Study of Access Site for Enhancing PCI in STEMI for Seniors (SAFE-STEMI for Seniors)

Statistical Analysis Plan (SAP)

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PROTOCOL VERSION AND AMENDMENT TRACKING

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ABBREVIATIONS

ARC	Academic Research Consortium
BMS	bare metal stent
CAD	coronary artery disease
CEC	Clinical Events Classification
CMS	Center for Medicare and Medicaid Services
CvLPRIT	Complete versus Lesion-only Primary PCI trial
DAPT	dual anti-platelet therapy
DCRI	Duke Clinical Research Institute
DES	drug-eluting stent
E	Eligible enrolled population
HR	hazard ratio
KM	Kaplan-Meier
iFR	instantaneous wave-free ratio
IILR	infarct related lesion revascularization
IIVR	infarct related vessel revascularization
IRA	infarct related artery
LTFU	lost to follow-up
MACCE	major adverse cardiac and cerebrovascular events
MACE	major adverse cardiac events
M	Medtronic Stent population among eligible enrolled population
MI	myocardial infarction
MVD	Muti-vessel CAD
INIVR	index non-infarct related vessels revascularization
PCI	percutaneous coronary intervention
RR	relative risk
SAP	statistical analysis plan
STEMI	ST Elevation Myocardial Infarction
T	Terumo analysis population among eligible enrolled population
TIMI	Thrombolysis in Myocardial Infarction
SD	standard deviation

RAO	radial artery occlusion
V	Phillips Volcano population among eligible enrolled population

1 PURPOSE

This statistical analysis plan (SAP) briefly overviews the study design and objectives, outlines the types of analyses and data presentations that address study objectives, and describes in detail the statistical methods for safety and efficacy analyses specified in the study protocol (Protocol titled "Study of Access Site for Enhancing PCI in STEMI for Seniors [SAFE-STEMI for Seniors] v 1.3 of 6 January 2020). Duke Clinical Research Institute (DCRI) will conduct all statistical analyses described in this SAP. Table shell will be documented in a separate file. SAP and table shell will be finalized prior to database lock.

2 STUDY OVERVIEW

This section summarizes the study objectives and design as background for the statistical methods presented in the SAP. For definitive details of the study objectives and design, consult the study protocol.

2.1 Study Design

This is a prospective, multi-center, unblinded, randomized clinical trial in primary PCI (percutaneous coronary intervention) subjects aged 60 years and older. All subjects will have radial arterial access attempted as principal access for primary PCI. Prior to vascular access, all patients will be selected as DES (drug eluting stent) patients by the study investigator based on clinical assessment regarding potential for interruption or non-compliance with DAPT (Dual Anti-Platelet Therapy) over a 1-year period. Per protocol, DES patients will be treated with a Medtronic Resolute® Family of Stents.

The intended population is subjects undergoing primary PCI for ST elevation myocardial infarction (STEMI) who are considered eligible for a DES. Subjects with single vessel disease will received the Medtronic Resolute® Family of Stents to the IRA. Subjects with multivessel disease will be enrolled and receive the Medtronic Resolute® Family of Stents to the IRA(infarct-related artery) regardless of their randomization assignment. The study design seeks to reflect the general population of seniors presenting with STEMI.

DES subjects in whom multi-vessel disease is identified with absence of shock or prohibitive angiographic anatomy (unprotected left main disease, CTO [chronic total occlusion] to large distributions, etc.) will be randomized by site in a 1:1 ratio to complete revascularization (guided by iFR using Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology) or infarct artery-only revascularization strategies. Only those randomized subjects that have a stable Thrombolysis in myocardial infarction (TIMI) 3 in the IRA using the protocol-specified treatment will complete the

randomized procedure. Subjects in whom IRA reperfusion with TIMI 3 flow is not achieved will be treated according to clinical best practice standard of care independent of randomized procedure assignment and will not be considered protocol violations. These patients will be followed identically to all study patients.

During the index hospitalization, no study assessments that are not part of standard of care will be performed. After hospital discharge, subjects will be seen for follow-up at their standard of care visit approximately 30 days (± 7 days) post-procedure. Subjects will be contacted by the DCRI Call Center at 1 year for data needed for the primary analysis of the study. Additionally, claims data follow up will be collected by DCRI at 18 months post-procedure after the final patient is enrolled.

Primary endpoint results will be reported after all enrolled and/or randomized subjects have completed a minimum of 12 months of clinical follow-up. The enrollment cap is controlled at 875 DES subjects regardless of the number of single-vessel or multi-vessel CAD patients.

2.2 Study Objectives

The objectives of the SAFE STEMI for Seniors study are:

1. To examine the effectiveness of zotarolimus-eluting stents for radial Primary PCI in STEMI.
2. To evaluate the safety and benefit of instantaneous wave-free ratio (iFR)-guided complete revascularization versus infarct artery only revascularization in Primary PCI of patients with multi-vessel coronary artery disease (CAD).
3. To obtain data on the real world application of radial access for Primary PCI in the public health focus on an elderly population.
4. To evaluate the safety of the Terumo Glidesheath Slender and TR Band on an elderly population.

The analysis of pre-specified primary endpoint (see section 2.5.1.1), pre-specified secondary endpoints (see section 2.5.3.1), and pre-specified device performance endpoint (see section 2.5.5.1) will accomplish objective 1. The analysis of pre-specified primary endpoint (see section 2.5.1.2), pre-specified secondary endpoints (see section 2.5.3.2), and pre-specified device performance endpoints (see section 2.5.5.2) will accomplish objective 2. The analysis of pre-specified primary observational endpoint (see section 2.5.2) and pre-specified secondary observational endpoints (see section 2.5.4) will accomplish objective 4.

2.3 Sample Size Determination

2.3.1 Medtronic Resolute® Family of Stents for STEMI

For the primary Medtronic Resolute® Family of Stents efficacy endpoint, this study uses a performance goal derived from historical controls. Event rates from the Bern-Rotterdam registry, COMPARE-AMI, Diaz de La Lera, EXAMINATION, HAAMU-STEMT, HORIZONS-AMI, KOMER, MISSION, PASEO,

PASSION, PROSIT, Resolute AC, SESAMI, STRATEGY, TYPHOON, and ZEST-AMI were pooled to derive major adverse cardiac events (MACE) estimates for bare metal stents (BMS), Cypher, Taxus, Resolute Integrity, and Xience platforms.

