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(ASSESSING MICROVASCULAR RESISTANCE VIA IMR TO PREDICT CUMULATIVE OUTCOME IN STEMI PATIENTS UNDERGOING PRIMARY PCI)

Clinical Investigational Plan (CIP)

SPONSOR

St. Jude Medical Italia S.p.A.
Centro Direzionale Colleoni
Palazzo Andromeda, 20/3
20864 Agrate Brianza (MB)
Italy
Tel: +39 039 6074700
Fax: +39 039 6074762

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1 Background

Despite the good results obtained with coronary arteries revascularization after primary percutaneous coronary interventions (PCI) in ST-elevation myocardial infarction (STEMI) patients, a significant portion of patients may have a poor outcome due to the presence of microcirculation coronary damage[1,2].

Microcirculation evaluation is now potentially possible through the index of microcirculatory resistance (IMR), which was first evaluated in animal models and in stable patients[3-6].

IMR measurement, which expresses the micro-vascular function, can be done through a pressure sensor / thermistor-tipped guidewire.

The potential advantages of IMR over current methods (Thrombolysis in myocardial infarction Myocardial Perfusion Grade (TMPG), coronary flow reserve (CFR), resolution of the sum of ST-segment elevation (ST-resolution), corrected Trombolysis in myocardial Frame Count (cTFC), Myocardial Contrast Echo Score Index (MCESI)) to evaluate the microcirculation are: relative ease of use and interpretation, quantitative nature, independence of the epicardial vessels and reproducibility[5,7].

The relative ease and measurement reproducibility of IMR shows lot of advantages if compared with the microcirculation assessment by traditional methods.

IMR obtained by this technique was measured in STEMI patients after primary PCI and compared to traditional methods to assess the microvasculature.

Compared to standard measures, IMR appears to be a better predictor of microvascular damage after STEMI, both acutely and in short term follow-up[8].

IMR is a reliable early on-site determinant of myocardial viability and LV recovery after stenting for acute myocardial infarction (AMI)[9]. However, the correlation between short and mid-term outcomes and IMR values measured during treatment with PCI in STEMI patients is currently not yet well defined.

The purpose of this study is to detect any correlation between IMR and the short and medium term outcomes, defined as cardiovascular death, re-Myocardial Infarct (MI), re-hospitalization for Heart Failure (HF), resuscitation or Implantable Cardioverter Defibrillator (ICD) appropriate shock, in this population.

2 Study Purpose

2.1 Objectives

Primary Objective

To assess whether the IMR can be considered a prognostic predictor for the occurrence of events (as hereinafter further defined) at one year of follow up after primary PCI in STEMI patients.

Secondary Objectives

Evaluation of:

- A better cut-off of IMR for the prognosis of study patients
- New CHF during index hospitalization

- Left Ventricular remodeling
- Incidence of new revascularization
- Incidence of stent thrombosis
- ST Resolution or residual ST elevation
- Possible predictors of patient outcomes

2.2 Endpoints

2.2.1 Primary Endpoints

Composite of: cardiovascular death*, re-myocardial infarct, re-hospitalization for heart failure (HF, CHF), resuscitation or ICD appropriate shock, at 1 year.

* Timing for mortality evaluation: once culprit lesion has been evaluated through IMR

2.2.2 Secondary Endpoints

- Evaluation of a better cut-off of IMR index based on primary endpoint events
- New CHF during index hospitalization
- Left Ventricular (LV) remodeling @ 1y (improvement of EF%, LVESV, LVEDV, LVEDD, LVESD, 16 segments WMSI and mitral insufficiency, assessed by TTE)
- Need for new revascularization @ 1y(revascularization yes/no)
- Stent thrombosis @ 1y (thrombosis yes/no)
- ST resolution or residual ST elevation post PCI (Electrocardiographic ST-segment elevation in two or more contiguous electrocardiogram (ECG) leads)
- Evaluation of possible events predictors including but not limited to age, sex, infarct area, Killip risk, number of PCI

2.3 Patient Selection Criteria

A patient who meets all the inclusion criteria and does not meet any of the exclusion criteria is eligible to participate in the investigation. A patient is enrolled in the investigation only when s/he has provided written informed consent. Once enrolled, a patient is expected to comply with the scheduled visits and required activities according to the protocol.

2.3.1 Inclusion Criteria

Patients meeting all the inclusion criteria could be considered for inclusion in the study:

- Patient of legal age in hosting country able and willing to provide informed consent form
- Hospital admission either within 12 h of symptom onset or between 12 and 24 h after onset with evidence of continuing ischemia
- Electrocardiographic ST-segment elevation ≥1 mm in two or more contiguous ECG leads, or with a left bundle-branch block (LBBB)
- Multivessel diseased patients with lesions in the proximal 2/3 part of the vessels
- Culprit Lesion EB identified during evaluation of basal angiography
- Presence of at least one non-culprit lesion >50% EB detected in the basal angiography and eligible for PCI for which the operators decision is to perform a staged pre-discharge angioplasty procedure

2.3.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Patients who cannot give informed consent
- A life expectancy of less than 1 year
- Patients who are pregnant or nursing
- Contra-indication to angiography
- Allergy/intolerance to Adenosine
- Contra-indication/Allergy/Intolerance to contrast media or to medical therapy foreseen for PCI
- Documented allergy to Adenosine diphosphate (ADP) inhibitors (aspirin and clopidogrel)
- New infarct on the same area of a previous infarct
- Critical non treatable Lesion EB>70% downstream of the culprit lesion
- Absence of non-culprit lesion/s
- Patient with hemodynamic instability not controllable with medical therapy and/or need intra aortic balloon pump implantation (IABP)
- Prior Coronary Artery Bypass Graft (CABG) or indication for CABG
- Patients with Left Main (LM) coronary artery disease requiring revascularization

2.4 Study Design

This is a prospective, multicenter study designed to evaluate IMR ability to predict events occurrence, defined as Cardiovascular death, re-MI, re-hospitalization for HF, resuscitation or ICD appropriate shock, during a 1 year follow-up period.

