentation, records of adverse events and their resolution and all other relevant subject information are complete and up to date.

The Investigator is responsible for the conduct of the study at the site. Prior to enrollment of first patient, the Investigator must read and understand the Protocol and must sign and complete the Clinical Trial Agreement. The Clinical Trial Agreement requires agreement to all conditions of the Protocol and agreement to conduct the study according to all applicable regulations and guidelines.

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities. The Investigator and/or designee must be available to respond to reasonable requests and queries made by authorized regulatory representatives during the audit process. The Investigator must provide the Sponsor or designee with copies of all correspondence that may affect the review of the current study or their qualification as an Investigator in clinical studies conducted by the Sponsor.

In the event the Investigator is contacted by a regulatory agency (such as the FDA) with regard to this study, the Investigator will notify the Sponsor immediately. The Investigator will ensure the capability for the inspection of applicable study-related facilities and records.

Discontinuation of the Trial by the Sponsor

Philips Volcano reserves the right to discontinue the trial at any time for any of the following reasons:

- Failure to meet expected enrollment goals,
- Any effectiveness/safety information that could significantly affect continuation of the trial or any other administrative reasons

Discontinuation of a Site by the Sponsor

Philips Volcano also reserves the option to terminate the participation of a study site at any time. Reasons for terminating the participation of a study site include, but are not limited to, the following:

- Subject enrollment is unsatisfactory
- Data recording is consistently inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- IRB/IEC decides to terminate or suspend approval for the Investigator
- Study center or Investigator violates GCP or the study contract, disrupting the appropriate conduct of the trial
- Investigator asks to withdraw from study participation

Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the local regulatory authority, as well as applicable US laws and regulations.

Personal Health Information (PHI) will be acquired during the consenting process of the subject and from the medical records. This information will be utilized to identify the subject and contact the subject for emergencies and follow up appointments. The PHI is part of the subject clinic chart, and will be secured in a locked office when not in use. To ensure that confidentiality is maintained, subject names will not be used in this evaluation in any other way. A unique identifying number will be used. This identification method will be consistent for each subject throughout the evaluation.

In the event that a subject revokes authorization to collect or use Protected Health Information (PHI), the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of the authorization.

Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts, abstracts, or presentation materials to Volcano prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator. Any formal publication of the study with the input of Volcano personnel exceeding that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Volcano personnel. Authorship will be determined by mutual agreement.

STATISTICAL ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

Target population

This analysis focuses on CAD Patients reporting an iFR < 90 in at least one coronary artery chosen from 25 US and International centers.

Data lock determination

The dataset will lock after all data needed for assessment of primary and secondary endpoints are reliably obtained, and any impossible data points are investigated and resolved.

Definition of Endpoints

This analysis classifies each patient into one of two categories: patients with residual ischemia (RI) and patients without. This data is distributed binomially, and the primary endpoint measures the proportion of patients with residual ischemia defined as iFR <0.90 after successful PCI (p).

Primary Endpoint Analysis

The primary endpoint, the proportion of patients with RI defined as iFR <90, is computed using maximum likelihood analysis. We compute the maximum likelihood estimate as $p = N^{-1}\sum_{s=1}^{N} y_s$, and Clopper – Pearson 95% confidence intervals.

The null hypothesis states no difference in the proportion of RI from 10%, or more formally, $H_0: p - 0.10 = 0$. The alternative hypothesis concludes any difference in RI from 10%, or $H_a: p - 0.10 \neq 0$.

Sample size computation

We assume a 10% rate of RI in the study (?) population which is defined as a residual stenosis of ≥50% on QCA.

With 500 enrolled patients, type I error held at 5%, and the ability to detect a proportion of 15% RI, this study is powered at 90%.

Secondary Endpoint analysis

Kaplan Meier's product limit estimate computed as $S(t) = \prod_{t_j<t}\left(1 - \frac{d_j}{n_j}\right)$, where we partition time into *j* intervals t_j based on events, will measure time to event endpoints (listed as secondary endpoints 1-5). We conclude a significant survival difference between any two groups with the logrank test, and hold the expected type I error to 5%. We correct the type I error of the 5 related survival hypothesis using Benjamini and Hochberg's False Discovery Rate.

This protocol models Quality of life (secondary endpoint 6) as a mixed linear model,

$Q_{ijt} \sim \mathrm{N}\left(\beta_0 + F_j\left[\beta_1 + b_{1j}T_j\right] + \beta_2 T_j, \Sigma\right)$, where β's describe fixed effects, *b*'s describe random effects, Σ describes a compound symmetric covariance matrix, and N the multivariate Gaussian distribution. We parameterize the covariance matrix with Compound symmetry, as opposed to autoregressive, because within time points will dominate variability compared to across time points.

The Kappa statistic will measure agreement between iFR and QCA's ability to detect RI by computing $\kappa = {(p_e - p_1)}/{(1 - p_1)}$, or the difference between empirical agreement and chance agreement divided by chance disagreement.

We estimate the proportion of cases in which the iFR would become non-significant if a focal stenosis demonstrated by iFR pullback were treated with PCI (Secondary endpoint 8) by

$$p = {\#(\text{Number of non} - \text{significant iFR pullbacks})}/{\#(\text{Patients})}$$

And assess the significance using a Binomial test.

The cause for impaired iFR is summarized using proportions, and the χ^2 test assess the null hypothesis that each cause of impaired iFR occurs at the same rate.

We use linear regression to associate a set of covariates with the change in post-PCI iFR minus pre-PCI iFR. In case of nonlinear associations of covariates with change in iFR, we use kernel regression.

Sensitivity Analysis

The sensitivity analysis evaluates the primary endpoint a second way, using the normal approximation to the binomial distribution. The null hypothesis argues the proportion of RI detected with iFR equals 10%. The alternative hypothesis concludes the proportion of RI detected by iFR is unequal to 10%. The normal approximation tests this hypothesis using the statistic $Z = \frac{\sqrt{n}(p-0.10)}{\sqrt{p(1-p)}}$, and compares this statistic to the standard normal distribution.

Handling Missing data

Any patients with missing primary or secondary endpoints will be list-wise deleted from the above analysis. If unable to recover missing covariates, we will impute missing values for covariates if the total amount of missing values is less than 5%. This analysis will exclude any covariates with a majority of values missing.

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Attachments

Study Sponsor Contacts

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Declaration of Helsinki

The following attachment is a copy of the World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (last amended: 64th WMA General Assembly, Fortaleza, Brazil, October 2013)
[http://www.wma.net/en/30publications/10policies/b3/ accessed 18Dec2013]

Draft Informed Consent Form

Attached

Instructions for Use

Attached