To adjust these rates for an elderly population, 1-year major adverse cardiac and cerebrovascular events (MACCE) rates for STEMI patients treated with DES from HORIZONS study are shown in *Table 1* below:

Table 1 1-Year Major Adverse Cardiac and Cerebrovascular Events Rates for STEMI Patients Treated with DES from HORIZONS Study

Endpoint	Group	DES	BMS
MACCE	**Overall**	8.0%	7.9%
	Age >65	13.4%	17.7%
	Age <65	5.0%	2.8%
	Age >60	10.0%	11.7%

Pooled 1-year MACE rates across available DES and BMS platforms from published studies and the Bern-Rotterdam Registry are included in *Table 2* below:

Table 2 Pooled 1-Year MACE Rates Across Available DES and BMS Platforms from Published Studies and the Bern-Rotterdam Registry

Stent	Events	Sample	Event Rate	Binomial 95% CI
BMS	**238**	**2788**	**8.54**	**(7.53, 9.65)**
Cypher	146	2179	6.70	(5.70, 7.85)
Endeavor	24	311	7.72	(5.09, 11.44)
Resolute*	17	284	5.99	(3.52, 9.41)
Taxus	452	4679	9.66	(8.84, 10.55)
Xience	204	2120	9.62	(8.42, 10.98)
All DES	**843**	**9573**	**8.81**	**(8.25, 9.39)**

Taking an upper bound for pooled DES of 9.39%, based on Horizons AMI study[1] we estimated a relative risk (RR) of 1.25 for MACE in patients at least 60 years old (assuming the age distribution in previous DES trials is similar to Horizons). The RR of 1.25 was estimated from HORIZONS AMI study which among subjects older than 60 years had a 1-yr adjudicated MACE rate of 10% (112/1114). The study had an overall 8% MACE rate at 1-year, thus 1.25 was estimated at 0.10/0.08). Thus, we set the performance goal for the intended population at 14% assuming a multiplier of 1.5 (i.e., an increase of 20% relative margin).

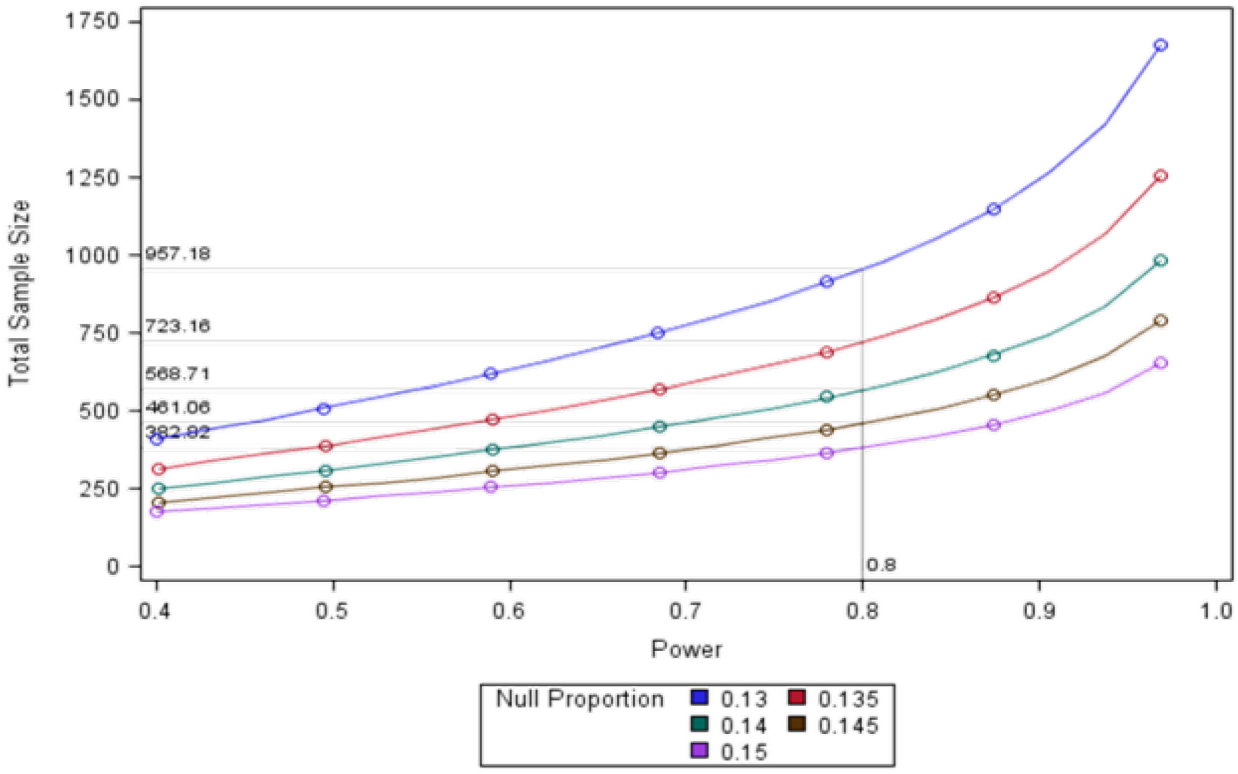
Thus for the hypothesis:

$$\mathrm{H}_0\colon P_1 \geq 0.14 \;\; vs. \;\; \mathrm{H}_a\colon P_1 < 0.14$$

Where P_1 is the proportion of MACE in the Medtronic Resolute® Family of Stents arm. The null hypothesis (H_0) will be rejected when the upper two-sided 95% confidence interval (CI) excludes 0.14.

Based on these assumptions, the study has about 80% power to meet the performance goal with upper two-sided 95% confidence using the exact binomial method [2] would be achieved with a total sample size of 569 analyzable DES patients (*Figure 1*). Assuming an attrition rate of 10%, this will lead to an enrollment goal of 632 DES patients overall.

Figure 1 Power to exclude the upper 95% confidence interval for the Medtronic Resolute® Family of Stents Performance Goal of 14% Using the Binomial proportions*.