Patients will be enrolled in the study at hospital admission after the pathology assessment has been done. All participants will have the culprit lesion treated following clinical practice and guidelines [10, 18]; Fractional Flow Reserve (FFR) and IMR will be measured after the primary PCI procedure to evaluate treatment success and myocardial viability. Non-culprit lesions will be functionally evaluated through FFR index and will be treated if FFR will show functional stenosis [11]. FFR and IMR will be measured to evaluate treatment success and myocardial viability. Patients will be followed-up at 1m, 6m and 1y periods.

Device used to assess FFR and IMR is already in use in clinical practice at participating centres. The wire is used following indication for use (IFU), guidelines and clinical practice in the selected centers.

Fig. 1: Study Flow-Chart

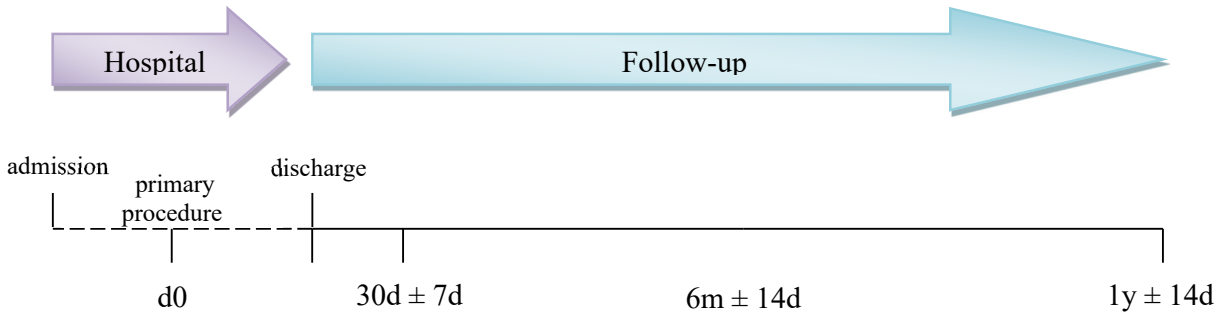

Fig. 2: Patient Procedure Flow

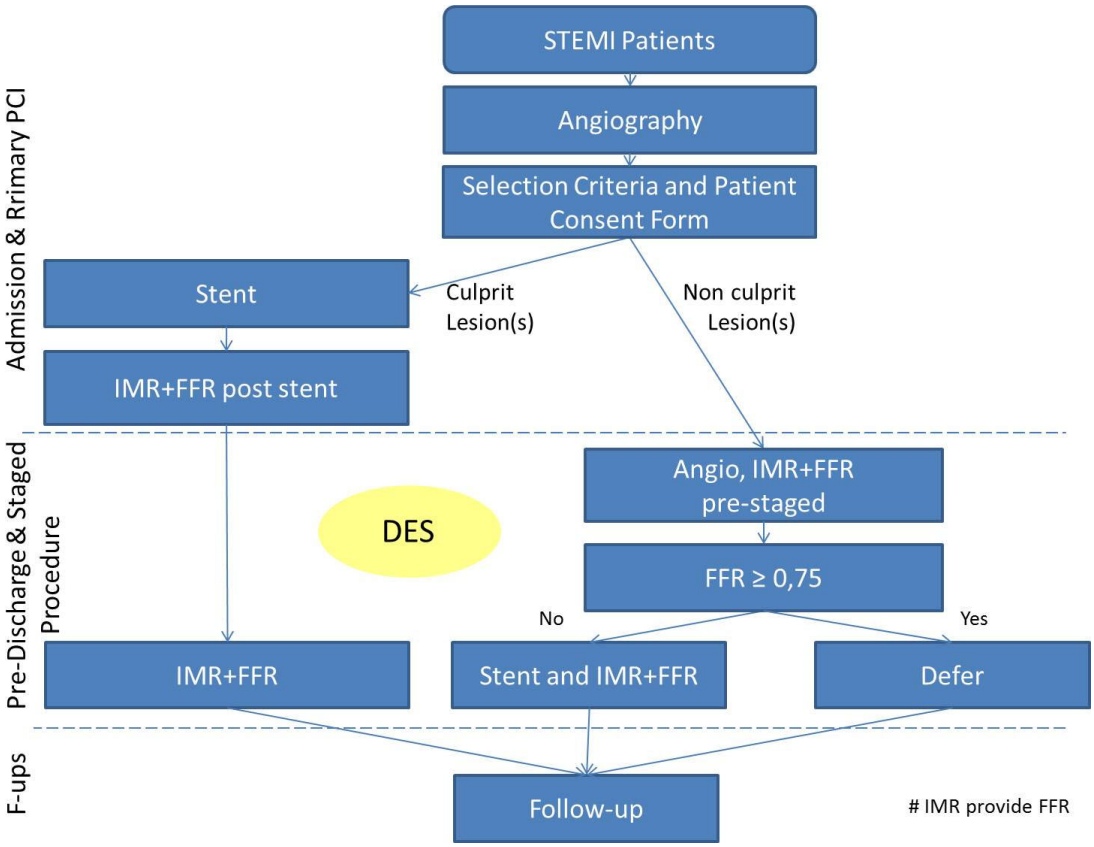

Table 1: Data Collection

	Enrollment	PCI Procedures	90 min post PCI	Pre Discharge	1m f-up	6m f-up (phone)	1y f-up
Patient Eligibility	√						
Informed consent	√						
Demographic data	√						
Medical History	√						
Risk and Functional Classifications	√	√		√	√	√	√
Medications	√	√		√	√	√	√
Enzymes	√@	√@		√@	√+		√+
Cholesterol/ Triglycerides	√ç	√ç		√ç	√+		√+
ECG	√	√#	√*	√			
TTE (echo)				√			√
Procedure Data		√					
IMR-FFR		√					
F-up clinical status					√	√	√
Adverse Events		√§	√§	√§	√§	√§	√§

#: post procedures
*: only for primary PCI *(cont.)*

§: if applicable
+: if available per center practice
ç: at least once during the patient hospitalization, values as available per local laboratory and center practice
@: at least twice during the patient hospitalization, strongly recommended at baseline and post-primary PCI visits, values as available per local laboratory and center practice

2.5 Devices Used

2.5.1 Device used to assess IMR and FFR

Index of Microcirculatory Resistance (IMR) and Fractional Flow Reserve (FFR) index will be assessed by St Jude Medical PressureWire® guidewire.

