Clinical Investigational Plan

Reference:
SJM-CIP-10136

PRESSUREwire; ClinicalTrials.gov identifier: NCT02935088

PRESSUREwire

"Practical Evaluation of Fractional Flow Reserve (FFR) and its Associated Alternate Indices During Routine Clinical Procedures"

Clinical Investigation Plan (CIP)

Sponsor

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Date 1 August 2016

PRINICPAL INVESTIGATOR SIGNATURE PAGE

Practical Evaluation of Fractional Flow Reserve (FFR) and its Associated Alternate Indices During Routine Clinical Procedures

PRESSUREwire Clinical Investigational Plan

Version B

Reference #: SJM-CIP-10136

I have read and agree to adhere to the clinical investigational plan and all regulatory requirements applicable in conducting this clinical study.

Principal Investigator

Printed name:_____

Signature:_____

Date: _____

Clinical Coordinating Investigator/ Regional Investigator

SIGNATURE PAGE

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Clinical Coordinating Investigator/ Regional Investigator

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Signature:_____

Date: _____

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1.0 SYNOPSIS

Title:	Practical Evaluation of Fractional Flow Reserve (FFR) and its Associated Alternate Indices During Routine Clinical Procedures
Acronym:	PRESSUREwire
Purpose:	The purpose of this study is to understand routine use of FFR and alternate indices in clinical practice. This study will determine the use and clinical outcome of FFR-guided PCI in patients presenting with either stable coronary artery disease, or in patients presenting with Acute Coronary Syndrome (ACS) on culprit and non-culprit lesions as well as during index and secondary procedures. The study will also collect data on the routine use of coronary physiologic measurements such as adenosine-induced hyperemia FFR, FFR by contrast-induced hyperemia, Pd/Pa, and other alternate indices measurements.
Objectives:	All objectives will be evaluated for all subjects enrolled, ACS subjects and stable coronary artery disease subjects separately. 1. Characterize the frequency of change in treatment plan when FFR is used compared to the initial decision based on angiography alone. 2. Characterize the 12 month clinical outcomes (MACE) in subjects in whom the use of FFR did not lead to a change in treatment decision vs subjects in whom the use of FFR led to a change in treatment decision. 3. Characterize the 12 month clinical outcomes (MACE) by FFR values and resting indices respectively. 4. Compare resting indices with FFR values. 5. Characterize the 12 month clinical outcomes (MACE) by other PressureWire-derived indices (coronary flow reserve (CFR), index of microcirculatory resistance (IMR), contrast FFR, resistance reserve ratio (RRR)). 6. Compare other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR) with FFR values.
Design:	This study is a prospective, multicenter, multinational, multicontinental open label observational study. The total duration of the study is expected to be 4 years, which includes 3 years for enrollment with 12 months of follow-up. The clinical study will be conducted in approximately 200 centers globally.

Sample Size and Planned Analysis	This is an observational study. No formal power analysis and sample size calculations were performed. Approximately 2000 subjects will be enrolled in this study. No single center is allowed to enroll more than 10% of the population. A target of 500 ACS patients will be included in the study. This sample size allows reasonable enrollment to detect a signal from events at 12 months.
Devices used:	Any commercially available St. Jude Medical PressureWire™ may be used for this study.
Study Population	A patient becomes a subject (enrolled) once he/she has been fully informed about the study, has agreed to participate, signed & dated the consent, has been determined to meet all inclusion criteria and none of the exclusion criteria, and at least one physiologic coronary pressure measurement with an SJM PressureWire™ has been recorded. Since this study is a routine clinical practice observational study, patients are allowed to be consented after the procedure, but must be consented prior to any data submission. Specific study population characteristics are defined as follows: Patients where FFR has been performed or is planned to be performed for further evaluation of PCI procedures, as per physician clinical practice.
Inclusion/Exclusion Criteria	Inclusion/Exclusion is defined as follows: <u>Inclusion Criteria:</u> 1. Patient is presenting with STEMI, NSTEMI, unstable angina, or stable coronary artery disease 2. Patient is planned to have FFR performed or underwent a cardiac catheterization where FFR was performed for further PCI consideration 3. Patient signs and dates written informed consent 4. Patient is eighteen years of age or older at the time of consent <u>Exclusion Criteria:</u> 1. Patient has extremely tortuous or calcified coronary arteries 2. Patient with a patent coronary artery bypass graft to the target vessel
Data Collection	Data collection will be comprised of baseline demographics and medical history, coronary anatomy, procedure, discharge, and 1 year follow up phone call for MACE events.
Publication of Data	Data is planned to be analyzed and released at enrollment intervals of 500, 1000, 1500, and 2000.