*Sample Sizes were generated using SAS Version 9.4 TS Level 12 procedure PROC POWER with using the onesamplefreq statement with the option test=adjz

If site operators designate 875 seniors enrolled into SAFE-PCI for STEMI as DES candidates, we expect about 45% (n=393) to have single-vessel disease, and from the multi-vessel disease subjects (n=482), 241 would be randomized to IRA-only revascularization. Thus, the available cohort for this indication could

reach a total of 634 Medtronic Resolute® Family of Stents DES exposures, all treated with IRA-only approach as used in the HORIZONS study.

2.3.2 IFR-Guided Multi-vessel PCI

The study is also powered for iFR-guided multi-vessel PCI with one-year modified CvLPRIT MACE endpoint, by assuming 1 year modified CvLPRIT MACE rate of 22% in the IRA only arm [3] and 12% (roughly 45% reduction) in the complete revascularization arm, yielding the multi-vessel cohort (n=482 subjects) which will provide approximately 83% power to detect 45% reduction in 1 year modified CvLPRIT MACE and accounts for 10% lost-to-follow up.

The difference in the Kaplan-Meier (KM) estimate at 1 year [4] will be the primary analysis for assessing outcome differences between the 2 randomized arms. The difference and the 95% CI of the difference of the KM estimates between the IRA only and the complete revascularization arms of difference at 1 year will be calculated using the product limit method and the greenwood variance. Thus, the following two-sided alternative hypothesis will be tested using the intent-to-treat (ITT) cohort:

$$\mathrm{H}_0\colon S\left(1Y_{IRA\ only}\right) - S\left(1Y_{Complete\ Revascularization}\right) = 0$$

$$vs.$$

$$\mathrm{H}_a\colon\ S\left(1Y_{IRA\ only}\right) - S\left(1Y_{Complete\ Revascularization}\right) \neq 0$$

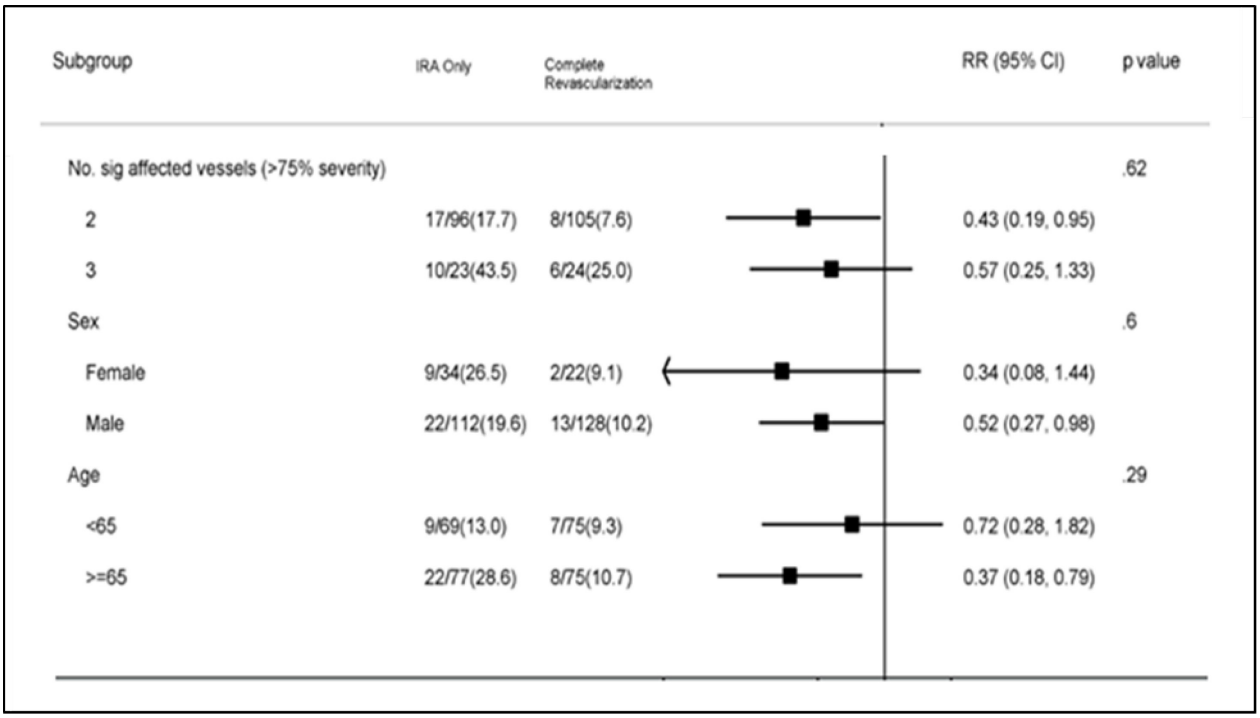
For the time-to-event (MACE) analysis above will be performed according to the principle of "intention-to-treat", subjects who did not experience an event, their efficacy measure will be censored on the last visit (or last contact date). For those with an event, their efficacy measure (in days) will be measured as the time from randomization to the first occurrence of any of the CvLPRIT MACE components.

We will examine the data for consistency and robustness of the findings across clinically important subgroups such as sex and geographical regions.

If this performance goal is met, and if the iFR complete revascularization endpoint was also met, additional labeling for Multi-vessel STEMI revascularization would be supported.

