PROTOCOL

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

Phase: U.S. Investigational Device Exemption # G160113
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PROTOCOL APPROVAL PAGE

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Date of Issue: June 15, 2017

I have read and approve this protocol and agree on its content.

David F. Kong, MD — Date

Sponsor:
Duke Clinical Research Institute

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date
Final protocol: Version 1.0	May 25, 2016
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PROTOCOL SYNOPSIS

Protocol Title	Study of Access Site for Enhancing PCI in STEMI for Seniors (SAFE PCI in STEMI for Seniors)
Main Criteria for Inclusion	Patients ≥ 65 years old with chest pain ≤ 12 hours and ST-elevation myocardial infarction or LBBB on ECG with intent to perform primary percutaneous coronary intervention (PCI) via right or left radial arterial access.
Study Objectives	To simultaneously address four potential advances in STEMI care for patients at least 65 years old. 1. To examine the effectiveness of zotarolimus-eluting stents for radial Primary PCI in STEMI 2. To evaluate the safety and benefit of iFR-guided complete revascularization vs. infarct artery only revascularization in Primary PCI of patients with multi-vessel 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.
Study Design	Multicenter, randomized, open-label, unblinded, active and historical-controlled trial in which approximately 875 seniors undergoing urgent PCI from approximately 70 centers will be enrolled. All consented subjects will undergo attempted radial arterial access. For DES (Drug Eluting Stent) eligible patients without randomization exclusion criteria and with multi-vessel disease will be randomized by site in a ratio of 1:1 to IRA-only revascularization or iFR-guided complete revascularization. After randomization, subjects with stable TIMI-3 flow established in the IRA using the protocol specified treatment will proceed with 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. After stent implantation, subjects will be contacted for follow-up at 30 days by the enrolling site and at 1 year by the DCRI Call Center.

	Primary endpoint results will be reported after all subjects have completed the 1 year (12 months) of clinical follow-up.
Treatment Regimen	**STEMI patients eligible for radial access:** DES Eligible with single vessel CAD will receive DES to IRA DES Eligible with Multi-vessel CAD will randomize by site in a ratio of 1:1 to IRA-only revascularization or iFR-guided complete revascularization.
Duration of Subject Study Participation	Patients will be seen by sites for their standard of care follow-up visit approximately 30 days after their procedure. Patients will be contacted by the DCRI Call Center at 1 Year to collect data for the primary endpoint analysis. Medicare Claims data will be collected at 18 months post-procedure after the final patient is enrolled.
Number of Patients	A total of approximately 875 patients ≥ 65 years old
Number of Sites	Approximately 70 centers are planned in the US and Canada.
Endpoints for Evaluating Medtronic Resolute® Family of Stents for Primary PCI in STEMI	*Primary Endpoint:* • Adjudicated 1-year infarct-related artery (IIVR) MACE as defined in HORIZON as cardiac death, index infarct -vessel MI, or ischemia-driven index infarct related vessel revascularization by percutaneous or surgical methods rate This endpoint has been powered to test the superiority of the primary endpoint rate when using the Medtronic Resolute® Family of Stents in STEMI versus HORIZON based performance goal. *Secondary Endpoints:* Using the Medtronic Resolute® Family of Stents 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-)MI at 30 days and 1 year. • Adjudicated Index Infarct Related-vessel (re-)MI at 30 days and 1 year.

	• Adjudicated Index Infarct Related Lesion Revascizlation (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 and 1 year. *Device Performance Endpoints:* • 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 revascularization at the time of the index procedures
Endpoints for Evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI	*Primary Endpoint:* The endpoint is 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. This endpoint has been powered to test the superiority of the primary endpoint rate when using iFR guided complete revascularization versus infarct related vessel only revascularization in STEMI. *Secondary Endpoints:*

	• Adjudicated cardiovascular death at post-procedure, 30 Days, and 1 Year • Individual components of the modified CvLPRIT MACE endpoint • Adjudicated Stroke at post-procedure, 30 Days and 1 year. *Device Performance Endpoints:* 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.
Endpoints to Evaluate the Terumo Slender GlideSheath and TR Band for radial access PCI in the elderly	Primary Observational Endpoint: • Estimate the incidence rate of RAO acute and at 30day stratified by whether or not the Terumo TR Band was employed (use of the TR Band is recommended not required) Secondary Observational Endpoints: • Time to Hemostasis stratified by whether the Terumo TR Band was employed • Incidence rate of cross over to 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 30day stratified by whether or not the Terumo TR Band was employed in combination with Glidesheath Slender These are observational endpoints.
Clinical Events Committee	An independent Clinical Events Committee (CEC) will be formed to provide independent central adjudication of suspected endpoints through the 1 year follow-up for each patient.
Data and Safety Monitoring Committee	An independent DSMC will monitor the trial conduct. The DSMC will consist of 2 clinicians and a statistician. The members of this committee will not participate in the enrollment or treatment of patients in this trial. The guidelines for the DSMC operations will be reported in a separate DSMC Charter.
Statistical Analysis **Sample Size/ Power Considerations**	There are two powered primary endpoints this study. 1-year infarct-related artery (IIVR) MACE: The SAFE-STEMI for Seniors study has been powered at 85% to meet a performance goal of 15% for the Medtronic Resolute® Family of Stents assuming 1-year infarct-related artery MACE of 10% in patients 65 years or older and a two-sided type I error of 0.05. To meet this performance goal endpoint a total of 477 DES patients will be required accounting for a 10% attrition rate. 1-year modified CvLPRIT MACE: The study is also powered for iFR-guided multi-vessel PCI with 0ne-year CvLPRIT MACE endpoint, by assuming 1 year MACE rate of 22% in the IRA only arm and 12% in the complete revascularization arm, yielding the multi-vessel cohort (n=550 pts) which will provide at least 85% power to detect a 45% relative reduction in 1 year MACE, accounting for approximately 10% attrition. Given that: • The iFR-guided complete revascularization arm of the multi-vessel patient cohort is not used for the 1-year MACE evaluation of Medtronic Resolute® Family of Stents • The single vessel patient used in the evaluation of the Medtronic Resolute® Family of Stents and is not used in the evaluation of iFR • The 1-year MACE evaluation of Medtronic Resolute® Family of Stents pools the single and multi-vessel patients and compares the binary endpoint to a performance goal;

	• iFR analysis compares randomized multi-vessel arms using the difference in the K-M estimates the two primary endpoint are considered to be statistically independent and there is no need to adjust the type I error for multiple endpoints

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ABBREVIATIONS

ACC	American College of Cardiology
ADE	Adverse Device Effect
ADP	Adenosine Diphosphate
AE	Adverse Event
AHA	American Heart Association
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CEC	Clinical Events Classification
CMS	Center for Medicare and Medicaid Services
CTO	Chronic Total Occlusion
CvLPRIT	Complete versus Lesion-only Primary PCI trial
DAPT	Dual Anti-Platelet Therapy
DCRI	Duke Clinical Research Institute
DES	Drug Eluting Stent
DSMC	Data and Safety Monitoring Committee
EC	Ethics Committee
ECMO	Extra Corporeal Membrane Oxygenation
EES	Everolimus Eluting Stent
FDA	Food and Drug Administration
FFR	Fractional Flow Reserves
GPIIb/IIIa	Glycoprotein IIb/IIIa
HF	Heart Failure
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction
IABP	Intra-Aortic Balloon Pump

IDE	Investigational Device Exemption
iFR	Instantaneous Wave Free Ratio
IIVR	Index Infarct Vessel Revascularization
IILR	Index Infarct lesion Revascularization
INIVR	Index Non-Infarct Vessel Revascularization
IRA	Infarct Related Artery
IRB	Institutional Review Board
IVUS	Intra Vascular Ultra Sound
MACCE	Major Adverse Cardiac and Cerebrovascular Event
MACE	Major Adverse Cardiac Events
NACE	Net Adverse Cardiac Events
NCDR	National Cardiovascular Data Registry
NCRI	National Cardiovascular Research Infrastructure
NDI	National Death Index
NOAC	Novel Oral Anti-Coagulant
NSTEMI	Non ST Elevation Myocardial Infarction
PCI	Percutaneous Coronary intervention
PES	Paclitaxel Eluting Stent
RAO	Radial Artery Occlusion
RR	Relative Risk
SAE	Serious Adverse Event
STEMI	ST Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction risk score
IILR	Index Infarct Related Lesion Revascularization
TR Band	Trans Radial Band
IIVR	Index Infarct Related Vessel Revascularization
UADE	Unanticipated Adverse Devise Effect
ZES	Zotarolimus Eluting Stent

1. INTRODUCTION AND BACKGROUND

1.1 Background

Ischemic heart disease is the leading cause of death in the United States, with ST-segment elevation myocardial infarction (STEMI) accounting for over 300,000 cases each year.[1] Multicenter registries have shown that myocardial loss, mechanical complications, and short-term mortality after STEMI have decreased over the past 3 decades due to aggressive antithrombotic therapy and accelerated access to primary PCI.[2, 3] Although rapid primary PCI with potent anti-thrombotic therapy is standard care for STEMI, unmet medical challenges remain, including multi-vessel disease, recurrent ischemia, and repeat revascularization. These complications prolong hospitalization and increase the risk for additional revascularization, bleeding, re-infarction, stroke, and death. Multi-vessel disease and comorbidities are more frequent in elderly patients,[4] who epidemiologically constitute a high impact public health challenge as the most rapidly increasing population sector in the United States [5]. Age is not only directly related to worse outcomes from STEMI [2, 6, 7] but also associated with higher complication rates with primary PCI and anti-thrombotic therapies used to interrupt STEMI [8, 9].