1.1 STUDY ASSESSMENT SCHEDULE

	Baseline	Procedure	Discharge	One Year* (± 30 days)	Interim Visit (Subject with potential MACE event)
Medical History, Demographics and Current Clinical Status	X				
Angiography and PCI procedure Details		X			
Coronary Physiologic Measurements		X**			
MACE Assessment		X	X	X	X
Medication Assessment	X		X	X	X

*Visit may be conducted via a phone call
**May occur at index or secondary procedures for patients presenting with ACS

1.2 STUDY CONTACTS

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2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Fractional flow reserve (FFR) has been demonstrated to be an effective index for determining percutaneous coronary intervention (PCI) approach. FFR is defined as the ratio of maximum blood flow in a stenotic coronary artery to maximum blood flow if the same artery were completely normal. An FFR of 0.80 or less, as measured with the use of a coronary pressure wire during invasive coronary angiography, indicates the potential of a specific stenosis to induce myocardial ischemia with an accuracy of greater than 90%. Therefore, FFR is recommended for the guidance of coronary revascularization.[1]

Randomized clinical trials have demonstrated that in patients with unstable angina and acute myocardial infarction (MI), there are substantial benefits of PCI, including prevention of myocardial infarction and reduced mortality rate.[2,3] In patients with stable coronary artery disease (CAD), PCI has been shown to improve anginal symptoms and quality of life. The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) 2 year data showed that in patients with mutivessel CAD undergoing PCI with drug-eluting stents, routine measurement of FFR as compared with PCI guided by angiography alone resulted in a significant reduction of the rate of mortality and myocardial infarction.[4]

Currently, there has been limited research conducted on the use of FFR in ACS patients. According to Depta, *"*a recent study determined that vasodilatory capacity of the microcirculation was similar between patients with non-ST elevation myocardial infarction and stable angina. Thus, FFR measurement during ACS or AMI may be reliable".[5] While clinical evidence in this setting remains sparse and non-conclusive, FFR use in ACS patients is expanding and more research needs to be conducted.[6] However, recent trials suggest increasing evidence that supports the role of FFR-guided strategy in ACS patients.[7]

For example, Leite notes that, "One of the most important studies about the use of FFR in ACS was from Ntalanis et al.[8] who studied 75 acute STEMI patients and 26 NSTEMI patients (<72 h post onset) and measured FFR in the non-culprit stenosis immediately following PCI of the culprit vessel and then repeated the FFR at 35 + 4 days post initial procedure. The FFR value remained unchanged between the acute and follow-up phases in patients with STEMI (0.78 + 0.10 vs. 0.77 + 0.20, p = NS). In only 2 patients, the FFR value was higher than 0.80 at the acute phase and lower than 0.75 at follow-up. The authors stated the data supports that FFR measurements are safe and reliable for evaluating the severity of non-culprit stenosis in the acute phase of ACS, even during primary PCI."[9]

Alternative indices utilizing pressure wires have also become important to understanding the physiologic significance of coronary artery disease.[10] Adenosine-induced hyperemia FFR, Pd/Pa, FFR by contrast-induced hyperemia, coronary flow reserve (CFR), the index of microcirculatory resistance (IMR), as well as other novel indices e.g. resistance reserve ratio (RRR), potentially aid in treatment decisions of patients with CAD.

To date, there has not been a large registry study analyzing the use of FFR and alternate indices in everyday practice. The PRESSUREwire study looks to expand on the current evidence by collecting additional data on the use and clinical outcome of FFR-guided PCI in patients presenting with stable coronary artery disease, patients presenting with ACS, as well as those who received routine coronary physiologic measurements of adenosine-induced hyperemia FFR, Pd/Pa, FFR by contrast induced hyperemia, and other alternate indices measurements.

The PRESSUREwire study is an observational study intending to collect additional data on the use and clinical outcome of FFR-guided PCI patients presenting with Acute Coronary Syndrome (ACS) on culprit and non-culprit lesions at index and secondary procedures.

3.0 STUDY DESIGN

3.1 PURPOSE

The purpose of this clinical study is to understand routine use of FFR and alternate indices in clinical practice in the treatment of subjects presenting with either an Acute Coronary Syndrome (ACS) or stable coronary artery disease.