PressureWire® is indicated to direct a catheter through a blood vessel and to measure physiological parameters (pressure, flow and temperature) in the heart and in the coronary and peripheral blood vessels.
This last generation coronary guidewire, with multifunctionality sensor chip on its tip, enables multiple parameters assessment with one wire. It allows FFR assessment through pressure measurements and Coronary Flow Reserve (CFR) and IMR assessment through temperature and pressure measurements.
These indexes allow the functional evaluation of coronary stenosis and the PCI optimization.

IMR is a diagnostic and reproducible index to quantitatively evaluate the microcirculatory pathology and is calculated dividing myocardial pressure drop by the flow.
Measuring the index in revascularized myocardial area and considering as null the effect of collateral flow, IMR is calculated through the following simplified formula [3, 4]:

$$IMR = P_d \cdot T_{mn}$$

(with the maximal hyperemia condition)

PressureWire Certus is a Class III marked release guidewire. As for all the traditional guidewire, it is not intended to be left in the human body. It is contraindicated for the use in the cerebrovascular system.

2.6 Study Size and Duration

The total sample size is calculated in 242 patients to be enrolled by participant centers following the protocol indication.

First enrollment has been done in June 2013.
Enrollment period will be approximately 30 months.
Patients will participate in this investigation for approximately 12 months from enrollment to the last follow-up.
Study duration will be approximately 3/4 years.
The number of participant centers is foreseen as up to 20.

3 Protocol Description

3.1 Overview

The following table lists study activities that are performed at each scheduled visit.

Table 2: Activities performed at each scheduled visit

Visit	When	Type	Activities
Enrollment & Procedures & Predischarge	In Hospital Visits	In-Clinic	▪ Patient Eligibility ▪ Patient Informed Consent ▪ Patient Demographics ▪ Patient Physical Examination ▪ Patient Cardiovascular History ▪ Patient Medical History ▪ Risk and Functional Classifications ▪ Patient Current Cardiac Medications ▪ Cholesterol/Triglycerides/Enzymes+ ▪ Echocardiography ▪ 12-Lead ECG ▪ Procedure data ▪ Discharge evaluation ▪ Adverse Events *
1M Follow Up	30 ± 7 days post-primary PCI	In-Clinic	▪ Patient clinical status and medication ▪ Cholesterol/Triglycerides/Enzymes+ ▪ NYHA & CCS class assessment ▪ Adverse Events *
6M Telephone Follow Up	183 ± 14 days post- primary PCI		▪ Patient clinical status and medication ▪ NYHA & CCS class assessment ▪ Adverse Events *
12M Follow Up	365 ± 14 days post- primary PCI	In-Clinic	▪ Patient clinical status and medication ▪ Cholesterol/Triglycerides/Enzymes+ ▪ NYHA & CCS class assessment ▪ Echocardiography ▪ Adverse Events *

*: If applicable

+: refer to table 1 for timing and details

3.2 In Hospital Visits

Enrollment activities are performed at hospital admission and during hospitalization time. After ECG & coronary angiogram required per clinical practice are performed, enrollment criteria are assessed and Patient Informed Consent will be asked to the selected patient. Demographic data, medical history, risk factors, medications and procedure information including blood and enzymes values will be collected during hospitalization.

Enrollment is possible only in case of patient eligibility (all the inclusion criteria met and all the exclusion criteria not-met) and after written consent is signed and dated by patient

(refer to Appendix H for Patient Informed Consent, PIC): the PIC is to be Local Ethical Committee approved.

Enrolment information are entered in the electronic case report form (eCRF) and authorized by the principal investigator or delegates. (Refer to “Appendix F for Data Collection Method” and refer to “Appendix G for Case Report Form” regarding patient data collected for this investigation).

All activities, performed after patient is enrolled in the investigation, are shown in the Table 2.

3.2.1 Procedures

Primary PCI is performed as soon as possible, following the center clinical practice, to treat the culprit lesion. Drug Eluting Stent (DES) of choice in the center and required by the lesion anatomy will be used following the usual clinical practice. FFR and IMR will be measured at the end of the procedure.

Staged procedure to treat the non-culprit lesion will be performed before hospital discharge as per normal clinical practice of the center. FFR and IMR will be measured and lesion will be treated only if FFR will show functional stenosis. Distal lesion that can’t be crossed with the guidewire will be treated as per clinical practice. Drug Eluting Stent (DES) of choice in the center and required by the lesion anatomy will be used following the normal clinical practice in each center. FFR and IMR will be measured at the end of the procedure. An ECG will be assessed approximately 90 minutes after primary PCI procedure. A TTE (Echo) will be performed before the patient discharge.

Medical therapy during the procedure and at the hospital discharge will be driven by usual clinical practice, guidelines and standard of care recommendations.

3.3 Follow-up Visits

According with the study design, patients are followed for a total duration of 12 months. As per protocol, scheduled Follow Up will be at 1, 6 and 12, months after primary PCI.

3.3.1 One Month In-Clinic Follow Up

One month In-Clinic Follow Up is performed by investigator or delegates as per standard practice and in accordance with the activities listed in the Table 2.

All information entered in the eCRF is authorized by the principal investigator or delegates. (Refer to “Appendix F for Data Collection Method” and refer to “Appendix G for Case Report Form” for information regarding patient data collected for this investigation).

3.3.2 Six Months Telephone Follow Up

Six months Follow Up is performed by investigator or delegates in accordance with the activities listed in the Table 2.

All information entered in the eCRF is authorized by the principal investigator or delegates. (Refer to “Appendix F for Data Collection Method” and refer to “Appendix G for Case Report Form” for information regarding patient data collected for this investigation).

3.3.3 Twelve Months In-Clinic Follow Up

Twelve months In-Clinic Follow Up is performed by investigator or delegates as per standard practice and in accordance with the activities listed in the Table 2.

All information entered in the eCRF is authorized by the principal investigator or delegates. (Refer to “Appendix F for Data Collection Method” and refer to “Appendix G for Case Report Form” for information regarding patient data collected for this investigation).

3.4 Protocol Deviation

Investigators are required to adhere to the Investigational Plan, signed Investigator’s Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate Ethics Committees or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the protocol was not followed. Should a protocol deviation occur, deviation information will be recorded in hospital records provided for the investigation; then the protocol deviation information is entered in the eCRF and authorized by the principal investigator or delegates as soon as possible (Refer to “Appendix F for Data Collection Method” and refer to “Appendix G for Case Report Form” for information regarding patient data collected for this investigation).