Traditional clinical trial approaches to addressing the many factors affecting the safety and efficacy of primary PCI in elderly STEMI patients are confounded by logistics [7]. The Safe STEMI for Seniors protocol represents a national network of clinical sites linked to Medicare claims data for long term clinical follow up (1 year and beyond). The prospective randomized design encourages innovation and robust evaluation of approved state-of-the-art technologies to support extensions to device regulatory labeling through IDE investigations. Collaborative models strategically partnering multiple manufacturers also help mitigate costs related to studying such labeling extensions, while encouraging the expansion of state-of-the-art devices into new markets to address previously unmet needs. The Safe STEMI for Seniors study is designed to simultaneously address four potential advances in STEMI care for patients at least 65 years old:

1. To examine the effectiveness of zotarolimus-eluting stents for radial Primary PCI in STEMI
2. To evaluate the safety and benefit of iFR-guided complete revascularization vs. infarct artery only revascularization in Primary PCI of patients with multi-vessel 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

1.2 New Generation DES in STEMI

Drug eluting stents have consistently been shown to significantly reduce restenosis rates after primary PCI for STEMI.[10] Underpowered, short term studies and concerns about stent thrombosis, strongly tempered use of DES for this indication until the HORIZONS trial was reported[11], leading to the approval of the Taxus paclitaxel-eluting stent (PES) for primary PCI for STEMI. Even this study, however, was underpowered for detection of stent thrombosis signals.

Multiple reports and meta-analyses have consistently shown that subsequent generation DES, with more biocompatible polymer delivering zotarolimus (ZES) and everolimus (EES) have significantly lower stent thrombosis rates than paclitaxel-eluting stents in elective, “all comers” and STEMI populations.[12] Clinical use of DES for primary PCI in STEMI has crossed equipoise (>50%) in many centers worldwide. However, there is no third generation DES yet approved for this indication in the United States.

The Medtronic Resolute® Family of Stents are highly flexible and deliverable third generation DES, well suited to investigation in the setting of seniors undergoing primary PCI for STEMI.

1.3 Multi-vessel Intervention during Primary PCI

Overall approximately 30-50% of patients with STEMI also have concomitant obstructive coronary artery disease in other non-culprit vessels, with additional patients presenting with borderline lesions in the non-infarct related artery (IRA). In seniors the incidence of multi-vessel CAD in the STEMI setting has been reported as 55-60%. [13, 14] Functional dependence on the non-infarct zones of myocardium to compensate for the “stunned” areas of reperfusion have raised concerns when coronary flow to the non-infarct zones is abnormal. Other than in shock states, however, observational studies have shown equivocal benefit when these other lesions are intervened upon during primary PCI,[15] possibly related to the very stimulated platelet environment that characterizes STEMI.

For example, a total of 505 patients from the Mid-America Heart Institute[16] with multi-vessel disease who presented with STEMI were subdivided in 3 groups on the basis of the revascularization strategy: 1) patients undergoing percutaneous coronary intervention (PCI) of the infarct-related artery (IRA) only; 2) patients undergoing PCI of both the IRA and non-IRA(s) during the initial procedure; and 3) patients undergoing PCI of the IRA followed by staged, in-hospital PCI of the non-IRA(s). There were no significant differences in procedural complications among these three (non-randomized) groups, but patients undergoing multi-vessel PCI during the initial procedure had significantly higher in-hospital mortality (p=0.003). Outcomes were compared among these three groups and to 314 AMI patients with single-vessel disease who were treated during the

same period. In patients with multi-vessel disease, compared with PCI restricted to the IRA only, multi-vessel PCI was associated with higher rates of re-infarction (13.0% vs. 2.8%, P <.001), revascularization (25% vs. 15%, P = .007), and major adverse clinical events (MACE) (40% vs. 28%, P = .006). This series and similar reports have led to a Class III recommendation (harmful; should not be performed) in the STEMI treatment guidelines.[1]

This recommendation has led to the routine use of multiple revascularization procedures in patients with multi-vessel disease presenting with STEMI, even within the initial hospitalization. Although some have argued early multi-vessel PCI after acute MI carries additional risk, an observational analysis of 239 multi-vessel disease patients from the Mayo Clinic[17] showed that multi-vessel PCI within 7 days after AMI compared with 1-vessel PCI was not associated with an excess risk of death or of combined death, myocardial infarction, coronary artery bypass graft, or target vessel revascularization. The multi-vessel PCI group had a significantly higher prevalence of adverse prognostic indicators. Despite this, observed event rates were similar between the multi-vessel PCI and 1-vessel PCI groups. The Kaplan-Meier estimated 1-year survival was 0.91 (95% confidence interval [CI] 0.87 to 0.95) for the multi-vessel PCI group and 0.93 (95% CI 0.92 to 0.95) for the 1-vessel PCI group (p = 0.43). Similarly, 1-year survival free of recurrent infarction and target vessel revascularization rates were similar between the 2 groups: multi-vessel PCI 0.78 (95% CI 0.73 to 0.84) and 1-vessel PCI 0.78 (95% CI 0.75 to 0.81).

The PRAMI randomized trial [18] has challenged these previous assumptions. In PRAMI the randomized strategy to do PCI in non-IRA lesion(s) immediately following successful primary PCI was associated with a significant reduction in intractable ischemia, re-MI and death compared with IRA-only intervention in an event-driven model that was terminated early for benefit by the Data and Safety Monitoring Board. Less than 2 years after the PRAMI study was publicly reported, the CvLPRIT study [19], in which 296 STEMI patients with multi-vessel CAD were randomized to complete revascularization vs. infarct artery only. The primary endpoint was a composite of all-cause death, recurrent myocardial infarction (MI), heart failure, and ischemia-driven revascularization within 12 months. The 65% reduction in this endpoint at 1 year was highly significant favoring complete revascularization.

Thus in the face of a large body of observational evidence suggesting that PCI in addition to the IRA during primary PCI may be more risk than benefit, and best practice guidelines long promoting those observations, two independent, contemporary randomized trials suggest that primary PCI with complete revascularization leads to significant clinical benefit. A meta-analysis [20] of 46,324 subjects in randomized and non-randomized studies suggests a long-term mortality benefit with complete revascularization if non-infarct-related artery (N-IRA) PCI is performed on a staged basis as opposed to being

undertaken the time of the index PCI. Contemporary aggressive anti-coagulant and anti-platelet regimens have likely improved the risk/benefit profile of non-IRA PCI immediately after primary intervention. In conjunction with radial vascular access which reduces bleeding risk, the potential clinical and economic value of more complete revascularization after acute STEMI warrants definitive study. Elderly patients, a population at particular risk for multi-vessel CAD and bleeding complications, represent current unmet needs for interventional device applications and modernize best practice guidelines. The SAFE STEMI for Seniors protocol has been developed to address these objectives.

One central concern about multi-vessel PCI in conjunction with STEMI intervention is the criteria with which to determine if non-IRA lesions are appropriate for PCI. Although IVUS and OCT assessments of plaque composition in non-culprit ACS lesions have been associated with subsequent MACE events, [21, 22] these techniques have not been validated in large studies. Most observational and randomized studies have used angiographic estimates of stenosis severity to determine non-IRA lesions requiring treatment.[15] However, there is often a disparity between angiographic and physiologic measurements of non-IRA lesion significance in STEMI patients.[23] In 408 STEMI patients with evidence of multi-vessel disease defined by presence of N-IRA lesions with diameter stenosis of >50 %, FFR measurements performed at the time of index procedure showed that in 56.5 % the FFR was negative (<0.8).[24] FFR measurements have been shown to be reliable and reproducible for non-culprit lesions in acute myocardial infarction. [25]The need for adenosine with FFR creates a safety concern in the STEMI setting, particularly in patients with high-grade AV block, concomitant pulmonary disease, hypotension, or bradycardia.[23] iFR in elective settings provides physiologic lesion assessment with outcome correlations without the need for provocative chemical infusion.[26] Thus, iFR guided non-IRA lesion assessment provides an objective physiologic lesion/vessel specific measurement that may be safe and logistically feasible for use in STEMI settings.[27]

The use of iFR in this protocol is intended to objectively avoid treating lesions that are not appropriate for revascularization. In the PRIMULTI trial[28], of 314 patients with angiographically significant lesions (50% or greater angiographic diameter stenosis) assigned to complete FFR-guided revascularization, 97 (31%) subjects had FFR values that were greater than the FFR discrimination threshold of 0.80, and these individuals received no further PCI. Likewise, in the COMPARE ACUTE study[24] the FFR assessment was negative in 56.5% of non-IRA with 50% or greater angiographic diameter stenosis. The use of iFR, rather than FFR, is intended to reduce the risk of physiologic assessment attributable to the vasodilators required for FFR. The risk attributable to revascularization of non-IRA vessels, even “obviously significant” ones, remains in equipoise. Retrospective registry data have indicated that non-IRA vessels should not be

treated during an initial admission, but the PRAMI and CvLPRIT trials suggest otherwise. Consequently, these subjects are expected to undergo randomization in SAFE-PCI in STEMI for Seniors.

1.4 Radial Access for Primary PCI

The most common complication of primary PCI for STEMI is bleeding in the setting of combined antithrombotic therapy and femoral arteriotomy. Studies have consistently shown that STEMI patients experience a higher rate of hemorrhagic complications compared with NSTEMI patients. Moreover, bleeding in this population is associated with an increased risk of short- and long-term morbidity and mortality.

Approximately half of the bleeding complications that occur among patients undergoing primary PCI occur at the femoral vascular access site. Since age is a strong predictor of bleeding, seniors are at particularly high risk for bleeding and bleeding-related morbidity. Radial access, compared with femoral access, is associated with a 60-70% reduction in bleeding complications, primarily driven by a reduction in access site bleeding. Three independent randomized studies conducted largely outside the United States have reported reductions in 30-day MACE and mortality rates with trans-radial compared with trans-femoral primary PCI. The RIVAL study[29] reported a pre-specified STEMI subgroup analysis from the larger ACS cohort comparing radial and femoral approach that, in the overall analysis, showed no advantage of radial access for ACS, but clinical benefit for the STEMI patients treated from the radial approach. RIFLE STEACS was a randomized trial conducted at 4 centers in Italy, randomizing STEMI patients to radial vs. femoral access and reporting clinical benefits, including a significant mortality reduction, in the radial group.[30] Most recently the MATRIX study[31], a multicenter European trial conducted in over 7000 patients with acute coronary syndrome (including STEMI) demonstrated a significant reduction in net adverse clinical events (NACE) defined as MACE plus BARC 3 or greater bleeding and a reduction in 30-day mortality, although the mortality reduction was not seen in STEMI patients per se.