3.2 STUDY DESIGN AND SCOPE

This study is a prospective, multicenter, multinational, multicontinental open label observational study.

This study will determine the use and clinical outcome of FFR-guided PCI on patients presenting with either stable coronary artery disease or ACS both for culprit and non-culprit lesions as well as during index and secondary procedures.

The FFR threshold for decision making is anticipated to be 0.80 in line with contemporary guidelines. Since the study is observational, there are no mandated thresholds for any of the physiologic measurements.

The study will also collect data on the routine use of coronary physiologic measurements such as adenosine-induced hyperemia FFR, FFR by contrast-induced hyperemia, Pd/Pa, and other alternate indices measurements.

The total duration of the study is expected to be 4 years, which includes 3 years for enrollment with 12 months of subject follow-up.

The clinical study will be conducted in approximately 200 centers in North America, EMEA, and Asia Pacific.

3.2.1 Number of subjects required

Up to 2000 subjects will be enrolled in this study. No single center is allowed to enroll more than 10% of the population. A target of 500 ACS patients will be included in the study.

3.3 OBJECTIVES

All objectives will be evaluated for all subjects enrolled, ACS subjects and stable coronary artery disease subjects separately.

1. Characterize the frequency of change in treatment plan when FFR is used compared to the initial decision based on angiography alone.

2. Characterize the 12 month clinical outcomes (MACE) in subjects in whom the use of FFR did not lead to a change in treatment decision vs subjects in whom the use of FFR led to a change in treatment decision.

3. Characterize the 12 month clinical outcomes (MACE) by FFR values and resting indices respectively.

4. Compare resting indices with FFR values.

5. Characterize the 12 month clinical outcomes (MACE) by other PressureWire-derived indices (coronary flow reserve (CFR), index of microcirculatory resistance (IMR), contrast FFR, resistance reserve ratio (RRR)).

6. Compare other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR) with FFR values.

Refer to section 12.0 for statistical analysis.

3.4 INCLUSION AND EXCLUSION CRITERIA

A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification code.

3.4.1 Inclusion Criteria

1. Patient is presenting with STEMI, NSTEMI, unstable angina, or stable coronary artery disease
2. Patient is planned to have FFR performed or underwent a cardiac catheterization where FFR was performed for further PCI consideration
3. Patient signs and dates written informed consent
4. Patient is eighteen years of age or older at the time of consent

3.4.2 Exclusion Criteria

1. Patient has extremely tortuous or calcified coronary arteries
2. Patient with a patent coronary artery bypass graft to the target vessel

3.5 SUBJECT POPULATION

3.5.1 Subject Screening

Potential subjects presenting at the investigational site will be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and asked to participate in the study. In case the subject agrees, a duly signed and dated Patient Informed Consent will be obtained.

3.5.2 Point of Enrollment

A patient becomes a subject (enrolled) once he/she has been fully informed about the study, has agreed to participate, signed & dated the consent, has been determined to meet all inclusion criteria

and none of the exclusion criteria, and at least one physiologic coronary pressure measurement with an SJM PressureWire™ has been recorded. Refer to section 3.6 for the Informed Consent Process.

3.6 INFORMED CONSENT PROCESS

3.6.1 General process

Prior to enrolling in the clinical study, all subjects will be consented, as required by applicable regulations and the center's IRB/EC. Informed consent must be obtained from each subject prior to any data collection. The consent form must be signed and dated by the subject and by the person obtaining the consent.

Medical circumstances may occur where potential subjects require emergent medical intervention, and thus measurements of their FFR and other metrics (i.e. patients experiencing ACS). As a result, and since this is a routine clinical practice observational study, subjects are allowed to be consented after the procedure, but must be consented prior to any data submission.

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical study that is relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's IRB/EC. Failure to obtain informed consent from a subject prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing center's IRB/EC consistent with the center's IRB/EC reporting requirements.

4.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

4.1 ANTICIPATED CLINICAL BENEFITS

This is a prospective observational study of market-released products. The potential benefit of participating in this study with standard of care treatment is that data from this study may enhance future treatment for PCI patients.

There are no direct benefits from participating in the study.

4.2 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

This is a prospective observational study of market-released products. Anticipated adverse events or adverse devices effects are the same whether the subject receives the assessment as part of the study or outside of the study.