The following details will be reported on the eCRF:

- Date of deviation
- Classification of deviation
- Deviation details
- Corrective actions

Minor deviations are defined as changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Minor deviations will be notified to St. Jude Medical by the investigator within 1 month after becoming aware of the minor deviation.

Serious deviations are defined as deviations that affect patient’s rights, safety, wellbeing and/or that affect the scientific integrity of the clinical investigation, including those which occur under emergency circumstances. Serious deviations will be notified to St. Jude Medical by the investigator within 3 calendar days after becoming aware of the serious deviation.

3.5 Adverse Events

3.5.1 Definition of Adverse Event, Adverse Device Effect, Serious Adverse Event and Serious, Unanticipated and Anticipated Adverse Device Effect

For the purposes of the clinical report, St. Jude Medical will classify each adverse events according to ISO 14155: 2011: Clinical investigation of medical devices for human subjects - Good clinical practice.

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 medical device.
NOTE: This definition includes events related to the medical device or the comparator.

NOTE: This definition includes events related to the procedures involved.

Adverse Device Effect (ADE)
An adverse event related to the use of a medical device

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

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

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 without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)
An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated Serious Adverse Device Effect (ASADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

3.5.2 List of Possible Adverse Events and Adverse Device Effects

There are no obvious risks associated with the study conduction.

Possible adverse device effects and adverse events include but are not limited to those foreseen with other normal coronary guidewire use and with normal PCI procedure.

Potential complications which may be encountered during all catheterization procedures include but are not limited to: vessel dissection or occlusion, perforation, embolus, spasm, local and/or systemic infection, pneumothorax, congestive heart failure, myocardial infarction, hypotension, chest pain, renal insufficiency, serious arrhythmias or death.

3.5.3 Procedure for assessing, recording and reporting Adverse Events, Adverse Device Effects, Serious Adverse Events and Serious Adverse Device effects

Safety surveillance and reporting will be done for all patients enrolled in this study.

Safety surveillance within this clinical investigation and safety reporting, both performed by the investigator, starts as soon as the patient is enrolled in this clinical investigation (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last follow-up visit has been performed or the patient is deceased or the patient/investigator concludes his participation into the clinical investigation.

NOTE: If an adverse event is documented at the patient's last follow up visit, both the notification and follow-up information on the AE CRF are to be provided to the sponsor.

- All serious Adverse Events and all Adverse Device Effects (serious or non-serious) are to be documented and reported to the sponsor maximum 3 calendar days after becoming aware of the event.
- Non-serious adverse events documentation and reporting are limited to cardiovascular and neurovascular events and to events endpoints related.

Should an AE occur, record AE information in the hospital records, document the information into the adverse event form as soon as possible. By completing the form, the sponsor will be notified. Refer to Table 1: Data Collection and Appendix F for Data Collection Method. In case of EDC failure, notify Sponsor via Fax (+800 2546 2546) or via AdverseEvent@sjm.com.

Sponsor will be responsible for ensuring the assessment of immediate AE 'reportability' or 'non-reportability' to the competent authorities. All the reported AEs will be documented and reported in a periodic report.

Additional information may be requested, when required, by the sponsor in order to support the reporting of AEs to regulatory authorities and to support AE analysis. The investigator must notify the EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the sponsor.

In case of disagreement between sponsor and investigator in the AE assessment, then both assessments will be reported.

3.6 Early Conclusion of Patient Participation

All reasonable efforts should be made to retain subjects within the clinical trial until completion of the required period of participation. In addition to withdrawal following completion of the clinical trial, reasons for withdrawal include, but are not limited to the following:

- Patient and/or Family Request
- Patient Lost to Follow-Up
- Patient Withdrawn by Investigator
- Patient Withdrawn by Sponsor
- Patient Death

In case of withdrawal the Sponsor will be notified filling the Termination eCRF.

All information entered in the eCRF is authorized by the principal investigator or delegate. (Refer to "Appendix F for Data Collection Method" and refer to "Appendix G for Case Report Form" for information regarding patient data collected for this investigation).

3.7 Patient Death

In case of patient death, all death information has to be recorded in either hospital records or the patient death worksheet provided for the investigation and immediately entered in the corresponding eCRF and authorized by the principal investigator or delegates (Refer to "Appendix F for Data Collection Method" and refer to "Appendix G for Case Report Form" for information regarding patient data collected for this investigation): it is Investigator's responsibility to inform the sponsor within 72 hours of becoming aware of the death. It is also Investigator's responsibility to notify the ECs, according to their required timelines.

It is Sponsor's responsibility to inform the competent authorities, locally and nationally as required.

The patient death eCRF must always be accompanied with the documentation of pertinent events; furthermore completing the appropriate eCRF (Adverse Event, Death and Termination) must be completed.

The following information will be reported on the patient death eCRF:

- Date of death.
- Place death occurred (e.g. hospital, nursing home, patient's home)
- If death was witnessed
- Cause of death
- Any other circumstances surrounding the death
- Approximate time interval to death from the initiating event (e.g. sudden, non sudden)
- Autopsy report (if performed)

3.8 Study Termination

The study can be prematurely or temporarily stopped or terminated, either at local or national level, at the request of Ethics Committees, Competent Authorities or the Sponsor.

The study may also be put on hold or even terminated by the Study Steering Committee, for safety, ethical or other reasons, at the request of Adverse Event Committee.

The study is terminated/has ended when:

- The sample size has been reached AND
- Follow up period has been completed AND

- The Database has been cleaned AND
- A Close Out visit has been performed AND
- Appropriate communication has been distributed AND
- The Final report has been provided.

After the study closure, the patients will be managed following the standard medical care.

4 Scientific Soundness

4.1 Sample Size

Study aim is to assess/explore, in a cohort of STEMI patients at 1 year of follow-up from primary PCI, if categorization of IMR based on the median value can be considered a predictive / prognostic for the occurrence of cardiovascular events such as death, re-MI, re-hospitalization for HF, resuscitation or appropriate ICD shocks.