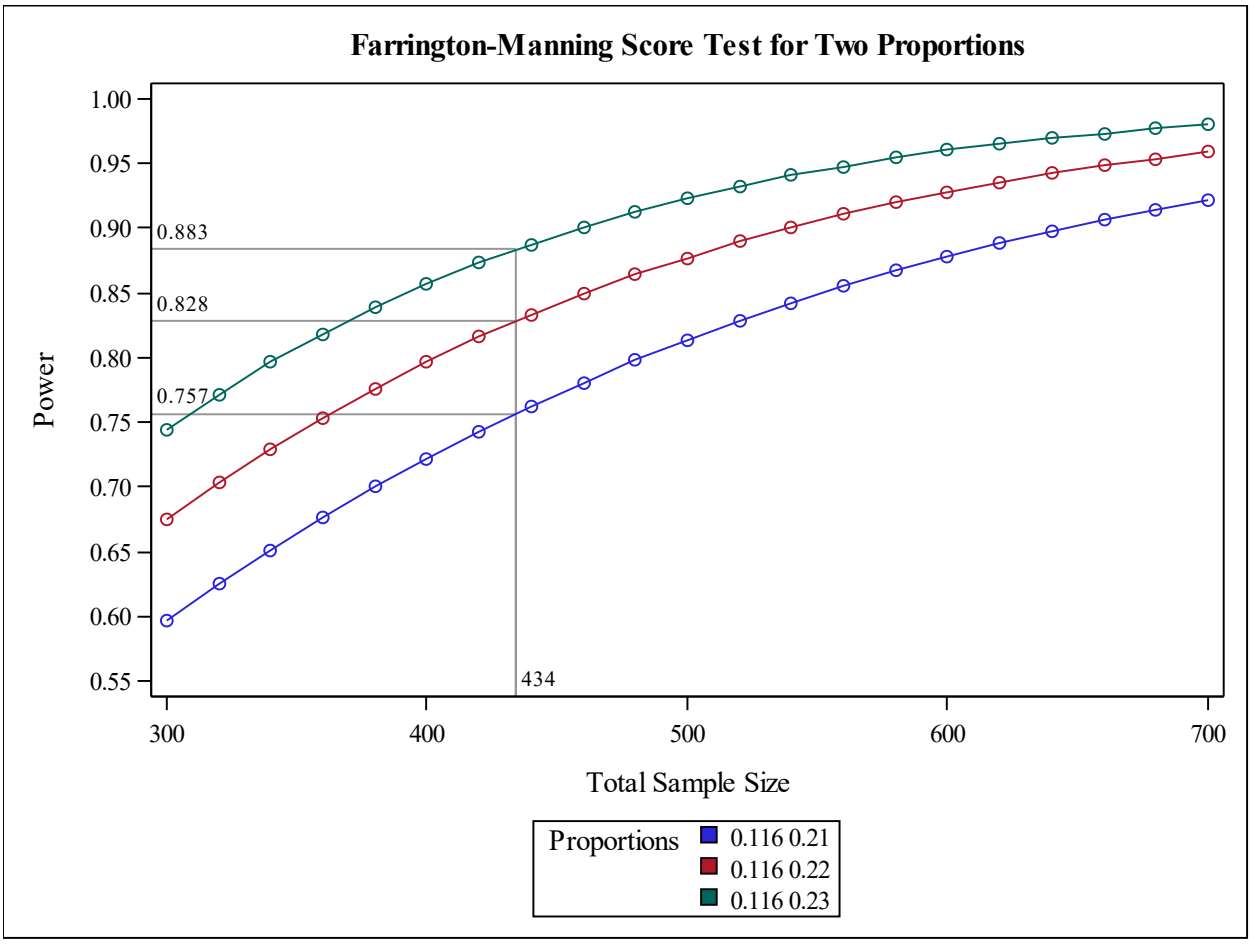
Figure 2 is a subgroup analysis from the CvLPRIT study [3] (presented at ESC 2014) which suggests that the relative risk reduction of complete revascularization in subjects 65 years of age and older is 0.37 (95% CI; 0.18, 0.79).

Figure 2 Subgroup Analysis from the CvLPRIT study



If there is no censoring and all events occur at one-time point, Greenwood's estimate is the same as the SD for a proportion based on the binomial distribution. Therefore, to estimate the sample size, a conservative method would be to determine the sample size for the difference between two proportions and adjusting the sample size up for attrition. *Figure 3* shows the power curves for the multi-vessel cohort using the Farrington Manning method for the difference between two rates. The power curves show that iFR-guided multi-vessel PCI with one-year CvLPRIT MACE endpoint, by assuming 1 year MACE rate of 22% in the IRA only arm[3] and 12% (roughly 45% reduction) in the complete revascularization arm, the power is 83% for 434 patients. Assuming a 10% attrition the total sample size is 482 patients.

Figure 3 Power Curves for Multivessel Cohort: Farrington Manning Score Test for Two Proportions.



*Sample Sizes were generated using SAS Version 9.4 TS Level 12 procedure PROC POWER with using the twosamplefreq statement with the option test=FM

2.4 Analysis Populations

There are five analysis populations defined for this protocol (see *Figure 4*, Study Schema):

1. Eligible enrolled population (**E)** – All eligible single vessel CAD (coronary artery disease) and multi-vessel subjects enrolled regardless of randomization in the study.

2. Randomized population (**R**) – Among E population, subjects who were randomized, including subject was randomized in error.

3. Medtronic Stent population (**M**) – Among E population, subjects who used Medtronic Drug Eluting stent during at least one CathPCI.

4. Terumo population (**T**) – Among E population, subjects who used Terumo products during at least one CathPCI. Terumo products include Terumo Glidesheath Slender and/or TR Band.