4.3 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

The risks of taking part in the PRESSUREwire study and undergoing FFR assessment or alternative indices are the same whether the subject receives the assessment as part of the study or outside of the study.

Refer to the Instructions for Use (IFU) in the package labeling for potential risks associated with an SJM PressureWire™.

A risk of study participation is that confidentiality cannot be guaranteed. Investigational site personnel, SJM, and SJM representatives will take measures to de-identify study subject personal health information in an effort to maintain subject anonymity.

5.0 DEVICE UNDER INVESTIGATION

5.1 DEVICE DESCRIPTION

Only market-released products will be used in this study. No comparisons are being made between devices.

St. Jude Medical pressure wires are guidewires with integrated sensor elements at the tip to enable measurements of physiological parameters. These guidewires are uniquely paired with specific transmitters and are available in different lengths.

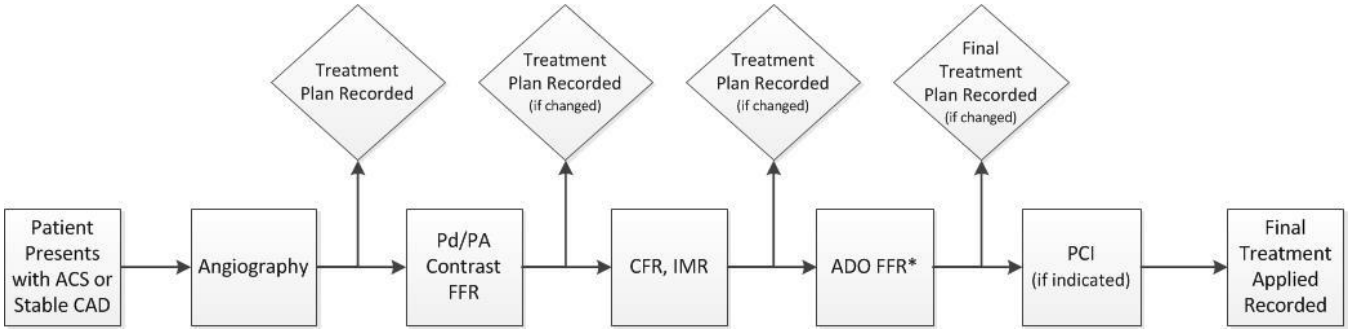
These guidewires are designed to fit inside a percutaneous catheter for the purpose of directing the catheter through a vessel. The signal output from the sensor is transmitted to associated equipment for analysis, used for calculations, and presentation display of physiological parameters functions or indices based on pressure or temperature, e.g. Fractional Flow Reserve (FFR).

Only a commercially available St. Jude Medical PressureWire™ may be utilized for this study.

6.0 PROCEDURES

6.1 STUDY FLOW CHART

Figure 1: Procedural Flow Chart



*ADO FFR – IV or IC adenosine, or another suitable agent (Appendix B), for FFR

6.2 PROCEDURES

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

The clinical study will not commence until St. Jude Medical receives written approval from the IRB/EC and relevant regulatory authorities and all required documents have been collected from the site(s).

Table 1: List of all study specific activities/procedures

	Baseline	Procedure	Discharge	One Year* (± 30 days)	Interim Visit (Subject with potential MACE event)
Medical History, Demographics and Current Clinical Status	X				
Angiography and PCI procedure Details		X			
Coronary Physiologic Measurements		X**			
MACE Assessment		X	X	X	X
Medication Assessment	X		X	X	X

*Visit may be conducted via a phone call
**May occur at index or secondary procedures for patients presenting with ACS

A lesion >50% severity by angiographic assessment is considered to be clinically significant.

6.3 BASELINE VISIT

The following enrollment activities are performed after the subject has been screened and may occur before or after the study procedure/visit.

- The principal or delegated study personnel determine subject eligibility for the study
- Record enrollment information (name of the study, date of consent and inclusion/exclusion information) in the hospital records and complete and submit the Enrollment form in a timely manner (recommended within 5 days)
- Notification of a consented subject to the sponsor will take place when the sponsor receives the baseline form

If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the study and cannot be enrolled.

In case the subject was already consented to participate in the study and an FFR was performed, and it was determined that they do not meet inclusion/exclusion criteria, the following actions will be taken:

- Document enrollment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Baseline and Withdrawal Forms. The form(s) must be authorized / approved by the principal or delegated investigator.
  - Inform the subject about the withdrawal.
  - The EC/IRB and Competent Authority should be notified appropriately, as per local regulations, about any deviations with regards to obtaining the informed consent.