It is believed, based on the events reported in similar cohort of patients [12-17], that the expected events at one year should be of 12-16%.

The present study aims to demonstrate that the incidence of events is significantly different in the two subpopulations of patients with IMR upper and lower of the value of 32, found by Fearon et al.[8]; other authors found the median value as event predictor[9].

Based on these assumptions, hypothesizing an incidence of events/year by 7% in the group of patients with IMR values below its median and 21% in the group with higher values of IMR, with an alpha error = 0.05, a power of 85% and applying the two tails Chi-square test, it is estimated that 218 patients are needed.

Providing a dropout rate of 10%, the number of patients who must be enrolled will be 242.

It is assumed that the participant centers will be up to 20. Based on number of cases in previous year evaluation, enrollment mean rate is assumed to be approximately 6-10 patients/year/center.

4.2 Statistical Methods

Data analysis will begin when all patients enrolled in the specified period will have completed 12 months of follow-up.

Descriptive statistics:

Continuous variables will be described by means of position indexes (mean, median, quantiles that best fit the needs of data analysis) and index of dispersion (standard deviation, interquartile distance, range).

Categorical variables will be described using absolute frequencies and relative frequencies rates.

The 95% confidence intervals (CI 95%) will accompany study parameters estimations.

Graphical representation (box plots, histograms, etc...) will complement the descriptive analysis.

Primary Objective Analysis:

The Chi-square test will be used to evaluate the existence of associations between IMR-values (above and below the median) and the outcome.

Secondary Objective Analysis:

IMR analysis as a possible predictive index will initially be carried out by evaluating whether there are quantiles that better identify classes of patients with higher risk of defined major cardiac event.

Discriminant model (ROC curve) will allow to assess whether there are IMR-threshold values (cut-off) to allow classification of patients at increased or decreased risk of future events.

The analysis of variance (ANOVA) for repeated measures or the analysis of covariance (ANCOVA) to multiple factors will be used to assess whether there are significant changes in continuous parameters during post-intervention.

Kaplan-Meier analysis of event-free survival (EFS) allows the assessment of possible risk factors (gender, age, smoking, cholesterol, etc…) testing the significance by log-rank test.

The significant results and other factors considered clinically relevant will be included, as independent variables in a Cox regression model having the appearance or not of composite event and the time as dependent variables.

Where multiple comparisons will be assessed, corrections for multiple comparisons will be applied and specified as needed.

Values of $p < 0.05$ are considered statistically significant.

Ad-interim analysis

Ad-interim reporting, providing the summary tables, may be performed if necessary or required by CCIs and/or investigators, or project leader.

5 Risk Description and Minimization

5.1 Risks

The risks involved with this study are similar to those associated to the same class of patient that underwent PTCA procedure to treat Myocardial Infarction.
Patients follow-up do not include invasive test avoiding any added risks.
There should be no additional risks to the patients assigned to this study. All devices will be market released.

5.2 Benefits

All patients will be more closely monitored by physician throughout the duration of the investigation. Patients will be evaluated at pre-determined time points to assess their status. In addition, similar benefits may accrue to future subjects through experience

gained in this clinical study. IMR information should give the possibility to better find the best health solution for patients enrolled in this study and for the future.

6 Study Organization

6.1 Study Sponsor

St. Jude Medical Italy, referred to SJMI, is the Sponsor of the study:

St. Jude Medical Italia S.p.A.
Clinical Department
Centro Direzionale Colleoni
Palazzo Andromeda, 20/3
20864 Agrate Brianza (MB)
Italy
TEL: +39 039 6074700
FAX: +39 039 6074762

6.2 Study Investigators

This clinical study will be conducted by qualified investigators who have experience with the use of device. Qualified Investigators are familiar with the PCI optimization by the assessment of stenosis functional evaluation through FFR and with IMR index for the myocardial viability assessment.

6.2.1 Coordinating Clinical Investigator

The following Investigators have been appointed by the Sponsor as the study Coordinating Clinical Investigator:

Dr. Massimo Fineschi
Policlinico S. Maria Le Scotte di Siena
V.le Bracci, 16
Loc. Le Scotte, Siena - I

Dr. Marco Valgimigli
Erasmus Medical Center,
Thoraxcenter, Room Ba-587
's Gravendijkwal 230,
3015 CE Rotterdam - NL

6.2.2 Investigator's responsibilities

A Principal Investigator should have experience in and/or will be responsible for:

- Providing signed Investigator/Co-Investigator (s) Agreement;
- Providing signed Financial Disclosure Form of Clinical Investigators;
- Providing appropriate Ethics Committees Approved Patient Informed Consent and Patient Informed Sheet;
- Conducting the clinical investigation in accordance with the signed agreement with SJMI, the investigational plan, all applicable laws and regulations and any

approval conditions imposed by the appropriate Ethics Committees or applicable regulatory authorities where the study is performed;
- Collection and archiving of data obtained prior to procedure, during procedure, at follow-up examinations and after the study has been completed;
- Strict adherence to the Investigational Plan testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation;
- Screening and selecting appropriate patients;

It is acceptable for the Principal Investigator to delegate one or more of the above functions to an associate or co-investigators; however, the Principal Investigator remains responsible for proper conduct of the clinical investigation, compliance with the investigational plan and collection of all required data. The Investigation is not transferable to other centers attended by the Investigator unless prior approval is obtained from SJMI.

In addition to the responsibilities of the Investigators, the study Coordinating Clinical Investigator will:

- Sign off the final version of the study protocol and after modifications to the protocol if any amendment will be required;
- Act as main contact for all study investigators in case of medical questions related to study conduction.

6.3 Amendment Procedure

Non-substantial changes to, or formal clarification of, the clinical investigational plan must be documented in writing, by Sponsor. Major changes to the protocol will be described in a “CIP Amendment”. Amendments will be submitted to the relevant EC and to authorities, where required. Approval/favourable opinion from the relevant EC will be required prior to implementation of the amendment.

Any amendment affecting the patient requires patient’s informed consent prior to implementation. Amendments will be signed by all signatories of the protocol. By signing the Amendment Signature Page, Investigators acknowledge the content of the Amendment and confirm that they will adhere to the Amendment change. Signature page will be filed in the Investigator Study Binder and in the Study Master File.