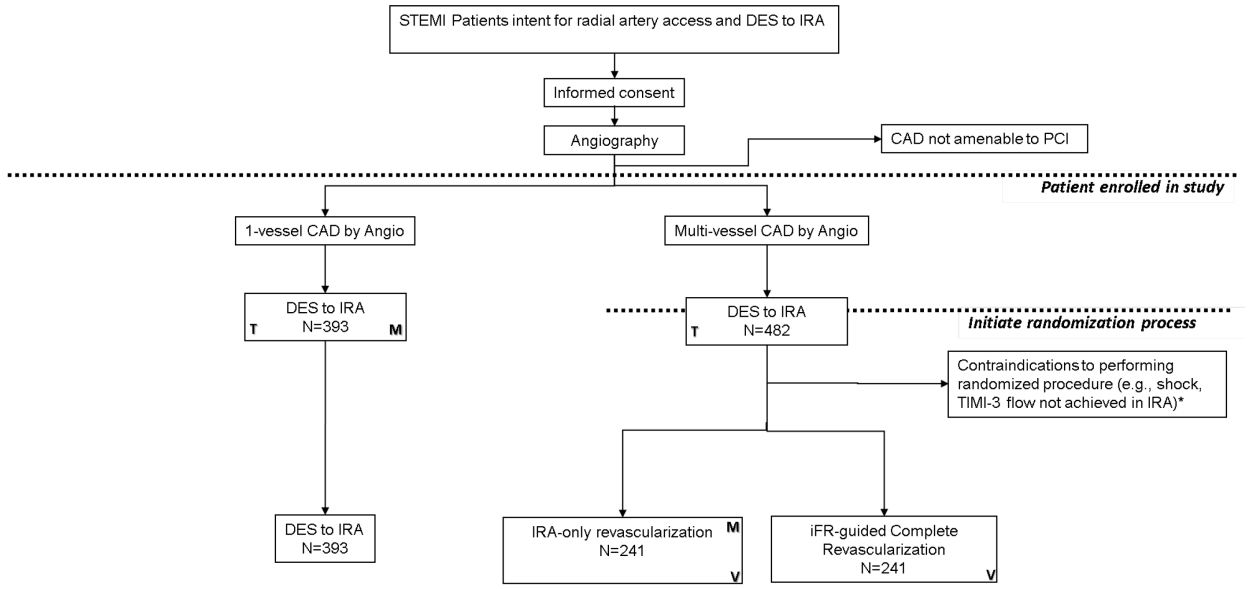
5. Volcano Verrata Pressure Guide Wire population (**V**) – Among E population, subjects who used Volcano Verrata Pressure Guide Wire during at least one CathPCI.

Per-Protocol Population (PP): The PP population includes all enrolled and treated subjects who comply with the study protocol, and treated as assigned treatment.

The following subjects, who satisfied any one of the conditions, will be excluded from PP population:

1. Subjects who were documented protocol deviations related to randomization in error.
2. Subjects who did not have PCI.
3. Subjects who were randomized MVD subjects without post-procedure TIMI-3 flow established per protocol. Although they are not considered protocol violations, they can be treated independent of randomized assignment.
4. Subjects who were not treated as the assigned treatment.
5. Subjects who did not have arterial access.

Figure 4 Study Design and Treatment Schema (includes estimated numbers for enrolled subjects)



T = Terumo Endpoint Cohort
M = Medtronic Endpoint Cohort
V = Phillips Volcano Endpoint Cohort

2.5 Study Endpoints

2.5.1 Primary Efficacy Endpoints

2.5.1.1 Primary Endpoint for evaluating the Medtronic Resolute® Family of Stents for primary PCI in STEMI

Adjudicated 1-year infarct-related artery MACE as defined in HORIZON as cardiac death, index infarct P1-MI or ischemia-driven index infarct related vessel revascularization (IIVR) by percutaneous or surgical methods (see **Appendix 1** for Horizon P1-MI definition).

2.5.1.2 Primary Endpoint for evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

Adjudicated 1-year modified CvLPRIT MACE defined as all-cause mortality, recurrent MI, heart failure (requiring hospitalization or 12 hour ER visit) or ischemia-driven revascularization. (see **Appendix 2** for modified CvLPRIT MI definition)

2.5.2 Primary Observational Endpoint **for evaluating the Terumo TR Band for radial access PCI in the elderly**

Estimate of the incidence rate of RAO acute and at 30 days stratified by whether or not the Terumo TR Band was employed (note: per protocol, use of the TR Band is recommended not required).

2.5.3 Secondary Endpoints

2.5.3.1 Secondary Endpoints for evaluating the Medtronic Resolute® Family of Stents for Primary PCI in STEMI

Efficacy:

- Adjudicated Death (all causes) at 30 days and 1 year.
- Adjudicated Cardiac death at 30 days and 1 year.
- Adjudicated Nonfatal (re-) P1-MI (see appendix 1 for definition) at 30 days and 1 year.
- Adjudicated Index Infarct Related-vessel (re-) P1-MI at 30 days and 1 year.
- Adjudicated Index Infarct Related Lesion Revascularization (IILR) (ischemia-driven) at 30 days and 1 year.
- Adjudicated IIVR (ischemia driven) at 30 days and 1 year.

Safety:

- Adjudicated Academic Research Consortium (ARC) definite/probable stent thrombosis at post procedure, 30 days and 1 year.
- Adjudicated ARC definite stent thrombosis at post procedure, 30 days and 1 year
- Adjudicated Stroke at post-procedure, 30 days and1 year.

2.5.3.2 Secondary Endpoints for evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

- Adjudicated All-cause death at post procedure, 30 days and 1 year.
- Adjudicated Cardiac death at post procedure, 30 days and 1 year.
- Adjudicated (re-) P2-MI at post procedure, 30 days and 1 year.
- Heart failure (requiring hospitalization or 12 hour ER visit) post procedure, 30 days and 1 year.

- Ischemia-driven revascularization for index infarct related vessel (IIVR) or any treated index non-infarct related vessels (INIVR).
- Adjudicated Stroke at post-procedure, 30 days and 1 year

2.5.4 Secondary Observational Endpoints **for evaluating the Terumo Slender GlideSheath and TR Band for radial access PCI in the elderly**

- Time to hemostasis stratified by whether the Terumo TR Band was employed
- Incidence rate of cross over from the initial access point to another stratified by whether or not Terumo Slender GlideSheath was employed (per protocol, use of the Slender GlideSheath is recommended, not required)
- Incidence rate of Access success defined as successfully deploying the stent through the right or left radial artery stratified by whether or not Terumo Slender GlideSheath was employed
- Incidence of RAO acute and at 30 day stratified by whether or not the Terumo TR Band was employed in combination with Glidesheath Slender

2.5.5 Device Performance Endpoints

2.5.5.1 Device Performance Endpoints for evaluating the Medtronic Resolute® Family of the for primary PCI in STEMI

- Site determination of device success, defined as attainment of less than 20% residual stenosis of the infarct related lesion at the time of the index procedure (IILR) using only the study stent.
- Site determination of lesion success, defined as attainment of less than 20% residual stenosis using any percutaneous method at the time of the index procedure.
- Site determination of procedure success, defined as lesion success without the occurrence of in-hospital death, nonfatal MI, stroke, or emergency Endpoints for Evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI.