Whether these results are generalizable to the US where the use of radial approach is less common is unclear. Furthermore, seniors may have more upper extremity atherosclerotic disease and tortuosity, and in STEMI patients a central concern would be whether radial access would delay reperfusion times sufficiently to offset benefits of bleeding reduction. With rapidly expanding use of radial approach in the USA, and these reports generating interest and expanding use of radial techniques for primary PCI more data on procedure techniques, antithrombotic medications, catheter choice, and outcomes is essential to understanding the features of successful trans-radial primary PCI programs and their impact on the public health in the United States.

1.5 Terumo® Glidesheath Slender and TR Band

Similar to trans-femoral catheterization, sheath size is an important predictor of access site-related complications after trans-radial catheterization with larger sheaths independently associated with increased pain as well as increased major and minor complications. In a randomized trial of 5 French (Fr) versus 6 Fr trans-radial PCI, procedural success was achieved in 95.4% of 5 Fr and 92.9% of 6 Fr patients, while 1.1% of 5 Fr and 5.9% of 6 Fr patients ($p = 0.05$) suffered a loss of radial pulse due to radial occlusion. The Terumo® Glidesheath Slender is a dedicated thin walled, hydrophilic radial sheath that combines an inner diameter compatible with a 6 Fr guiding catheter with an outer diameter close to current 5 Fr sheaths. Conceptual advantages of the Glidesheath Slender include smaller arteriotomies (especially important in women with small radial arteries) and the flexibility to perform diagnostic (5 Fr) and interventional procedures (6 Fr) without upsizing to a larger sheath. In a feasibility study of 114 patients at a single center undergoing trans-radial catheterization with the Glidesheath Slender, procedural success was 99.1%. Complications included 6 minor hematomas (no major vascular complications), a 4.4% rate of symptomatic radial spasm, and 1 case of radial artery occlusion (RAO; 0.88%). At present, the generalizability of these results to elderly patients undergoing primary trans-radial PCI for STEMI is not known.

In addition to sheath-to-artery ratio, achieving patent hemostasis after trans-radial catheterization is among the most important factors in reducing RAO. The Terumo® TR Band is a radial artery compression device consisting of dual balloons within a transparent wrist band. As air is introduced into the dual balloons, compression of the radial artery occurs, achieving patent hemostasis. Advantages of the TR Band include ease of use, the ability to precisely titrate the amount of air (compression) within the band, and the ability to continuously observe the access site.

1.6 SAFE Site Network

The SAFE site network includes experienced radial operators who have demonstrated willingness and ability to randomize subjects for clinical investigations, such as the SAFE PCI for Women study, with more than 1,800 women randomized at 60 US sites.

In addition, the SAFE network of sites are experienced with workflow utilizing timely hospital-based NCDR data entry, including NCDR data checks and data quality processes, for NCRI clinical trial application. This workflow in the SAFE PCI for Women study utilized programming from the NCRI to auto populate a Part-11 compliant Oracle database, providing historical descriptors, concomitant medications, PCI procedural details and MACE events for the index hospitalization without duplicative case report form

data entry work for the site coordinators. This structure also seamlessly supports Part 11 compliance in conjunction with the conduct of IDE studies.

An upgrade of the NCDR CathPCI Registry database from v4.0 to v5.0 is currently scheduled for 2018. The data definitions for SAFE STEMI for Seniors will be harmonized with CathPCI v5.0 to permit future auto-population of index hospitalization data from the CathPCI Registry when interfaces become available. Until that time, all data will initially be entered directly into the part 11 compliant database by site personnel. This approach allows the study to approach non-SAFE sites in the United States as well as Canadian sites to participate in SAFE STEMI for Seniors.

Finally, with the focus of SAFE PCI in STEMI for Seniors, long term follow up at and beyond 18 months can be efficiently incorporated by linking directly to Medicare claims data (for US sites) which will provide long term follow up for death, MI, stroke, hospitalizations and repeat revascularizations data for the study database. This method has been proven to provide more complete information, with fewer subjects lost to follow-up, and at a reduced effort for sites and local site IRBs.

See Appendix A, Section 15.1.

2. STUDY OBJECTIVES

The SAFE STEMI for Seniors study is designed:

1. To examine the effectiveness of zotarolimus-eluting stents for radial Primary PCI in STEMI
2. To evaluate the safety and benefit of iFR-guided complete revascularization vs. infarct artery only revascularization in Primary PCI of patients with multi-vessel 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.

These objectives are accomplished by the evaluation of the primary and secondary endpoints.

3. STUDY DESIGN

3.1 Overview of Study

This is a prospective, multi-center, unblinded, randomized clinical trial in primary PCI subjects 65 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 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. By protocol, DES patients will be treated with a Medtronic Resolute® Family of Stents.

The intended population is subjects undergoing primary PCI for STEMI, who are considered eligible for a drug-eluting stent. Subjects with multivessel disease are enrolled and receive the Medtronic Resolute® Family of Stents to the IRA regardless of their randomization assignment. The design seeks to reflect the general population of seniors presenting with STEMI.

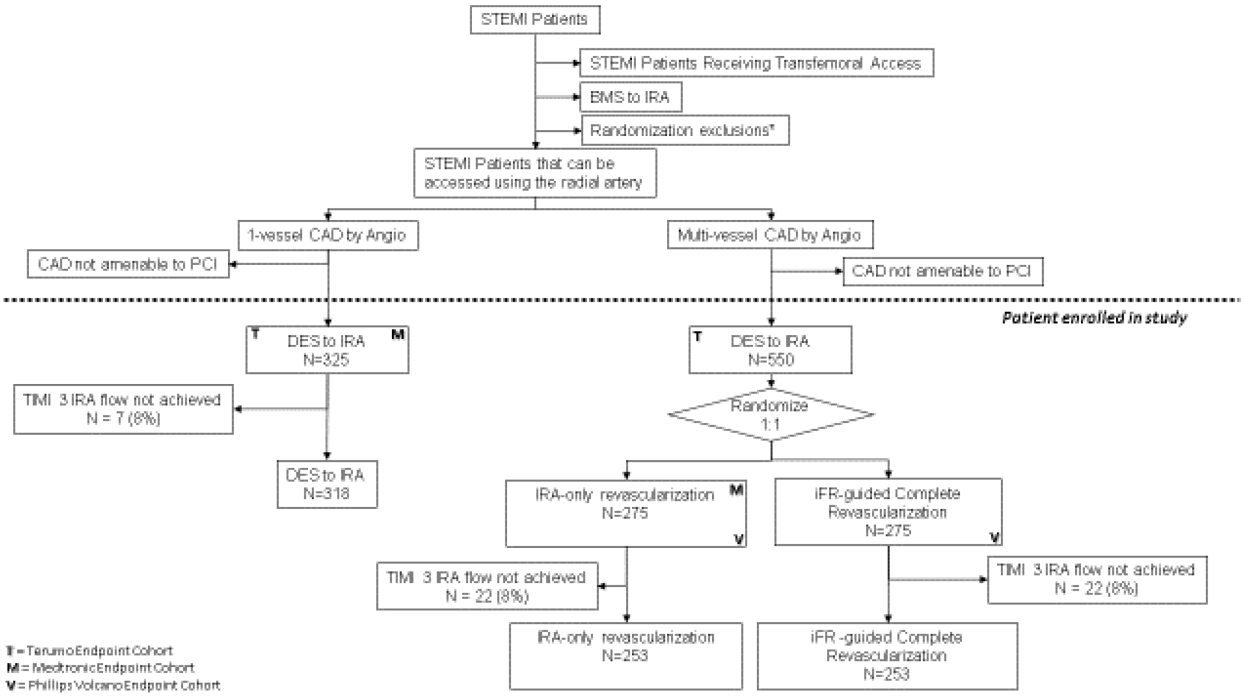
DES subjects in whom multi-vessel disease is identified with absence of shock or prohibitive angiographic anatomy (unprotected left main disease, CTO to large distributions, etc.) will be randomized by site in a ratio of 1:1 to complete revascularization (guided by iFR using Volcano based pressure wires 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 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 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 numbers in Figure 1 are estimates, although we will not enroll more than 875total. The enrollment cap is controlled at 875 DES subjects regardless of the number of single-vessel or multi-vessel CAD patients.

Figure 1 Study Design and Treatment Schema



For additional detail regarding data sources reference 15.2 Appendix B.

3.2 Endpoints

3.2.1 Endpoints for Evaluating Medtronic Resolute® Family of Stents for Primary PCI in STEMI

3.2.1.1 Primary Endpoint

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. 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.

This endpoint has been powered to test the superiority of the primary endpoint rate when using the Medtronic Resolute® Family of Stents in STEMI versus HORIZON performance goal.

3.2.1.2 Secondary Endpoints

Using the Medtronic Resolute® Family of Stents 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 section definition in 3.2.1.1) 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.

3.2.1.3 Device Performance Endpoints

- 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

3.2.2 Endpoints for Evaluating iFR Guided iFR-Guided Complete Revascularization in STEMI

3.2.2.1 Primary Endpoint

The endpoint is 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. The definition of P2-MI 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)

This endpoint has been powered to test the superiority of the primary endpoint rate when using iFR guided complete revascularization versus infarct related vessel only revascularization in STEMI.

3.2.2.2 Secondary Endpoints

- 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 (see definition in section 3.2.2) 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 (IIVR) or any treated index non-infarct related vessels (INIVR).
- Adjudicated Stroke at post-procedure, 30 Days and 1 year

3.2.2.3 Device Performance Endpoints

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.

3.2.3 Endpoints to Evaluate the Terumo Slender GlideSheath and TR Band for radial access PCI in the elderly

3.2.3.1 Primary Observational Endpoint

Estimate of the incidence rate of RAO acute and at 30day stratified by whether or not the Terumo TR Band was employed (use of the TR Band is recommended not required)

3.2.3.2 Secondary Observational Endpoints

- Time to Hemostasis stratified by whether the Terumo TR Band was employed
- Incidence rate of cross over to 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

3.2.4 Endpoint Adjudication

The DCRI Clinical Events Committee will adjudicate the following protocol-specified endpoint events through 1 year as defined in the CEC Charter (see Section 12.3):

- Death
- MI
- Heart Failure
- Revascularizations
- Stroke
- Stent thrombosis

Events occurring beyond 1 year will not be adjudicated.