The following information will be collected at the baseline visit:

- Medical history
- Demographics- include subject's Year of Birth and Gender
- Current clinical status

6.4 PROCEDURE

Refer to the Instructions For Use (IFU) for procedural steps.

Fractional Flow Reserve (FFR) is an index determining the functional severity of narrowing(s) in the coronary arteries. FFR specifically identifies which coronary narrowing(s) are responsible for significantly obstructing the flow of blood to the heart muscle. FFR is used in conjunction with cardiac catheterization by placing the pressure wire distal to the coronary lesion and measuring pressure inside the artery. The pressure wire is then retracted until pressure is measured in the entire coronary artery.

The following data points will be collected during the procedure for all evaluated lesions (index or secondary procedures):

- Measurements of Pd/Pa
- Measurements of FFR with Adenosine induced hyperemia (IC or IV)
- MACE assessment (required)
- Prospective treatment decisions; initial treatment plan documentation shall be prior to FFR.

Other indices may be collected, according to the investigator's clinical practice and availability of appropriate devices (index or secondary procedures), as follows;

- IMR measurements
- CFR measurements
- Measurements of FFR with Contrast induced hyperemia
- Measurements of any additional novel resting indices (RI)

6.5 SCHEDULED FOLLOW-UPS

Follow-up visits will occur at Discharge and 1-year.

The following assessments will be completed at the Discharge visit:

- MACE assessment

The following assessment will be completed at the 1-Year visit (±30 days):

- MACE assessment

Note: the 1-Year visit may be conducted via a phone call to the subject.

6.6 INTERIM VISITS

An Interim Visit is defined as any visit that occurs as a result of a potential MACE event outside the windows of the standard assessment schedule.

The following assessments will be completed at an Interim visit:

- MACE assessment

6.7 SUBJECT STUDY COMPLETION

When the subject's participation in the clinical study has been completed after one year follow up, no further patient data will be collected.

6.8 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject does not meet the inclusion/exclusion criteria
- Subject is deceased (cause must be documented)
- Subject's participation is terminated by the PI or investigator, although the subject consented, since participation is no longer medically appropriate
- Subject is 'lost to follow-up': Subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study. (This does not apply to missed visits). Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:
  1. A subject will be considered 'Lost to Follow Up' after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's hospital records.
  2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the subject's hospital records.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal, on a Withdrawal CRF.

7.0 COMPLIANCE TO CIP

7.1 STATEMENTS OF COMPLIANCE

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and Competent Authority approval, if applicable, and authorization from the sponsor in writing for the study.

In case additional requirements are imposed by the IRB/EC or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an IRB/EC, and regulatory requirements with respect to the study, that information will be forwarded to St. Jude Medical.

7.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan (CIP), IRB/EC requirements or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form (CRF). The site will submit the CRF to St. Jude Medical.

Regulations require investigators obtain approval from St. Jude Medical and the IRB/EC [as required] before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB/EC. Such deviations shall be documented and reported to the sponsor and the IRB/EC as soon as possible, but no later than 5 working days.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the investigator's control, must be reported on a CRF.

To obtain approval, the Principal Investigator may call or email and discuss the potential deviation with St. Jude Medical or designee prior to initiating any changes.

All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

Investigator will notify St. Jude Medical and the reviewing IRB/EC within 5 working days of:

- Any deviation to protect the life or physical well-being of a subject in an emergency
- Any failure to obtain informed consent

Investigators or the designee must notify St. Jude Medical, Inc. as soon as possible and complete the Deviation CRF.

The investigator is required to adhere to local regulatory requirements for reporting deviations to IRB/EC.

7.3 REPEATED AND SERIOUS NON-COMPLIANCE

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

8.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT, DEVICE DEFICIENCY

8.1 DEFINITIONS

8.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under study.

8.1.2 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
  - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect
  Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

8.1.3 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

For this study, ADEs include events related to any St. Jude Medical pressure sensor guidewires.