2.5.5.2 Device Performance Endpoints for evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

Using iFR guided revascularization with Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology

- Site reported index hospitalization bleeding and vascular complication defined as bleeding or vascular complication requiring intervention
- Total procedure time

- Total contrast used
- Occurrence of renal insufficiency (increase from baseline creatinine of at least 0.5 mg/dL or at least 25%) assessed at 48-72 hours post-procedure, 30 days.

3 PATIENT DISPOSITION

Patient disposition will be summarized by vessel and randomization status if applicable for the analysis populations defined in Section 2.4.

Counts and percentages for all patients and will include the following at end of study:

- Subject completed study - Alive
- Subject completed study - Deceased
- Incomplete -subject withdrew consent
- Incomplete –investigator decision
- Incomplete - lost to follow-up

Other

Also, 12 Month call follow-up, disposition will be displayed as following:

- Complete
- Incomplete
- Not done

4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

4.1 Demographics

Patient demographics will be summarized as mean (SD), median (25, 75 percentiles), min and max for continuous and counts (percentages) for categorical variables. Demographics will include age, sex, race, ethnicity, country for the analysis populations in Section 2.4.

4.2 History and Risk Factors

Medical history and risk factors shown below will be summarized by counts (percentages) for the analysis populations shown below.

HISTORY AND RISK FACTORS
Hypertension
Dyslipidemia
Coronary Artery Disease
Family History of CAD
Prior MI
Prior PCI
Unprotected LM PCI
Prior Cerebrovascular Disease
Peripheral Artery Disease
Chronic Lung Disease
Tobacco Use
Never
Former
Current
Heart Failure
NYHA Class prior to first Cath lab visit
Class I
Class II
Class III
Class IV
Diabetes Mellitus
Insulin Therapy prior to Arrival
COMORBIDITIES
Depression
Arthritis
Liver Disease
Cancer
Atrial Fibrillation
Hyperlipidemia
Dementia

On the following populations:

- Medtronic Stent population
- IFR population by treatment group (IRA only revascularization vs. complete revascularization)
- Terumo population by use of Terumo TR band or not
- Terumo IFR population by use of Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology or not

5 MEDICATIONS

5.1 Pre-Procedure Medications

Specific pre-procedure medications will be summarized by counts (percentages) for the following populations:

- Medtronic Stent population
- IFR population by treatment group (IRA only revascularization vs. complete revascularization)
- Terumo population by use of Terumo TR band or not
- Terumo IFR population by use of Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology or not

6 SAFETY ASSESSMENTS

6.1 Device Related Serious Adverse Events

Device related serious adverse events, grouped by body system and preferred term will be summarized. In addition, a detailed listing of device related serious adverse events will be provided for the following:

- Possibly related to the Medtronic Stent in the Medtronic Stent population

- Probably/definitely related to the Medtronic Stent in the Medtronic Stent population
- Possibly related to the iFR study procedure in the iFR population by treatment group
- Probably/definitely related to the iFR study procedure in the iFR population by treatment group
- Possibly related Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology
- Probably/Definitely related Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology.

Relatedness will be determined by a medical monitor assessment for all except for the iFR study procedure which will be based on the investigator's assessment.

7 EFFICACY ANALYSES

7.1 Primary Efficacy Analyses

7.1.1 For evaluating the Medtronic Resolute® Family of the for primary PCI in STEMI

For the primary Medtronic Resolute® Family of Stents efficacy endpoint, this study uses a performance goal derived from historical controls. (see section 8.1) for determination of historical control to be used as a comparator. The performance goal is set at 14% for the primary endpoint, Adjudicated 1-year infarct-related artery MACE as defined in HORIZON as cardiac death, index infarct MI or ischemia-driven index infarct related vessel revascularization (IIVR) by percutaneous or surgical methods.

Thus for the hypothesis:

$$H_0: P_1 \geq 0.14 \; vs. \quad H_a: \; P_1 < 0.14$$

Where P_1 is the proportion of MACE in the Medtronic Resolute® Family of Stents arm. Two-sided 95% confidence interval (CI) will be calculated utilizing the exact method based on the binomial distribution. The null hypothesis (H_0) will be rejected when the upper two-sided 95% CI excludes 0.14.
The primary analysis will be on the Medtronic Stent population. As a sensitivity analysis, the analysis will be also be done on the Medtronic Stent population per protocol population.

7.1.2 For evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

The difference in the Kaplan-Meier(KM) estimate at 1 year will be utilized as the primary analytic tool for assessing differences between the 2 randomized arms on the primary endpoint, Adjudicated 1-year modified CvLPRIT MACE defined as all-cause mortality, recurrent MI, heart failure (requiring hospitalization or 12 hour ER visit) or ischemia-driven revascularization. (see Appendix 2 for CvLPRIT MI definition). The difference and the 95% CI of the difference of the KM estimates between the IRA only and the complete revascularization arms of difference at 1 year will be calculated using the product limit method and the greenwood variance. Thus, the following two-sided alternative hypothesis will be tested using the intent-to-treat (ITT) principle on the IFR population (**I**):

$$\mathrm{H}_0: S(1Y_{IRA\ only}) - S(1Y_{Complete\ Revascurilzation}) = 0$$

$$vs. \quad \mathrm{H}_A\ S(1Y_{IRA\ only}) - S(1Y_{Complete\ Revascurilzation}) \neq 0$$

If the p-value of the log-rank test is less than or equal to 0.05 the null hypothesis will be rejected for the alternative demonstrating a significance different between to two randomized arms.

For the time-to-event (modified CvLPRIT MACE) analysis above will be performed according to the principle of "intention-to-treat", subjects who did not experience an event, their efficacy measure will be censored on the last visit (or last contact date). For those with an event, their efficacy measure (in days) will be measured as the time from randomization to the first occurrence of any of the CvLPRIT MACE components.

In addition, Cox proportional hazards model will be utilized to calculate the hazard ratio (HR) and the 95% CI of the complete revascularization to IRA only treatment arms.

For sensitivity analyses, the above will be also be performed on the IFR population per protocol (**IPP**).