4. SELECTION AND WITHDRAWAL OF PATIENTS

A total of approximately 875 STEMI patients $\geq$ 65 years of age who are eligible for radial access will be enrolled. Approximately 550 STEMI patients with multi-vessel CAD will be randomized to IRA vs. complete revascularization PCI.

4.1 Inclusion Criteria

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

1. Have the capacity to understand and sign an informed consent or have a Legally Authorized Representative that can understand and sign an informed consent prior to initial arteriotomy access.
2. Age ≥ 65 years of age at the time of signing the informed consent and/or randomization.
3. Significant ST-elevation myocardial infarction or left bundle branch block (LBBB) on ECG with chest pain ≤ 12 hours.
4. Accessible right or left radial artery conduit for PCI.
5. Physician intent to perform trans-radial PCI.
6. Willing to be contacted at 1 year by the DCRI Call Center

Study Randomization Inclusion Criteria

To be eligible for randomization in the 'IRA only vs. Complete Revascularization' phase of this trial, subjects must meet all of the above criteria and all of the following criteria subsequent to arterial access:

1. Subject eligible for DES implantation.
2. Angiographic multi-vessel CAD determined by local visual estimation.

4.2 Exclusion Criteria

If a subject meets any of the following criteria, he or she may not be consented for enrollment in the SAFE STEMI for Seniors study:

1. Patient that have known medical conditions that would prevent or interrupt the recommended post procedure DES treatment regimen.
2. Patients that have known medical conditions that would prevent catheterization through the radial artery.
3. Patients that have known medical conditions that increase patient's risk above standard when using IFR.
4. Patients with a known history of Coronary Artery Bypass Grafting (CABG).
5. Has had a cerebrovascular accident or transient ischemic neurological attack within the past 6 months.
6. Known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause noncompliance with the protocol
7. Any condition associated with a life expectancy of less than 1 year.

8. Participation in another clinical study using an investigational agent or device within the past 3 months.

Study Randomization Exclusion Criteria

If a subject who has been consented into the SAFE STEMI study develops or is found to have any of the following, they will not be eligible for randomization to an iFR guided complete revascularization vs. IRA-only primary PCI and will be excluded from the study.

1. Shock requiring pressors or mechanical circulatory assist support (IABP, Impella, ECMO, etc.)Significant chronic renal disease (eGFR < 30) and/or on dialysis
2. Other angiographic exclusions:
    - Single vessel CAD
    - Unprotected left main coronary artery disease
    - One or more major coronary distributions with CTO or indeterminate IRA
3. Clinical circumstances, which, in the judgment of the operator, preclude randomization.

4.3 Randomization Completion

To be eligible to complete randomized procedures, stable TIMI 3 must be established in the IRA using the protocol specified treatment.

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.

4.4 Withdrawal of Patients

Patients may voluntarily withdraw for any reason without penalty or loss of benefits to which they are entitled. Patients may be withdrawn because of the appearance of a new health condition suspected to require care, refusal to continue treatment, or at the Investigator's discretion if it is in the patient's best interest according to the Investigator's clinical judgment.

If a patient withdraws from the study at any time either at his or her request or at the Investigator's discretion, the reason(s) for withdrawal must be recorded on the relevant page of the patient's electronic Case Report Form (eCRF). Patients who withdraw from the study prematurely should undergo all end-of-study assessments, if possible. Study site personnel should make every effort to prevent losing patients to follow-up.

Any adverse experiences that are ongoing at the time of discontinuation / withdrawal should be reported and followed up in accordance with the safety requirements. Any adverse experiences that are ongoing at the time of discontinuation/withdrawal should be reported and followed up in accordance with the safety requirements outlined in Section 7.3.

5. STUDY PROCEDURES

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) regulations and guidelines, International Council on Harmonization (ICH) guidelines, and all other applicable laws and regulations.

Medical questions regarding subject eligibility, procedures, or patient care should be directed to the study Principal Investigator who can be reached as follows:

Dr. David F. Kong at 919-668-8946 during U.S. business hours, or 919-684-8111 after U.S. business hours.

5.1 Screening Procedures

Potentially eligible subjects will be screened upon presentation with ischemic symptoms of acute myocardial infarction of duration $\leq$ 12 hours.

After a diagnosis of STEMI is made and primary radial PCI is planned, the patient will be screened to determine eligibility for SAFE STEMI for Seniors. Study personnel will assess each subject against study inclusion and exclusion criterion, and the investigator will determine the subject's eligibility for participation.

5.2 Informed Consent

Each site will submit the study protocol, ICF, and other study documents to their ethics committee (EC)/institutional review board (IRB) for approval. A copy of the signed and dated EC/IRB approval for each enrolling center will be stored at the Data Coordinating Center. Any amendments to the protocol, other than minor administrative changes, must be approved by the site's EC/IRB before the changes are implemented at the site.

The informed consent process will be documented in the subject's medical record or comparable source document.

Consent will be obtained from the subject or their legally authorized representative prior to arterial access and, if the subject is consenting, prior to the administration of any medications that might affect patient cognition.

5.3 Enrollment

Once a subject has met all inclusion / exclusion criteria and provided informed consent, the subject will be considered to be enrolled in the study. Operators are encouraged to appropriately identify candidates for DES, consistent with study objectives.

Subjects who are DES eligible and have unequivocal 1-vessel disease by angiography will receive their stent via IRA.

5.3.1 Stent Deployment

In a manner comparable to Horizons-AMI[11] and current clinical practice, direct stenting will be permitted in SAFE-PCI in STEMI for Seniors at the discretion of the physician. Pre-dilation is encouraged if needed to demonstrate eligibility for DES implantation.

5.4 Randomization for Subjects with Multi-vessel CAD Receiving a DES

Subjects with investigator determined angiographic stenosis with a > 50% diameter reduction in a non-infarct artery will be randomized prior to the primary PCI procedure once clinical and angiographic criteria are met (excluding shock, left main, major distribution CTOs, etc.) Subjects will be randomized by site in a ratio of 1:1 to an iFR-guided complete revascularization strategy or an IRA-only strategy.

The investigator may determine that some subjects need a staged approach for revascularization. As long as the additional procedure(s) are planned and performed within the index hospitalization, they are considered part of the index intervention. Use of the Medtronic Resolute® Family of Stents is strongly encouraged for all index interventions in the complete revascularization arm, regardless of staging.

5.4.1 iFR Guided Complete Revascularization

In the iFR guided arm, all stenoses with a > 50% diameter reduction via angiographic determination and reference vessel diameter ≥2.25 mm in the non-infarct artery will be evaluated with iFR.

Stenoses with iFR measurement < 0.90 will be re-vascularized using a stent from the Medtronic Resolute® Family of Stents.

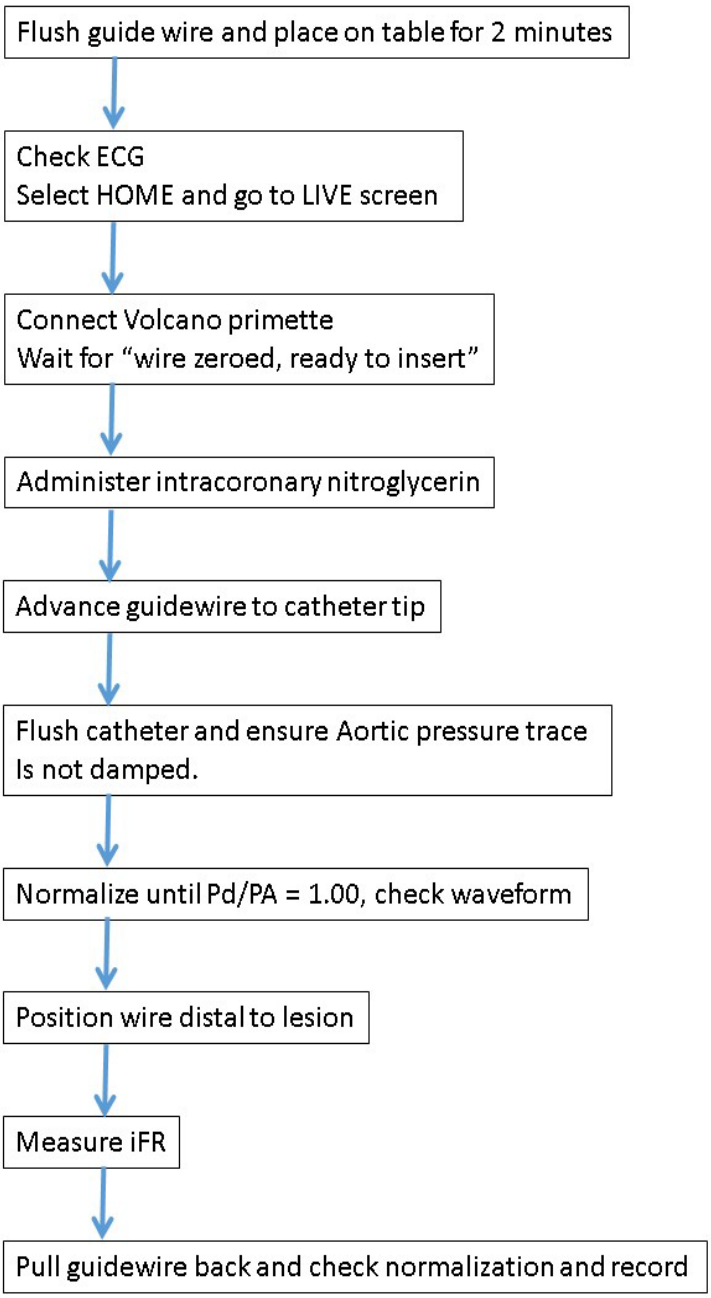
Stenoses with iFR measurement >= 0.90 will be managed medically.