8.1.4 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

8.2 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS, DEVICE DEFICIENCIES/COMPLAINTS, ADVERSE DEVICE EFFECTS, SERIOUS ADVERSE EVENTS, AND SERIOUS ADVERSE DEVICE EFFECTS:

Safety surveillance within this study and the safety reporting both performed by the investigator, starts as soon as the subject is enrolled in this study. The safety surveillance and the safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

Events considered reportable to sponsor are:

- Major adverse cardiac events (MACE) defined as all cause death, documented non-fatal myocardial infarction, and unplanned hospitalization leading to urgent revascularization
    - Myocardial infarction is defined according to the Universal Classification of Myocardial Infarction[11] (Appendix B)
    - Unplanned hospitalization leading to urgent revascularization is defined as unexpected hospitalization due to persisting or increasing complaints of chest pain (with or without ST-T changes) AND a revascularization is performed within the same hospitalization.
- Adverse device effects

All above events will be reported to the Sponsor, as soon as possible, but no later than 72 hours of first learning of the event. These will be reported to the Sponsor on dedicated case report forms or through the EDC system. The Investigator will record all adverse events and device deficiencies on the appropriate case report forms

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

The Sponsor will ensure that all events and device deficiencies are reported to the relevant authorities as per regulations.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

The investigator must notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

8.3 SUBJECT DEATH

8.3.1 Procedure for recording and reporting subject death

All subject deaths are to be documented on the Death case report form and reported to the Sponsor within 72 hours after becoming aware of the event.

8.4 DEVICE DEFICIENCY (DD)/COMPLAINT

During the trial, the investigator will be responsible for reporting all device deficiencies. A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance and includes malfunctions, user errors and inadequate labeling.

If the device deficiency involves an adverse event, the principal investigator must complete an adverse event form including information on the device deficiency and report to the sponsor within 5 days after becoming aware of the event.

If the device deficiency/complaint does not involve an adverse event, the investigator must notify St. Jude Medical as soon as possible after becoming aware of the device deficiency/complaint by emailing the information to CAT_VASC_Complaints@sjm.com or calling +1 651.756.5400. This information will not be collected on a CRF for the study.

St. Jude Medical will manage all device deficiencies related to the identity, quality, durability, reliability, safety or performance of the study device and the reporting to the appropriate regulatory bodies.

9.0 DATA MANAGEMENT

Overall, the Sponsor will be responsible for the data handling.

The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information collected or maintained for this clinical trial. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical trial. All data will be secured against unauthorized access.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, IRB/EC review and regulatory authority inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

9.1 DATA MANAGEMENT PLAN

A detailed Data Management Plan (DMP) will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by St. Jude Medical.

Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system deployed by St. Jude Medical. An electronic audit trail will be used to track any subsequent changes to the entered data.

9.2 DOCUMENT AND DATA CONTROL

9.2.1 Traceability of documents and data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.

9.2.2 Recording data

Source documents will be created and maintained by the investigational site team throughout the clinical study.

The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

The CRFs will be validated (eCRF) by the authorized site personnel.

10.0 MONITORING

Centralized monitoring will occur through routine review of real-time data to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at a site as documented in the Data Management Plan. Additionally, copies of event source documents will be reviewed remotely to ensure data quality/validity.

On-site monitoring may occur at the discretion of the sponsor.

11.0 REGULATORY INSPECTIONS

The investigator and/or delegate should contact St. Jude Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or IRB/EC have not been submitted or are incomplete, inaccurate, false or misleading.

12.0 STATISTICAL CONSIDERATIONS

12.1.1 Sample Size

This is an observational study. No formal power analysis and sample size calculations were performed. Approximately 2000 subjects will be enrolled in this study. To ensure enrollment balance across study centers, no single center will enroll more than 10% of the maximum sample size (200 subjects). A target of 500 ACS subjects will be included in the study.

12.1.2 Analysis Populations

Data from up to 2000 subjects enrolled in this study will be collected and reported. The statistical analyses described in this section will be performed for all enrolled subjects, ACS subjects and stable coronary artery disease subjects separately.

12.1.3 Statistical Method and Analysis

This section describes the statistical method and analysis per subject basis unless otherwise specified. If more than one lesion is measured for a subject, the data analysis may be performed and presented on a per lesion basis, as appropriate.

The following criteria will be used to define the variables per subject level for subject with multiple lesions:

- Treatment decision is defined as “changed” if there is at least one decision change based on FFR for multiple lesions; if none of the decisions has been changed for the multiple lesions, the treatment decision is defined as “unchanged”.
- For all the continuous variables of FFR, resting indices, CFR, contrast FFR, and RRR, we will use the lowest value in all lesions as the value for that variable in each subject. For the continuous variable of IMR, we will use the highest value in all lesions as the value for IMR in each subject.