7.2 Primary Observational Efficacy Analyses

7.2.1 For evaluating the Terumo TR Band for radial access PCI in the elderly

Number and percentage of subjects with RAO acute and at 30 day stratified by whether or not the Terumo TR Band was employed will be provided (note: use of the TR Band is recommended not required) in the Terumo population. No formal hypothesis testing will be performed. The above summary will be also performed on the Terumo population per protocol.

7.3 Secondary Efficacy Analyses

All secondary efficacy endpoints will be presented as descriptive statistics with no formal hypothesis testing.

7.3.1 For evaluating the Medtronic Resolute® Family of the for primary PCI in STEMI

KM estimates and 95% confidence intervals using the product limit method and the greenwood variance for the secondary efficacy endpoints below will be provided for the Medtronic Stent population and (**M**) Medtronic stent per protocol population (**MPP**):

- Adjudicated Death (all causes) at 30 days and 1 year.
- Adjudicated Cardiac death at 30 days and 1 year.
- Adjudicated Nonfatal (re-) MI (see appendix 1 for definition) at 30 days and 1 year.
- Adjudicated Index Infarct Related-vessel (re-)MI (see definition in appendix 1) at 30 days and 1 year.
- Adjudicated Index Infarct Related Lesion Revascularization (IILR) (ischemia driven) at 30 days and 1 year.

7.3.2 For evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

KM estimates and 95% confidence intervals using the product limit method and the greenwood variance for the secondary efficacy endpoints below will be provided for the iFR population (I) and the iFR per protocol population (**IPP**):

- Adjudicated All-cause death at post procedure, 30 days and 1 year.
- Adjudicated Cardiac death at post procedure, 30 days and 1 year.
- Adjudicated (re-)MI (see definition in appendix 2) at post procedure, 30 days and 1 year.
- Heart failure (requiring hospitalization or 12 hour ER visit) post procedure, 30 days and 1 year.
- Ischemia-driven revascularization for index infarct related vessel (IIVR) or any treated index non-infarct related vessels (INIVR).
- Adjudicated Stroke at post-procedure, 30 Days and 1 year

7.4 Secondary Observational Analyses

All secondary observational endpoints will be presented as descriptive statistics with no formal hypothesis testing.

Number (percent) of subjects meeting the categorical secondary observations endpoints and mean (SD), median (25, 75 percentiles), min and max for the continuous endpoint (time to hemostasis) below will be provided for the Terumo population (T):

- Time to hemostasis stratified by whether the Terumo TR Band was employed
- Incidence rate of cross over from the initial access point to another stratified by whether or not Terumo Slender GlideSheath was employed (Use of the Slender GlideSheath is recommended not required)]
- Incidence rate of Access success defined as successfully deploying the stent through the right or left radial artery stratified by whether or not Terumo Slender GlideSheath was employed
- Incidence of RAO acute and at 30 day stratified by whether or not the Terumo TR Band was employed in combination with Glidesheath Slender

8 DEVICE PERFORMANCE ANALYSES

All device performance endpoints will be presently descriptively with no formal hypothesis testing.

8.1 For evaluating the Medtronic Resolute® Family of the for primary PCI in STEMI

Number and percent of subjects meeting the device performance endpoints below will be provided for the Medtronic stent population and the Medtronic stent per protocol population:

- Site determination of Device success, defined as attainment of less than 20% residual stenosis of the infarct related lesion at the time of the index procedure (IILR) using only the study stent.
- Site determination of Lesion success, defined as attainment of less than 20% residual stenosis using any percutaneous method at the time of the index procedure.
- Site determination of Procedure success, defined as lesion success without the occurrence of in-hospital death, nonfatal MI, stroke, or emergency Endpoints for Evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

8.2 For evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

Number (percent) of subjects meeting the categorical device performance endpoints and mean (SD), median (25, 75 percentiles), min and max for the continuous device performance endpoints below will be provided for the iFR population and the iFR per protocol population:

- Site reported index hospitalization bleeding and vascular complication defined as bleeding or vascular complication requiring intervention
- Total procedure time
- Total contrast used
- Occurrence of renal insufficiency (increase from baseline creatinine of at least 0.5 mg/dL or at least 25%) assessed at 48-72 hours post-procedure, 30 days.

9 SUB-GROUP ANALYSES

We will examine the data for consistency and robustness of the findings of primary efficacy endpoint for evaluating iFR-Guided Complete Revascularization in STEMI across clinically important subgroups such as sex and geographical regions.

10 SITE POOLABILITY FOR PRIMARY EFFICACY ENDPOINTS

Analysis will be performed pooling data across sites. Site poolability the primary efficacy endpoint for evaluating iFR-Guided Complete Revascularization in STEMI will be assessed by descriptive analyses (rates of primary endpoints) by site. For analysis of site effect, data from smaller sites may be combined for the analysis.

11 DATA SOURCES

SAS datasets created from the SAFE-STEMI for Seniors eCRF will be used for analyses. The eCRF is managed by DCRI data management. The eCRF will contain entered by participating sites, as well as event adjudication entered by DCRI Clinical Events Classification (CEC) personnel. For events occurring within 30 days, data provided by the sites will used for event adjudication. For events occurring subsequent to 30 days, the Center for Medicare and Medicaid Services (CMS) database will be utilized.

12 TIMING OF ANALYSES AND HANDLING OF DATA

A CMS data pull will occur 6 months after the last subject has reached 1 year of follow-up. Once event adjudication has been completed and database is complete, the eCRF database will be frozen and transferred into SAS datasets for analyses. A clinical study report will be developed with 1 year primary endpoints results. After the SAS datasets are created, the eCRF database will be unfrozen and data collection will continue until 6 months after last subject has reached 18 months of follow-up. A second clinical study report will be developed including updated 1 year results and 18 month results after database lock.

13 STATISTICAL CONSIDERATIONS

13.1 General Analysis Conventions/Rules

Continuous variables will be summarized as number of observations, mean, standard deviation (SD), minimum, 25th percentile, median, 75th percentile, and maximum. Categorical variables will be summarized as frequency counts and percentages.

13.2 Statistical Software

The majority of the statistical analyses will be performed using SAS®, version 9.4 or higher (SAS Institute Inc., Cary, NC). Additional statistical software will be utilized as needed.