The iFR cut point of 0.9 is based upon the recognition that an iFR cut-point of 0.89 to 0.90 matches best with an FFR ischemic cut-point of 0.80, with a c-index of 0.87.[32-34] Also, similarly to what has been observed with FFR, an iFR value of >0.90 increases the negative predictive value of iFR to 95% to exclude ischemic stenoses (FFR ≤ 0.75).

In the event that the iFR measurement is not evaluable (due to ECG artifacts, pressure artifacts, or transducer drift), revascularization will be performed if the investigator-determined angiographic stenosis is >= 70% diameter reduction. Medical management will be performed if the angiographic stenosis is < 70% reduction.

The recommended schema for obtaining iFR is provided below. The dose of intracoronary nitroglycerin is left to the discretion of the investigator; 50-300 mcg is the recommended range. If clinical circumstances dictate, the pullback to verify normalization may be performed after PCI of the vessel is complete.

Figure 2 iFR Guided Complete Revascularization Procedure Flow



5.5 Post-procedure Follow-up

Subjects will be followed clinically with device related serious adverse events collected per Safety Section 7.0. Subjects will be seen for their standard post-procedure visit (30 days post-procedure). Additional follow up will be completed by the DCRI Call Center for a minimum of 12 months. Patients will be asked to report current medications, hospitalizations and general health assessments.

5.6 Use of Medicare Claims Data

For US patients, Medicare claims data will be obtained and study patients identified. Relevant data will be collected for subjects at 18 months post-procedure after the final patient is enrolled.

5.7 Schedule of Events

The schedule of study assessments and procedures is provided in Table 1:

Table 1 Schedule of Assessments

	Screening and Pre-randomization	Enrollment and Randomization/ Implantation	Post-procedure	30 (± 7) Days	1 Year DCRI Call Center (± 30 Days)	18 Month Last Patient Post-Procedure CMS (± 60 Days) Follow-up
Inclusion/exclusion criteria - enrollment	X					
Informed consent and Patient Contact Form details	X					
Medical history	X					
Physical assessment, vital signs (standard of care)	X[a, b]			X		
Concomitant medications	X[a]			X	X	
Diagnostic angiogram	X					
Assess eligibility for randomization to IRA only vs. complete revascularization	X	X				
Implant Stent in IRA		X				
iFR assessment		X				
Full revascularization, depending on randomization arm		X				
Collection of device performance measures		X[c]	X[c]	X[c]		
Collection of investigational device related serious adverse events		X[d]	X[d]	X[d]		
Event data collection for instances of specified cardiovascular endpoint events		X[e]	X[e]	X[e]	X[e]	X[e]

[a] Within 7 days or immediately before randomization.
[b] If not done within the previous 7 days.
[c] OIfstandard of care is to do the Reverse Bardeau by pulse oximetry tests, the test performed before discharge and at 30 days will be collected
[d] All serious adverse events related to the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology. Specified cardiovascular endpoint events data collection will be reported on the eCRF endpoint pages only.
[e] See section 3.2

6. CONCOMITANT MEDICATIONS/THERAPIES

6.1 Pre-PCI Medications

6.1.1 Aspirin

Preloading with at least 81 mg aspirin is mandatory. For subjects receiving chronic aspirin therapy, the loading dose of between 81 and 325 mg aspirin, according to regional standard of care, should be given.

6.1.2 Platelet Adenosine Diphosphate Receptor Antagonists

Procedural antiplatelet treatment with an adenosine diphosphate (ADP) receptor antagonist or a glycoprotein IIb/IIIa receptor antagonist is mandatory.

The choice of either clopidogrel, prasugrel, cangrelor, ticagrelor, or other approved thienopyridines, or the choice of GPIIb/IIIa agents, is left to the discretion of the investigator.

6.1.3 Other Medications

The use of other medications (e.g., beta-blockers, angiotensin-converting enzyme inhibitors) before PCI is left to the discretion of the treating physicians. Best medical practice is recommended.

As additionally noted in the ACC/NCDR PCI Guidelines, lipid management is strongly recommended.

6.2 During PCI Medications

During the procedure, subjects will receive appropriate anticoagulation medications according to standard hospital practice. The use of any approved anticoagulant agent at the discretion of the investigator is acceptable.

The use of glycoprotein GPIIb/IIIa receptor inhibitors is allowed at the discretion of the investigator.

6.3 Post-PCI Medications

It is very important that the subject is compliant with the post procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medications could result in a higher risk of thrombosis, MI or death.

DAPT should not be discontinued within the first year after DES implantation, according to recommended standard of care, unless absolutely necessary due to major bleeding, major trauma, or major surgery (e.g., intracranial surgery) necessitating discontinuation of antiplatelet therapy.

6.3.1 Aspirin

Dosing with aspirin will be at least 81 mg daily after PCI while in the hospital and after discharge, according to regional standard of care. Dosing should then continue with at least 81 mg per day indefinitely. Daily aspirin should be given through the 1 year follow-up. Aspirin should not be discontinued for CABG or other reasons unless absolutely necessary.

6.3.2 Platelet Adenosine Diphosphate Receptor Antagonists

All subjects must receive chronic daily DAPT according to regional standard of care, with the choice of agent left to the discretion of the investigator.

DAPT should not be discontinued within the first year after DES implantation, according to recommended standard of care, unless absolutely necessary due to major bleeding, major trauma, or major surgery (e.g., intracranial surgery) necessitating discontinuation of antiplatelet therapy. Major surgeries can safely be performed while the subject is on DAPT. If a subject on DAPT requires surgery, strong consideration should be given to performing the surgery without antiplatelet agent discontinuation.

Investigators may continue DAPT for longer than 12 months at their discretion, as suggested by current ACC/AHA clinical guidelines [35].

7. SUBJECT SAFETY AND ADVERSE EVENTS

The SAFE-STEMI for Seniors study will be overseen by DCRI Safety Surveillance who will provide real time site reported Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology related serious adverse event collection, evaluation, and expedited regulatory reporting from informed consent to the 30 day visit. A DCRI Safety Medical Monitor will be responsible for evaluating site reported UADEs to confirm protocol-specific serious reporting criteria, causality assessment, and expectedness compared to product labels. Details of this process can be found in the study-specific Safety Management Plan.

7.1 Definitions

7.1.1 Adverse Event

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, related to the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology.

Any pre-existing condition known to the investigator will not, in general, be reportable as an AE, unless the investigator believes that the participation of the subject in this study contributed to the progression of that condition.

When an AE has, by its nature, a prolonged course, the event will be considered a single event and not multiple events; for example, if a subject develops end-stage renal failure requiring regular dialysis, the event is considered end-stage renal failure, not multiple single renal events.

7.1.2 Serious Adverse Event

Any AE that:

- Led to death
- Led to a serious deterioration in the health of the subject that resulted in
  - Life-threatening illness or injury or
  - Permanent impairment of a body structure or a body function or
  - In-patient hospitalization or prolongation of existing hospitalization.
  - Medical or surgical intervention to prevent permanent impairment of a body structure or a body function

- Led to fetal distress, fetal death, or a congenital abnormality or birth defect
- The following hospitalizations are not considered AEs/SAEs:
  - Visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered "important medical event" or “event life threatening”).
  - Elective surgery, planned before signing consent.
  - Admissions per protocol for a planned medical/surgical procedure.
  - Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
  - Medical/surgical admission for purpose other than remedying ill health state and planned before entry into the study. Appropriate documentation is required in these cases.
  - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

7.1.3 Anticipated Adverse Device Effects

A serious adverse device effect (ADE) that by its nature, incidence, severity or outcome has been previously identified as noted in the device’s IFU/IB.

7.1.4 Unanticipated Adverse Device Effects

Per United States Code of Federal Regulations (CFR) Title 21, Part 812.3, an unanticipated ADE (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated ADEs will include events meeting either A or B as stated below:

A. Events meeting ALL of the following criteria:
   - Not included in the list of anticipated events (see IFU)
   - Possibly, probably, or definitely related to the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology

- Serious (meets any of the following criteria):
  - Life-threatening illness or injury
  - Results in permanent impairment of a body structure or a body structure
  - Necessitates medical or surgical intervention to prevent permanent impairment of a body function or a body structure
  - Led to fetal distress, fetal death, or a congenital abnormality or birth defect
  - Led to death

  (Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.)

B. Any other unanticipated serious problem associated with the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology that relates to the rights, safety, or welfare of subjects.

7.1.5 Device Failure and Device Malfunction

A device has failed or malfunctioned if it is used in accordance with the IFU but does not perform according to the IFU and negatively impacts the treatment. Device failures include:

- Inability to position at desired location
- Inability to activate/deploy device
- Incorrect activation/deployment of device

Because all devices used in this study are marketed and being used from hospital supply, any device failures or malfunctions will be reported to the device manufacturer and FDA per local policy.

7.1.6 User Error

A device is used by the investigator in a manner that is an act, or omission of an act, that results in a different medical device response than intended by the manufacturer or expected by the user. The term "user error" refers to an error made by the person using the device, for example an error of use of the device outside of the IFU/IB. If user error leads to a UADE, it will be reported and captured as a UADE.

7.2 Assessment

7.2.1 Causality

Table 2 Causality

RELATIONSHIP	CAUSALITY	DEFINITION	REPORTING
Not related to investigational device	**Unrelated**	An event for which an alternative explanation (e.g., concomitant drug or concomitant disease) is conclusively identified and/or the relationship in time suggests that a causal relationship is highly unlikely	No AE/SAEs that are not related to the investigational device will be reported. Specified cardiovascular endpoint events collection will be reported on the eCRF endpoint pages only

Related to investigational device	**Possible** **Probable** **Definite**	An event that might be due to the use of the study device. An alternative explanation (e.g., concomitant drug or concomitant disease) is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.	All SAEs related to the investigational device, except events listed as protocol-specific endpoints occurring from informed consent to the 30 day visit will be reported in the eCRF as soon as possible. Specified cardiovascular endpoint events collection will be reported on the eCRF endpoint pages only.

7.3 Reporting

If required, the site investigator or their delegate is responsible for notifying the site director of a reported SAE within the expected time frame. The investigator or qualified designee will enter the required information about the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technologytechnology related SAE into the SAE page of the eCRF, which will be distributed to the appropriate manufacturer contact.