6.4 Study Boards

The clinical study will be conducted as up to 20 sites. A complete list of Study Coordinators, Study Sites, Sites Principal Investigators and Institutions (i.e Core Labs, Clinical Event Committee) will be maintained by the Sponsor.

6.5 Ethical Basis

This study will be conducted according to ISO14155:2011 “Clinical Investigation of medical devices for human subjects – Good clinical practice”, as guidance. It will comply with the World Medical Association Declaration of Helsinki concerning medical research and will be carried out in accordance with local legal and regulatory requirements.

An Institutional Review Board (IRB) and/or Medical Ethic Committee (MEC) written approval is required for center participation in this study. According to Italian Laws about

post marketing clinical trials, with marked release medical device (Decreto Legislativo 46/97, art. 14, comma 8 and Decreto legislativo 502/97, art. 7, comma 7, as modified by Decreto Legislativo 37/10), St Jude Medical Italy will have to provide Italian Competent Authority (CA) a communication with all the information concerning the beginning of the study, including the end or interruption date, through MoH website.

In case additional requirements will be imposed by the Ethics Committee or National Competent Authority/National Regulatory Authority, they shall be followed, if appropriate.

All devices used in this investigation have received regulatory approval and are marked release and used within labeling.

6.6 Insurance

As Sponsor of this study, St. Jude Medical Italy has taken out insurance for all patients participating in this study.

6.7 Study Management

The study had to be conducted, recorded and reported in accordance with the Clinical Investigational Planand the applicable laws and regulations.

6.7.1 Study initiation visit

Before any study activities, SJMI personnel will contact the Investigator to discuss the investigational plan and review the data requirements in detail.

6.7.2 Monitoring visits

Centralize monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance. On site monitoring may occur at the discretion of the Sponsor.

6.7.3 Competent Authority (CA) Inspections

The Investigator and/or designate should contact St. Jude Medical Italy, immediately upon notification of impending CA inspection. A clinical monitor will assist and immediately review study documentation with the investigator and/or designate to prepare for the audit.
An investigator who has authority to grant access shall permit authorized CA 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 other person acting on behalf of such a person with respect to an investigation, shall permit authorized CA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to the study.
An investigator shall permit authorized CA employees to inspect and copy records that identify subjects, upon notice that CA 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 EC have not been submitted or are incomplete, inaccurate, false, or misleading.

6.8 Contacts

SJM Study Management:

Alessandra DENARO Clinical Department Manager	Phone: Fax Mobile: Email:	+39 039 6077123 +39 039 6074762 +39 342 7528882 adenaro@sjm.com
Massimo SCANDELLA CVD Clinical Project Manager	Phone: Fax Mobile: Email:	+39 039 6074761 +39 039 6074762 +39 335 7297716 mscandella@sjm.com
Benedetta VANONI CVD Clinical Project Leader	Phone: Fax Mobile: Email:	+39 039 6074761 +39 039 6074762 +39 340 5710642 bvanoni@sjm.com

Appendix A: Abbreviations & Definitions

Abbreviations	Termes
AMI	Acute Myocardial Infarction
AN(C)OVA	Analysis of (Co)Variance
CABG	Coronary Artery Bypass Graft
Class 1A	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Data derived from multiple randomized trials or meta-analyses.
CRF	Case Report Form
CVA	Cerebral Vascular Accident
DES	Drug Eluting Stent
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFS	Event-Free Survival
ESC	European Society of Cardiology
FFR	Fractional Flow Reserve
Fup	Follow Up
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
IMR	Index of Microcirculatory Resistance
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LV EF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular end Systole Volume
LVEDV	Left Ventricular end Diastole Volume
LVESD	Left Ventricular end Systole Diameter
LVEDD	Left Ventricular end Diastole Diameter
MACE	Major Adverse Cardiac Events
NA	Not Applicable
ND	Not Done
NK	Not Known
NYHA	New York Heart Association
OTW	Over The Wire
PCI	Percutaneous Coronary Intervention
PIC	Patient Informed Consent
PIS	Patient Informed Sheet
PTCA	Percutaneous Transluminal Coronary Angioplasty
RA	Right Atrium
RV	Right Ventricular
SD	Standard Deviation
SJM(I)	St Jude Medical (Italy)
SSR	Statistical Study Report
STEMI	ST segment Elevation Myocardial Infarction
TIA	Transient Ischemia Attack
TTE	Transthoracic Echocardiogram
WMSI	Wall Motion Score Index

Killip AMI mortality risk evaluation

Killip class of the patient at the time of hospital admission:

- Class 1: Absence of rales over the lung fields and absence of S3
- Class 2: Rales over 50% or less of the lung fields or the presence of an S3
- Class 3: Rales over more than 50% of the lung fields
- Class 4: Cardiogenic Shock (An event with systolic BP < 90 mmHg for greater than 1 hour, not responsive to fluid resuscitation alone, and felt to be secondary to cardiac dysfunction. Associated signs of hypoperfusion (cool and clammy skin, oliguria, or altered sensorium) or a

cardiac index of less than 2.2 L/min/m2 are present. This includes when the systolic BP increases to > 90 mmHg in response to inotropic agents in less than 1 hour.)

NYHA functional evaluation

Functional classification generally relies on the New York Heart Association functional classification. The classes (I-IV) are:

- Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities.
- Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.
- Class III: marked limitation of any activity; the patient is comfortable only at rest.
- Class IV: any physical activity brings on discomfort and symptoms occur at rest.

CCS angina evaluation

Canadian Cardiovascular Society Grading System score for describing and categorising effort-related angina.

- Class I : Angina with strenuous, rapid, or prolonged exertion (Ordinary physical activity such as climbing stairs does not provoke angina.)
- Class II : Slight limitation of ordinary activity (Angina occurs with postprandial, uphill, or rapid walking; when walking more than 2 blocks of level ground or climbing more than one flight of stairs; during emotional stress; or in the early hours after awakening)
- Class III : Symptoms with everyday living activities, ie. moderate limitation. Marked limitation of ordinary activity (Angina occurs with walking 1-2 blocks or climbing a flight of stairs at a normal pace.)
- Class IV : Inability to perform any activity without angina or angina at rest, ie. severe limitation

Syntax score

The SYNTAX Score™ is a tool to help researchers, cardiologists and cardiac surgeons grade the complexity of coronary artery disease (CAD).