The following cutoff values will be used to categorize a continuous variable into a binary variable:

- FFR group is defined as “low FFR” if it is equal to or below 0.8 (the cutoff value of 0.8 is selected in line with contemporary guidelines and previous findings[11]). However, since this is an observational study, there are no mandated cutoff values for this. Therefore, we will also use cutoff value of 0.75[12] in the analysis.
- Resting indices group is defined as “low resting indices” if it is equal to or below 0.86 (the cutoff value of 0.86 is selected based on previous findings that a baseline Pd/Pa ≤ 0.86 is associated with a positive predictive value of 100% for FFR measurement[13]). We will also use the cutoff value of 0.92[14] in the analysis.

- CFR is defined as “low CRF” if it is below 2.0 (the cutoff value of 2.0 is selected based on previous findings[15,16]).
- IMR is defined as “high IMR” if it is equal to or above 25 (the cutoff value of 25 is selected based on previous findings[17]).
- Contrast FFR is defined as “low Contrast FFR” if it is equal to or below 0.83 (the cutoff value of 0.83 is selected based on previous findings[18]).
- RRR is defined as “low RRR” if it is smaller than 2.0 (the cutoff value of 2.0 is selected based on previous foundings[19]).

The following statistical analysis will be performed for each of the study objectives:

1. Characterize the frequency of change in treatment plan when FFR is used compared to the initial decision based on angiography alone

Frequency and percentage of change in treatment decisions when FFR is used compared to the initial decision based on angiography alone will be presented both per subject level and per lesion level.

2. Characterize the 12-month clinical outcomes (MACE) in subjects in whom the use of FFR did not lead to a change in treatment decision vs. subjects in whom the use of FFR led to a change in treatment decision.

12-month MACE event rate will be summarized using frequency and percentage. Fisher Exact test will be performed to evaluate the association between 12-month MACE event and prospective treatment decisions, i.e. change or no change, based on FFR measurements. A repeated measures logistic regression with generalized estimating equations (GEE) per lesion level will be performed if needed.

3. Characterize the 12 month clinical outcomes (MACE) by FFR values and resting indices respectively.

Fisher Exact test will be performed to evaluate the association between 12-month MACE event and binary FFR and binary resting indices variables respectively using the following FFR and resting indices groups:

1) Low FFR group (FFR ≤ 0.8) and high FFR group (FFR > 0.8).
2) Low FFR group (FFR < 0.75) and high FFR group (FFR ≥ 0.75).
3) Low resting indices group (Pd/Pa ≤ 0.86) and high resting indices group (Pd/Pa > 0.86).
4) Low resting indices group (Pd/Pa ≤ 0.92) and high resting indices group (Pd/Pa > 0.92).

A repeated measures logistic regression with generalized estimating equations (GEE) per lesion level will be performed if needed.

A logistic regression will be performed to evaluate the association between 12-month MACE event and continuous FFR and continuous resting indices respectively. A repeated measures logistic regression with generalized estimating equations (GEE) per lesion will be performed if needed.

4. Compare resting indices with FFR values.

Kappa coefficient will be used for binary variables, and correlation will be used for continuous variables to examine agreement between FFR values and resting indices.

5. Characterize the 12 month clinical outcomes (MACE) by other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR).

Fisher Exact test will be used for binary variables, and logistic regression will be used for continuous variables to evaluate the association between 12-month MACE event and other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR) respectively.

6. Compare other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR) with FFR values

Kappa coefficient will be used for binary variables, and correlation test will be used for continuous variables to examine agreement between FFR values and other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR) respectively.

12.1.4 Additional Analysis

Descriptive statistics will be used to summarize each component of MACE rate at 12 months, and FFR, Pd/Pa and other PressureWire-derived indices (CFR, IMR, contrast FFR, RRR) measurements during index procedure and secondary procedures.

12.1.5 Reporting

The following data will be summarized and reported after 500, 1000, 1500 subjects complete 12-month follow-up visit:

- Investigator sites and enrollment status
- Demographic and baseline characteristics
- Serious Adverse events
- 12-month MACE rate

When all enrolled subjects complete 12-month follow-up visit, all statistical analyses described in this section will be conducted and a final clinical report will be completed.

13.0 DOCUMENT RETENTION

The Principal Investigator will maintain all clinical study documents from prior to, during and (as specified) after the clinical study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the Sponsor prior to destroying or archiving off-site any records or reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the Sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit.

The Sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as the CIP, CRFs, Informed Consent form and other subject information, and other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the Sponsor and the coordinating investigator (if applicable).

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB/EC and regulatory authorities, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up per IRB/EC requirements.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

15.0 STUDY COMMITTEES

15.1 STEERING COMMITTEE

The Steering Committee (SC) may be used to advise the sponsor during a clinical study, such as in the development of the study CIP, during the conduct of the study, during data analysis and/or presentation/publication of the study results. Membership may include National PIs or site investigators for the study under review.

16.0 INVESTIGATION SUSPENSION OR TERMINATION

16.1 PREMATURE TERMINATION OF THE WHOLE CLINICAL STUDY OR OF THE CLINICAL STUDY IN ONE OR MORE INVESTIGATIONAL SITES

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.

Possible reasons for early termination of the study by the Sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision
- Recommendation from Steering Committee and Sponsor
- Request from Regulatory bodies
- Request of Ethics Committee(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity

- Failure to report unanticipated adverse device effects within 72 hours to St. Jude Medical and the EC
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles

The study will be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor.

Should either of these events occur, the investigator will return all documents to the sponsor; provide a written statement as to why the premature termination has taken place and notify the IRB/EC and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the IRB/EC or regulatory authority, St. Jude Medical may suspend the clinical study as appropriate while the risk is assessed. St. Jude Medical will terminate the clinical study if an unacceptable risk is confirmed.

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and St. Jude Medical will keep each other informed of any communication received from IRB/EC or regulatory authority.

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the IRB/EC are notified, either by the Principal Investigator or by St. Jude Medical. If the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

If suspension or premature termination occurs, St. Jude Medical will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical study, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

16.2 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

When St. Jude Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, St. Jude Medical will inform the Principal Investigators, IRB/EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision.

Concurrence will be obtained before the clinical study resumes from the IRB/EC or regulatory authority where appropriate.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

16.3 STUDY CONCLUSION

The study will be concluded when:

- All sites are closed AND
- The Final report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure

17.0 PUBLICATION POLICY

The results of the clinical study will be submitted for publication. Details of future publication and presentations will be outlined in a separate publication policy.

18.0 BIBLIOGRAPHY

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APPENDIX A: ABBREVIATIONS

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
CABG	Coronary artery bypass graft
CIP	Clinical Investigational Plan
CFR	Coronary flow reserve
CRF	Case Report Form
eCRF	Electronic Case Report Form
FFR	Fractional Flow Reserve
IB	Investigational Brochure
IC	Informed Consent
IMR	Index of Microcirculatory Resistance
IFU	Instructions For Use
IRB	Institutional Review Board
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PI	Principal Investigator
RDC	Remote Data Capture
RPI	Report of Prior Investigation
RRR	Resistance reserve ratio
SADE	Severe Adverse Device Effect
SAE	Severe Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
STEMI	ST-elevation myocardial infarction
USADE	Unanticipated Severe Adverse Device Effect

APPENDIX B: STUDY GUIDELINES

Universal Classification of Myocardial Infarction

Type 1: Spontaneous myocardial infarction Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, Assuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type 2: Myocardial infarction secondary to an ischemic imbalance In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: Myocardial infarction resulting in death when biomarker values are unavailable Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI) Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (<99thpercentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG) Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Hyperemic agent recommended doses

Agent	Recommended dose (IV)	Recommended dose (IC)
Adenosine	140 µg/kg/min	100 µg for right coronary artery 200 µg for left coronary artery
Adenosine 5'-triphosphate (ATP)	150 ug/kg/min	N/A
Nicorandil	N/A	2 mg
Regadenoson	0.4 mg	N/A

APPENDIX C: CIP REVISION HISTORY

Revision History				
Amendment Number	Version	Date	Rationale	Details
Not Applicable	A	15APR2016	First release of CIP	NA
1	B	22JUL2016	Clarifications and minor enhancements	NA

Appendix D: DECLARATION OF HELSINKI

The most current version of the document will be followed.

Appendix E: LIST OF CLINICAL INVESTIGATION SITES AND IRB/EC

A list of Clinical Investigational sites and IRB/EC will be kept under a separate cover and is available upon request.

Appendix F: SAMPLE INFORMED CONSENT

The study specific informed consent template will be provided under separate cover

Appendix G: CASE REPORT FORMS

Final Case Report Forms will be provided under separate cover.