It is understood that complete information about a potential Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology related SAEs potential UADE may not be known at the time the initial report is submitted. The investigator must assess the relationship of the event to the investigational device (including the rationale for the assessment) and should make every attempt to obtain as much information as possible concerning the event. Additional information pertaining to a device related SAE should be reported in the eCRF as it becomes available.

Protocol-specified endpoints (Section 3.2), which include anticipated Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology related serious adverse events, will be reported on the eCRF endpoint page.

Safety data, which includes events reported on the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology related serious adverse events and protocol specified endpoint page, will be periodically reviewed by the Data Safety and Monitoring Committee to monitor subjects' safety from informed consent to the 30 day visit. Study leadership will be monitoring any aggregate events that are occurring at an unexpected rate for this study population. Risks will be continually assessed to determine if a protocol or ICF revision is warranted.

Any safety reporting on devices other than Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology will be the responsibility of the site per local site policy.

7.3.1 Time Frame for Reporting

7.3.1.1 Device Related Serious Adverse Events

Except events listed as protocol-specific endpoints (Section 3.2), Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology device-related SAEs that occur after informed consent through the first 30 day visit will be reported by the site on the device related SAEs page of the eCRF as soon as possible.

If the eCRF reporting capability is not available for more than 24 hours, the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology device related SAE should be reported on the paper back-up SAE form and faxed or e-mailed to DCRI Safety Surveillance. If eCRF, e-mail, and FAX are not available, the event should be reported by telephone (see contact information below). If the report is initially given by e-mail, FAX, or telephone, then the required information about the SAE will be entered into the appropriate module of the eCRF immediately after the eCRF system is available by the site.

SAE FACSIMILE TRANSMISSION:

Duke Clinical Research Institute (DCRI) Safety Surveillance

Fax: +1-919-668-7138; toll-free within the U.S.: 1-866-668-7138

SAE e-mail: DCRISafetySurveillance@dm.duke.edu

SAE telephone: +1-919-668-8624 or toll-free within U.S.: 1-866-668-7799

7.4 Device Failures, Device Malfunctions, and User Error

In the case of a device failure or malfunction related to the investigation, the manufacturer should be notified and the device returned to the manufacturing company, if possible. Since these are approved devices, device failures, malfunctions, and user errors will be reported to the appropriate company and FDA per local site policy.

7.5 Regulatory Reporting of Unanticipated Adverse Device Effects

There are situations that may necessitate rapid communication of the occurrence of events to the regulatory authorities. The DCRI Safety Medical Monitor will determine if a device-related event meets “unanticipated” criteria (i.e., is not identified in the IFU/IB or literature) for the Medtronic Resolute® Family of Stents, Volcano based pressure wires Verrata®, Verrata Plus® and any subsequent marketed Volcano pressure wire technology. Unanticipated ADEs will be reported by the sponsor to the FDA, all reviewing IRBs/ECs, and all participating investigators within 10 working days of when the sponsor determines that the UADE meets the criteria for reporting (per FDA guidance) or within accordance of country regulations.

Investigators are responsible for:

- Reporting investigation medical device UADEs to their reviewing IRB/EC within 10 working days of notification from sponsor.
- Any regulatory, IRB or manufacturer reporting requirements for the other devices used in this study

The sponsor will notify the FDA and site investigators of any adverse events that are occurring at an unexpected rate and which meets the criteria for a UADE.

8. STATISTICAL ANALYSIS AND DETERMINATION OF SAMPLE SIZE

This is a prospective, multi-center, randomized clinical trial designed to assess the safety and effectiveness of the Medtronic Resolute® Family of Stents in elderly subjects with STEMI undergoing primary PCI, and the efficacy of an iFR-guided complete revascularization strategy for complete revascularization in elderly STEMI subjects. The full details of the statistical design and analysis will be included in a Statistical Analysis Plan (SAP) which will be finalized prior to database lock.

8.1 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 MACE estimates for BMS, Cypher, Taxus, Resolute Integrity, and Xience platforms (Table).

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 3 below:

Table 3 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%
Death or ReMI	**Overall**	6.7%	6.9%

Endpoint	Group	DES	BMS
	Age >65	8.5%	11.4%
	Age <65	5.7%	4.6%

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

Table 4 below:

Table 4 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[11] we estimated a relative risk of 1.67 for MACE in patients at least 65 years old (assuming the age distribution in previous DES trials is similar to Horizons). The RR of 1.67 was estimated from HORIZONS AMI study which among subjects older than 65 years had a 1-yr adjudicated MACE rate of 13.4% (109/814). The study had an overall 8% MACE rate at 1-year, thus 1.67 was estimated at 0.134/0.08). Thus we set the performance goal for the intended population at 15.68%.

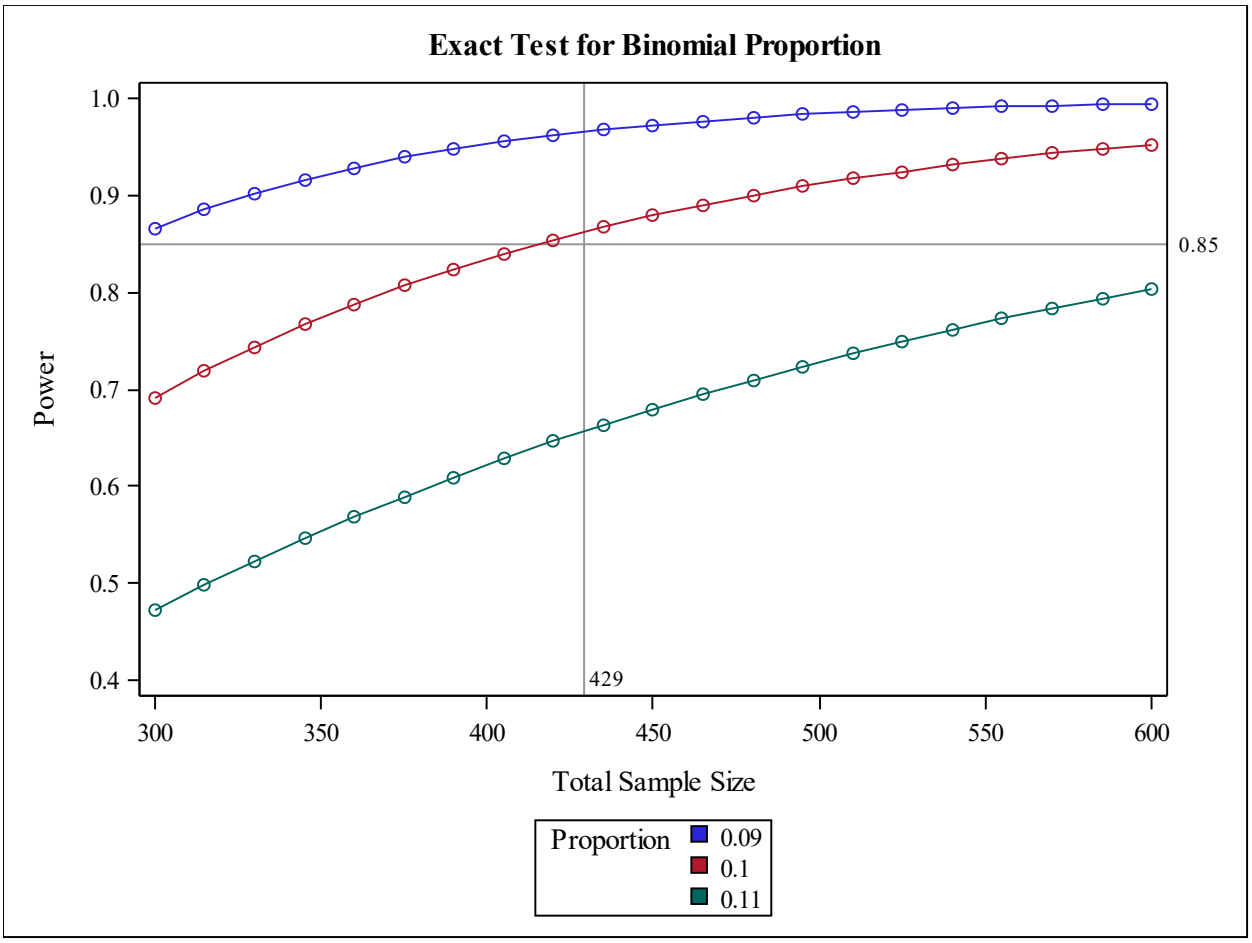
If we assume a Medtronic Resolute® Family of Stents MACE rate of 6% in an unselected population, the expected Medtronic Resolute® Family of Stents rate in a population age ≥65 might be 10%, if the same relative risk applies to Integrity as applies to other DES. Thus for the hypothesis:

$$\mathrm{H}_0\colon P_1 \geq 0.15\ vs.\quad \mathrm{H}_a\colon\ P_1 < 0.15$$

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 0.15.

Based on these assumptions, the study has about 85% power to meet the performance goal with upper two-sided 95% confidence using the exact binomial method[36] would be achieved with a total sample size of 429 analyzable DES patients (Figure 3). Assuming an attrition rate of 10%, this will lead to an enrollment goal of 477 DES patients overall.

Figure 3 Power to exclude the upper 95% confidence interval for the Medtronic Resolute® Family of Stents Performance Goal of 15% Using the Exact Binominal Method*.



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

If site operators designate 875 seniors enrolled into SAFE-PCI for STEMI as DES candidates, we expect about 37% (n=325) to have single-vessel disease, and from the multi-vessel disease subjects (n=550), 275 would be randomized to IRA-only revascularization. Thus, the available cohort for this indication could reach a total of 600 Medtronic Resolute® Family of Stents DES exposures, all treated with IRA-only approach as used in the HORIZONS study.

8.2 IFR-Guided Multivessel 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 [19] and 12% (roughly 45% reduction) in the complete revascularization

arm, yielding the multi-vessel cohort (n=550 pts) which will provide at least 85% 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 [37] will be utilized as the primary analytic tool 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:

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

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

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 4 is a subgroup analysis from the CvLPRIT study [19] (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).