The SYNTAX Score is calculated by analyzing the answers to 12 questions grading characteristics of the patient's coronary artery disease (CAD). The sum of the individual classifications for each lesion and the complexity factor is the patient's general SYNTAX Score. Higher SYNTAX Scores indicate a more complex disease, a greater therapeutic challenge and potentially worse acute and long-term outcomes.

Tutorial and Calculator is available online at http://www.syntaxscore.com/

Functional Syntax Score

The Functional SYNTAX Score (FSS) is an FFR-guided SYNTAX score: the SYNTAX score is recalculated counting only ischemia-producing lesions as assessed by FFR[19]. FSS can be calculated by the online SYNTAX score Calculator.

Definition of Heart Failure

The clinical outcome of Heart Failure will include re-hospitalization for CHF and new or worsening CHF occurring during the hospitalization. New CHF during the hospitalization must have an onset or persist >24h after hospital admission. Worsening of CHF must occur or persist >24h after hospital admission.

Congestive heart failure is defined on the basis of the physician's decision to treat CHF with an IV diuretic, IV inotropic agent, or IV vasodilator, and at least 1 of the following:

- Presence of pulmonary edema or pulmonary vascular congestion on chest radiograph believed to be of cardiac cause.
- Rales >1/3 up the lung fields believed to be due to CHF.
- Pulmonary capillary wedge pressure or left ventricular end diastolic pressure >18 mm Hg.
- Dyspnea, with documented pO_2 <80 mm Hg on room air or oxygen saturation <90% on room air, without significant lung disease.

Rehospitalization for CHF is readmission to an acute care facility primarily for the treatment of CHF and includes treatment of CHF with an IV diuretic, IV inotropic agent, or IV vasodilator.
Readmission also includes patients who are treated and under observation for at least 12 hours at a medical care facility but are not formally admitted as inpatients.
Patients readmitted primarily for treatment of a recurrent ischemic episode will not be considered to have met the rehospitalization for CHF criteria.

Definition of Cardiovascular Death

The determination of the specific cause of cardiovascular death is complicated by the fact that we are particularly interested in one underlying cause of death (acute myocardial infarction (AMI)) and several modes of death (arrhythmia and heart failure/low output). It is noted that heart attack-related deaths are manifested as sudden death or heart failure, so these events need to be carefully defined.

- Cardiovascular death includes: death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes

- Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause.
The following is a suggested list of non-cardiovascular causes of death:
Non-Malignant Causes: Pulmonary, Renal, Gastrointestinal, Hepatobiliary, Pancreatic, Infection (includes sepsis), Non-infectious (e.g., systemic inflammatory response syndrome (SIRS)), Haemorrhage (not intracranial), Non-cardiovascular system organ failure (e.g., hepatic failure), Non-cardiovascular surgery, other non-cardiovascular, Accidental/Trauma, Suicide, Drug Overdose.
Malignancy should be coded as the cause of death if: Death results directly from the cancer; or results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy); or results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer.

- Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients[20].

Appendix B: References

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Appendix C: Declaration of Helsinki

(reference: World Medical Association Official Website,
http://www.wma.net/en/30publications/10policies/b3/)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
- 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
- 59th WMA General Assembly, Seoul, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

<u>Risks, Burdens and Benefits</u>

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers

must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the

research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix D: Data Collection Method

Sponsor/investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each subject 1:1. Source documents include all original records from which Case Report Forms (CRFs).

Worksheets can be provided. The purpose of these worksheets is to aid investigators in the capture of clinical investigational data and ensure all protocol required data, which is not captured in medical records, is recorded to support data for the clinical study. These will not be a copy of the eCRFs, but will contain entry blanks for study required data not routinely collected by the investigators.

All documentation pertaining to clinical assessments and medical evaluations should be signed and dated by the appropriate clinical site personnel.
Electronic Data Capture (EDC) will be used for this investigation, therefore please find below instructions on how to access and use the Electronic Case Report Form (eCRF) application.

Access to eCRF application

The eCRF application is accessed through the internet and requires the use of a personal user name and password.

The following are required prior to receipt of personal user name and password:

- Current signed and dated CV
- Completed Signature and Delegation List
- Documented training
- Email address and telephone.

Personal user name and password are provided via email. The first time the eCRF is accessed, the password will need to be changed.

If password is forgotten and/or lost, a new password will be provided via email by following the instructions on the webpage.

Each centre must be authorized to start enrolling patients in the investigation before access privileges to the eCRF application is made available.

Access privileges are based on the tasks assigned on the Signature and Delegation List and will be either:

- Data entry and review
- Data entry, review and sign off

All eCRFs are completed, saved (‘save complete’) and approved by an investigator (privileges) in a timely manner.

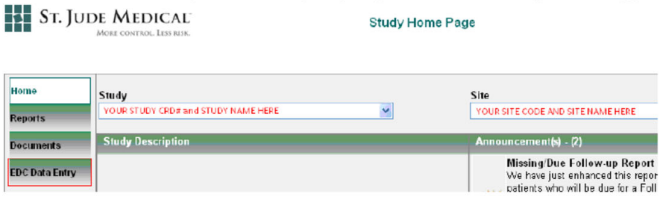
RDC OnSite Tip Card

- **For protocol related questions please contact your FCE or project team.**
- **For any technical issues with RDC OnSite please call our toll free help line at 866-593-2910 or send an e-mail to EDC@sjm.com.**

Logging Into RDC OnSite:

1. Click on the SJM Portal link provided to you by email. Enter your username and password. Pressing "Enter" will take you to the Study Site Portal. Click on the link to access the SJM Study Site Portal, where you can access information regarding your Study/Site.
2. Select the appropriate Study and Site Name from the dropdown menus. Pressing "Go" takes you to the Portal Study Home Page. **NOTE:** Applies to users with multiple SJM EDC studies. Users with access to a single EDC study are taken directly to the Portal Study Home Page upon entry.
3. Locate the 'EDC Data Entry' hyperlink on the left side. Clicking this hyperlink launches a new web browser opened to the RDC OnSite login screen.
4. Enter your Username and password again. You will be taken to the RDC OnSite Home Page where you can begin working with your study.