13.3 Verification of SAS® Codes

All tables, listings, and graphs will be verified and reviewed before being considered final. The verification process will ensure that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Suitably qualified personnel who have not been previously involved in the production of the original SAS® code will perform the verification procedures. Methods of verification will include independent programming of all analysis datasets and comparison to data listings as specified in the verification plan. Tables will be reviewed for accuracy, consistency with this analysis plan, consistency within tables, and consistency with corresponding output. Once verification is complete, all documentation of the verification process will be filed in the study statistical documentation repository for SAFE-STEMI for Seniors as required by the Statistical Standard Operations Procedures (SOP) of the Duke Clinical Research Institute (DCRI).

13.4 Handling of Missing Data and Early Withdrawals

All efforts will be made to make sure all data needed for primary and secondary analyses are complete. However, it is possible that some data will be missing. No data imputation will be performed as part of the primary analyses. The impact of missing data on the primary and secondary efficacy analyses will be minimized by performing the analyses using Kaplan-Meier estimates, where the subjects will be censored at their last assessed time point.

13.5 Exploratory Analyses

All analyses that are not specified as the primary efficacy endpoints are to be considered exploratory. These are broadly classified in the protocol as additional pre-specified endpoints. Any other proposed analyses designed to provide information for future investigations involving the study device(s) will also be exploratory in nature. All exploratory analyses are considered descriptive and non-inferential. If exploratory analyses are to be included in the final study report, the SAP will be amended.

13.6 Multiple Comparisons

The cohort that will be used to evaluate the 1-Year MACE endpoint for Medtronic Resolute® Family of Stents includes the single vessel patients and the multi-vessel patients randomized to index infarct vessel only revascularization (IIVR). The cohort that will be used to evaluate the IFR endpoint of 1-Year CvLprit MACE includes the multi-vessel patients than have been randomized to IIVR or complete revascularization. Even though these two analyses share the IIVR patients, for the one year MACE endpoint, the IIVR patients are pooled together with the single vessel patients and the result will be compared a performance goal; whereas the IFR endpoint of 1-Year CvLprit MACE is looking at the different between the IIVR and the complete revascularization patients. Success in the 1 Year MACE endpoint would not predict success in the 1 Year Cvlprit MACE endpoint. Therefore, the two endpoints are considered to be statistically independent and there is no need for any adjustment in type I error.

14 REFERENCES

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3. Gershlick, A.H., et al., Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol, 2015. **65**(10): p. 963-72.

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15 APPENDICES

Appendix 1:

P1-MI is defined according to the HORIZON protocol:

(A) MI diagnosis before angiography, or, in medically treated patients.

Patients with unstable angina (without NSTEMI):

i. Any elevation of troponin or CPK-MB (or CPK) greater than the upper limits of normal (ULN).

Patients with NSTEMI:

(1) If the peak troponin or CPK-MB (or CPK) has not yet been reached: Recurrent chest pain lasting ≥30 minutes, or new electrocardiographic changes consistent with MI and the next troponin or CPK-MB (or CPK) level measured approximately 8 to 12 hours after the event be elevated by at least 50% above the previous level.

(2) If the elevated troponin or CPK-MB (or CPK) levels are falling or have returned to normal: A new elevation of troponin or CPK-MB (or CPK) >ULN if the troponin or CPK-MB (or CPK) level has returned to <ULN, or a rise by >50% above the previous nadir level if the troponin or CPK-MB (or CPK) level has not returned to <ULN.

(B) MI diagnosis after PCI:

If the elevated CPK-MB (or CPK) levels are falling or are normal:

(1) any CPK-MB (or CPK) ≥3 × ULN within 24 hours after PCI that is also increased at least 50% over the most recent pre-PCI levels, or new, significant (≥0.04 second) Q waves in ≥2 contiguous electrocardiographic leads with CPK-MB (or CPK) >ULN.

Patients with NSTEMI: If the peak CPK-MB (or CPK) has not yet been reached before PCI:

(1) Recurrent chest pain ≥30 minutes, or new electrocardiographic changes consistent with a second MI and the next CPK-MB (or CPK) level measured approximately 8 to 12 hours after the event is elevated by at least 50% above the

previous level; or new, significant (≥0.04 second) Q waves in ≥2 contiguous electrocardiographic leads.

(C) MI diagnosis after CABG. Any CPK-MB (or CPK) ≥10 × ULN within 24 hours of CABG and increased at least 50% over the most recent pre-CABG levels, or any CPK-MB (or CPK) ≥5 × ULN within 24 hours of CABG and increased at least 50% over the most recent pre-CABG levels and new, significant (≥0.04 second) Q waves in ≥2 contiguous electrocardiographic leads.
(D) Q-wave versus non–Q-wave MI. Once the enzymatic criteria for MI are met, a Q-wave MI will be diagnosed if new pathologic Q-waves develop in ≥2 electrocardiographic contiguous leads as adjudicated by the Clinical Events Committee. An MI not meeting this definition will be considered a non–Q-wave MI.

Appendix 2:

The definition is a modified MI definition from CvLPRIT, and is based on the Third Universal definitions for myocardial infarction:

Myocardial (re)infarction will require a hospital admission, or be diagnosed in hospital, with one or more of the following:

- **Type 1** – Spontaneous re-MI: Recurrent angina symptoms or new ECG changes occurring before PCI or < 48 hours from PCI that is compatible with re-MI associated with an elevation of CK-MB, troponin, or total CK beyond ULN and 20% or more above the previous value.
- **Type 4a** – CK-MB or total CK > 3 times the ULN within 48 hours following PCI, if the pre-PCI CK-MB or total CK level is higher than the ULN, there also needs to be:
    - Either the demonstration of a falling CK-MB or total CK level prior to the onset of the suspected event,
    - Or a subsequent peak of the cardiac biomarker of at least 20% above the previous value obtained prior to the onset of the suspected event.
    - With either an appropriate clinical presentation or new ischemic ECG changes (ST-segment depression or ST-segment elevation or development of new pathological Q waves /LBBB).

- **Type 4b** – Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy AND fulfilling the criteria of spontaneous MI (Type 1)