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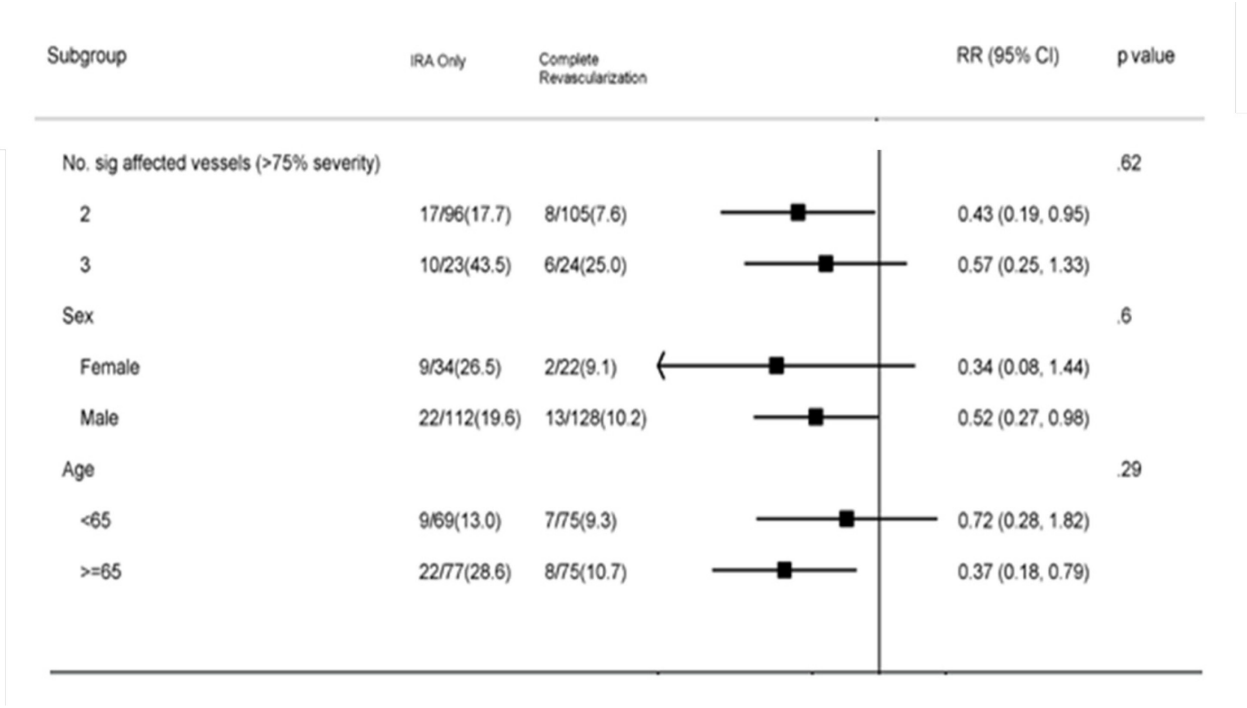
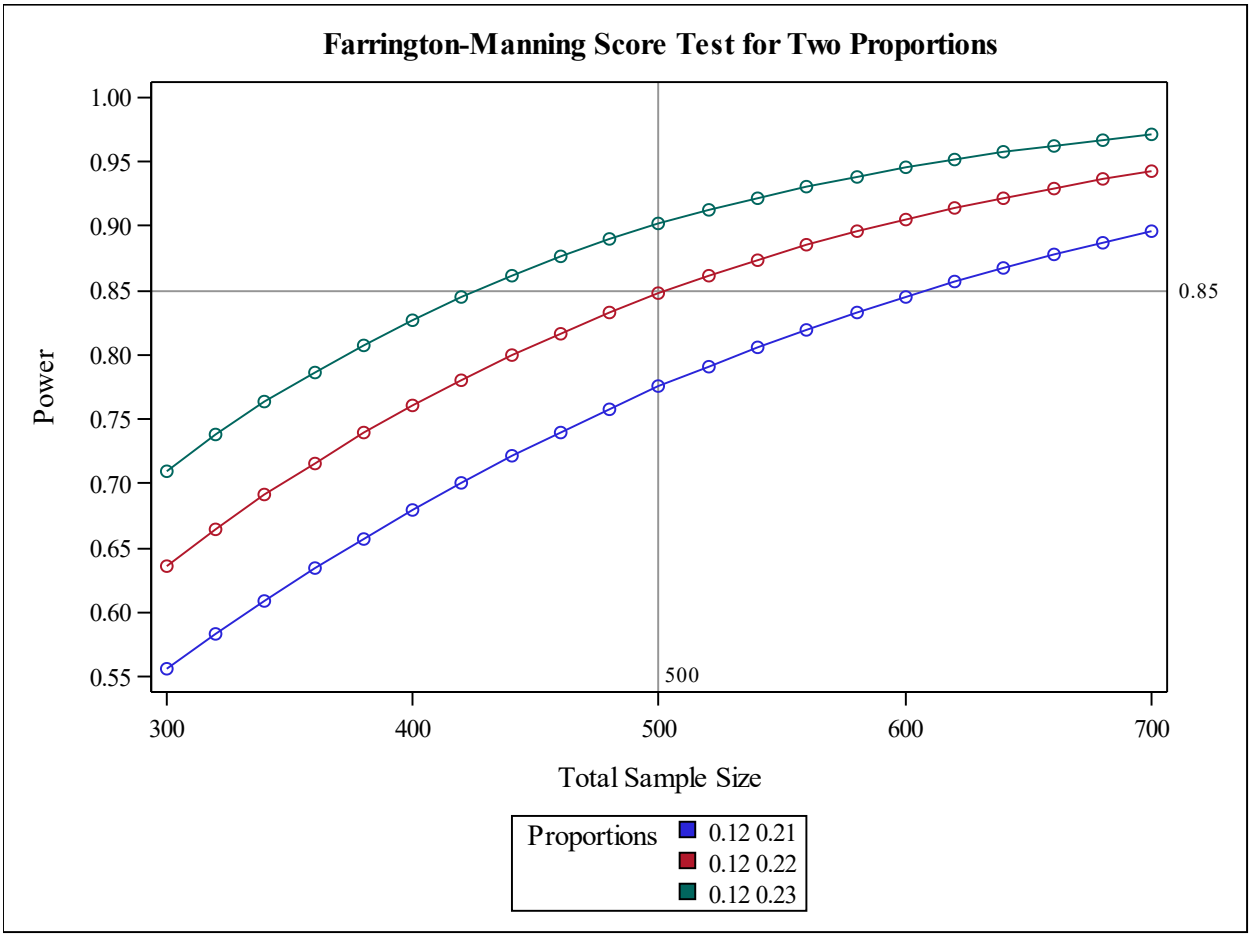
Figure 4 Subgroup Analysis from the CvLPRIT study



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 LTFU. Figure 5 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[19] and 12% (roughly 45% reduction) in the complete revascularization arm, the power is 85% for 500 patients. Assuming a 10% LTFU, the total sample size is 550 patients. The sample size calculation was also confirmed using simulations. The details about the simulations will be in the statistical analysis plan.

Figure 5 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

In addition, Cox proportional hazards model[37] will be utilized as to determine the hazard ratio (HR) and the 95% CI of the complete revascularization to IRA only treatment arms for descriptive purposes only.

8.3 Performance of Terumo TR Band

The incidence rate of RAO acute and at 30day stratified by whether or not the Terumo TR Band was employed is an observational endpoint. No formal hypothesis testing will be performed. Therefore, there is no need to control for Type I or Type II error for this endpoint.

8.4 Secondary and Device Performance Endpoints

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

8.5 Controlling Bias

8.5.1 Type I Error

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.

All secondary endpoint analyses will be reported after all subjects have completed a minimum of 12 months of follow-up.

8.5.2 Blinding and Randomization

For both primary endpoints, given the nature of the treatment and the trial design, neither patient nor sites can be blinded. However, the primary and secondary endpoints will be adjudicated by an independent Clinical Events Committee (see section12.3) and the safety will be evaluated on an ongoing basis by an independent Data Safety Monitoring Board (see section 12.2) to reduce bias in endpoint assessment.

8.5.3 Poolability across sites

The site poolability will be assessed by testing whether there is a site by treatment interaction effect for both primary endpoints using the methods described in the statistical analysis plan. If there is a strong ($p < 0.05$) interaction effect, the data will be investigated as to the source of the interaction effect and the analysis will be adjusted as described in the statistical analysis plan.

9. ESTIMATED DURATION OF THE STUDY

It is estimated that the study involvement for all sites will extend approximately four months after the last entered subject's procedure.

US Medicare fee-for-service subjects will have their data reviewed at 18 months post-procedure after the final patient is enrolled using the CMS database. Data will be analyzed to check if any endpoints have occurred. At Year 1, since data will be obtained both from the call center and CMS, a comparison of the quality and completeness of each method can be performed.

10. STUDY ETHICAL CONSIDERATIONS

10.1 Confidentiality of Patients

Patient confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique patient identification code will be used that allows identification of all data reported for each study patient.

Patient information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated in the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All records will be kept confidential, and the patient's name will not be released at any time. Patient records will not be released to anyone other than sponsor or its designees, and responsible regulatory authorities, when requested. For endpoint ascertainment, the patient has agreed that their social security number and/or Medicare identifier will be used for endpoint ascertainment using the CMS and/or NDI database. In all cases, caution will be exercised to assure the data are treated confidentially and that the patient's privacy is guaranteed.