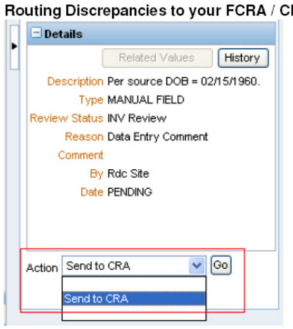
NOTE: Only one RDC OnSite session window can be open at a time. If you try to open additional sessions you will be logged out of any open sessions.



Opening a Subject Casebook / Case Report Form (CRF):

1. From the RDC OnSite Home Page mark the checkbox under the "Select" column for each subject casebook to be viewed.
2. Select from the "Select Patients and…" dropdown menu field the "Open Patient Casebook" option and press "Go". You will be taken to the Casebook Page, where each selected subject casebook will be listed in table format.
3. From the Casebook Page click a CRF icon to open the CRF. A new web browser window will open known as the **Data Entry Window (DEW)**.
4. If required, change the Study Visit by selecting it through the "Visit" dropdown menu.

Routing Discrepancies to your FCRA / CRA – DEW Navigator Pane:



Route Discrepancies to your FCRA / CRA for resolution when:

- Data changes for Automated Edit Checks still violate Edit Check Rules; and
- Addressing manually entered Discrepancies.

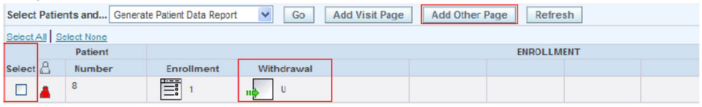
1. Expand the Navigator Pane by clicking on the arrow on the right-edge of the DEW.
2. Click on an Active Discrepancy within the List sub-pane.
3. Review the Discrepancy Description within the Details sub-pane to assess the appropriate action. Change data on the CRF if required.
4. At the bottom of the Navigator Pane locate the "Action" dropdown menu field and select the "Send to CRA" option. Press "Go".
5. In the Discrepancy Action – Send to CRA dialogue window enter a Comment and press "OK" to route the Discrepancy to the FCRA / CRA.
6. After all CRF activities are completed save your changes by pressing the "Save" icon. Click the DEW Close icon "X" to return to the Casebook Page.

Adding Scheduled and Unscheduled CRFs to a Study Visit – Casebook Page:

- **Add Visit Page** – Adds CRFs scheduled for the Study Visit (eg, another Implant form).
- **Add Other Page** – Adds CRFs not scheduled for the Study Visit (eg, an AE form to a 6-Month visit).

1. Mark the checkbox for the Subject casebook you want to add the CRF to and press either the "Add Visit Page" or "Add Other Page" button to open the appropriate dialogue window.
2. In the dialogue window select the radio button for the CRF to be added. Press the "Continue" button.
3. In the dialogue window the CRF sub-visit field will automatically be set to the next available number, therefore, you won't need to change it (for Add Visit Page only). Press the "Apply" button to continue. The CRF icon will appear in the Study Visit.
4. **If the CRF was added in error** and no data was saved onto the form, press the "Refresh" button and the CRF will be removed from the Study Visit.

NOTE: Add Visit Page can be used only after data entry is started on at least one scheduled CRF in that Study Visit.



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Summary of Casebook Status Icons – Home Page

	No Data Entry is started.
	At least some Data Entry is saved. No Open Discrepancies.
	At least some Data Entry is saved. Active Discrepancy present on at least one CRF requiring current user's attention. May also include Other Discrepancies.
	At least some Data Entry is saved. Other Discrepancy present on at least one CRF requiring current user's attention. No Active Discrepancies present.

Summary of CRF Status Icons – Casebook Page

	CRF not started. Data entry is expected.
	Save Incomplete CRF – The CRF was started and only the Visit Header Date was completed.
	Save Incomplete CRF – Data Entry is incomplete. User is not done inputting all the data, and will finish at a later time.
	Save Complete CRF – Data Entry is complete. User has met all the requirements for the form, and the responses are considered complete. Automated Discrepancy Edit Checks are activated. CRF has no open issues.
	Save Complete CRF – Data Entry is complete. CRF contains Other Discrepancies that another user group must address.
	Save Complete CRF – Data Entry is complete. CRF contains Active Discrepancies that the current user group must address.
	*Approved CRF – CRF Data responses have been approved by an investigator. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	*CRF requires Re-Approval – Looped arrow next to signature indicates Data, an Investigator Comment, and/or Discrepancy was updated since the CRF was Approved. (If Open Discrepancies are present, the icon would also be red or yellow.)
	Verified CRF – CRF Data responses are verified against source documents. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Active Discrepancies present.
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Other Discrepancies present.
	*CRF is Verified and Approved – CRF Data responses are verified against source documents by the FCRA / CRA, and the Data responses approved by the Principal Investigator.
	CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Active Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Other Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF at Pass 2 Complete. This icon indicates Data Entry was completed by the sponsor in-house using data submitted on paper CRFs.

*APPROVAL FEATURE CURRENTLY AVAILABLE TO INVESTIGATORS FOR THE DEATH CRF ONLY.

Summary of Discrepancy Status Icons – Data Entry Window (DEW) Navigator Pane

	Active Discrepancy that the current user group must address.
	Other Discrepancy that another user group must address.
	Resolved Discrepancy requiring no further action by any user group.

NOTE: Obsolete Discrepancies due to Data updates or Validation Procedure / Automated Edit Check updates will be removed from the List sub-pane.

Summary of Data Entry Window (DEW) Toolbar Icons

	Add Discrepancy		Delete Row		Approval History		*Print		First/Previous Page		Close
	Investigator Comment		Verification History		Approval		Save		Next/Last Page		

*DO NOT USE THESE TOOLBAR FUNCTIONS

Helpful Hints:

1. **CRF Deletions** – If a CRF with saved data requires deletion notify your SJM contact, providing information about the form.
2. **Refresh** – Press the "Refresh" button to refresh RDC OnSite with current information (statuses, etc.)
3. **Printing a Subject Casebook / CRF** – Go to the RDC OnSite Report Page to print a Patient Data Report. Report types include casebooks with saved Subject data and blank Subject casebooks.
4. **Logout** – Use the web browser close icon "X" to exit. To re-enter, navigate through the SJM Portal.

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