11. ADMINISTRATIVE PROCEDURES

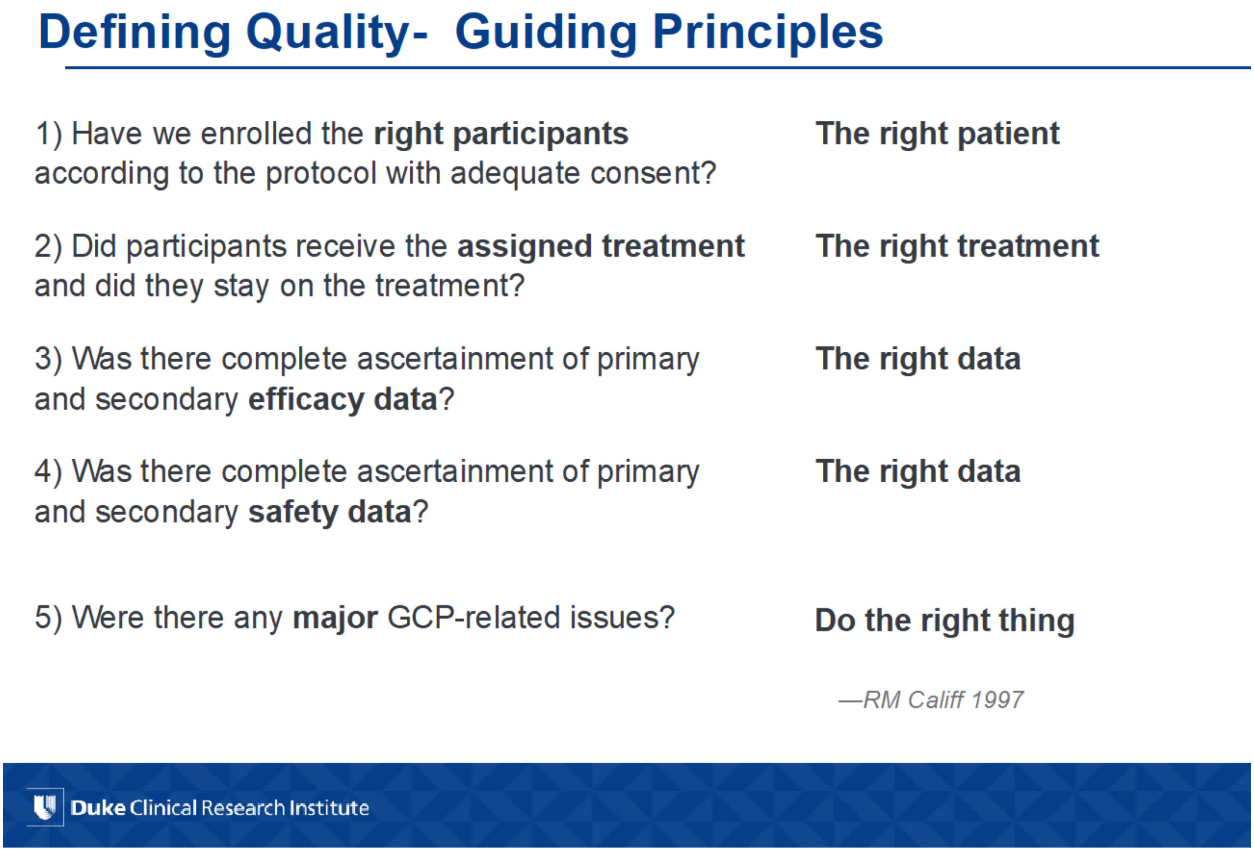
11.1 DCRI Coordinating Center Responsibilities

11.1.1 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures. This training will take place prior to enrollment of the first patient at each study center.

11.1.2 Study Monitoring

The study will be monitored by sponsor or its designee according to the Clinical Monitoring Plan (CMP) will be developed using a risk-based monitoring approach. This will focus on the following quality guiding principles for this trial.



- For cause site visits will be scheduled based on the sites' risk-based performance metrics that are based on the guiding principles for the patient data collected through 30 days. The key risk indicators and performance metrics will be provided in the CMP.

Questions around eCRF completion or study procedures should be directed to the site's Clinical Research Associate (CRA).

11.2 Investigator's Responsibilities

11.2.1 Reporting and Recording of Study Data

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported on the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures and patient's clinical status from informed consent though the 1 year DCRI call center contact.

11.2.2 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each patient are based. They are to be separate and distinct from eCRFs.

These records should include detailed notes on:

- The medical history prior to participation in the study
- The basic identifying information, such as demographics, that link the patient's source documents with the eCRF
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the patient
- The patient's exposure to study treatment
- The patient's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the patient throughout the study
- The oral and written communication with the patient regarding the study treatment (including the risks and benefits of the study)
- The date of informed consent must be recorded in the source documentation.

11.2.3 Records Retention

The Investigator must inform, and receive approval from, the Sponsor prior to the destruction of any documents, if documents are to be transferred to a different facility, or transferred to a different owner.

The Investigator shall maintain the records required for this investigation for a period of 2 years after the later of the two date:

- The date on which the investigation is terminated or completed, or
- The date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

12. STEERING COMMITTEE, DATA SAFETY AND MONITORING COMMITTEE, AND ADJUDICATION COMMITTEE

12.1 Steering Committee

The Steering Committee for this study will supervise the conduct, administration, and course of the clinical trial. They will provide scientific and clinical oversight and will meet periodically to monitor subject enrollment and overall study progress. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.

12.2 Independent Data and Safety Monitoring Committee (DSMC)

An independent DSMC will monitor the trial conduct. The DSMC will consist of 2 clinicians and a statistician. The members of this committee will not participate in the enrollment or treatment of patients in this trial. The guidelines for the DSMC operations will be reported in a separate DSMC Charter.

The DSMC will review safety data at predefined times established prior to the start of enrollment. The DSMC is responsible for making recommendations regarding any safety or compliance issues throughout the course of the clinical trial and may recommend to the Steering Committee to modify or stop the clinical trial. However, all final decisions regarding trial modifications rest with the Steering Committee.

All analyses required for the DSMC assessment of feasibility and efficacy will be performed and/or supported by statisticians at the DCRI. Full details of the composition and the operation of the DSMC and how the analyses are to be performed will be detailed in a separate DSMC Charter and associated Statistical Analysis Plan.

12.3 Independent Clinical Events Committee (CEC)

An Independent Clinical Events Committee (CEC) will provide independent central adjudication of death, cardiac death, P1-MI (for definition, see section 3.2.1), index infarct

related vessel P2-MI (for definition, see section 3.2.1), IIVR and INIVR. IILR (ischemia driven) revascularizations, stroke, heart failure and stent thrombosis (ARC Definition). The guidelines for the adjudication process will be reported in a separate document, the CEC Charter. The members of this Committee will not participate in the enrollment or treatment of patients in this trial, nor will they participate in the DSMC or the steering or executive committee.

13. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The sponsor will encourage the scientific publication of data from clinical research trials. However, Investigators may not present or publish partial or complete study results individually. The Principal Investigators and the Partners may propose appropriate scientific manuscripts or abstracts from the study data. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by the SAFE STEMI for Seniors Steering Committee before submission for publication. Names of all investigators enrolling in the study will be included in the manuscript.

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15. APPENDICES

15.1 Appendix A: National Cardiovascular Research Infrastructure CathPCI Registry

The SAFE-PCI in STEMI for Seniors trial is a large trial that could potentially leverage the NIH-funded National Cardiovascular Research Infrastructure (NCRI). The NCRI is a research platform that utilizes the ongoing American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) CathPCI registry as the data collection platform. The CathPCI registry is the largest ongoing registry of PCI in the world and includes over 1500 US sites and over 5 million patient records. The Duke Clinical Research Institute (DCRI), in collaboration with the American College of Cardiology Foundation (ACCF), will develop a software interface through which data collected as part of the new CathPCI v5.0 Registry "auto populates" a clinical trial case report form. This significantly reduces workload at the site, and can produce cost savings up to 30% of overall trial costs. In addition, access to the CathPCI Registry allows for "evidence-based" site identification to enhance patient recruitment.

This construct was impressively successful in its first implementation in the SAFE PCI for Women study, reported as the featured late breaking clinical trial at TCT 2013, and is proposed to drive efficiencies, reduce timelines and reduce cost for the SAFE STEMI for Seniors study in support of both its IDE and public health missions. A unique feature of this construct to be executed in SAFE STEMI for Seniors will be the electronic linkage of the NCRI-NCDR data accrual network to Medicare claims data for US sites, yielding long term (1 year and beyond) follow up of death, MI, stroke, re-hospitalization and repeat revascularization.

An upgrade of the NCDR CathPCI Registry database from v4.0 to v5.0 is currently scheduled for 2018. The data definitions for SAFE STEMI for Seniors will be harmonized with CathPCI v5.0 to permit future auto-population of index hospitalization data from the CathPCI Registry when interfaces become available. Until that time, all data will initially be entered directly into the part 11 compliant database by site personnel.

This approach allows the study to approach non-SAFE sites in the United States as well as Canadian sites to participate in SAFE STEMI for Seniors.

15.2 Appendix B: Clinical Data Sources

The submission timeline is illustrated in figure 1 below. This figure shows the first submission of the 1-year primary endpoint clinical report within 6 months of the last patient's 1-year follow-up. The figure also shows an updated 1-Year primary endpoint clinical report that includes events out to 18 months ascertained using the CMS database that will be submitted within 6 months after the CMS data pull.

The event ascertainment process for first submission of the 1-year primary endpoint clinical report is outlined in figure 2. The task in green in each column in figure 2 is the process start and the task in red is the process end. There is approximately a 3 – 6 month lag between when UB-04 claim form is submitted and the information from that form is included in the CMS database. Therefore, 6 months after the last patient reaches his/her 1 year follow-up, data will be pulled from the CMS database for the all patients in the ITT population starting from the date of the first patient's index procedure up to the latest CMS update. For patients that were lost-follow-up before their 1-year follow-up, the CMS data will be used to ascertain whether a primary endpoint event occurred between the date of last contact and the 1-year follow-up date. The ascertainment process is outlined in the 30-Day and 1-Year column of figure 3. For all patients, the CMS data will be used to ascertain primary endpoint events between 1-year and 18 months according to the process outlined in the 18-month column in figure 3. The task in green in each of the column of figure 3 is the process start and the task in red is the process end. The 1-year primary endpoint report event tables will updated with the primary endpoint event information ascertained through the CMS database for the patients that were lost to follow-up before their 1-year follow-up date. In addition, a table will be added to the1 year primary endpoint report with the events ascertained from CMS between 1-year and 18 months each patients of follow-up. In addition a Kaplan-Meier Curve with a landmarked start at 1 year out up to the time where 75% of the patients have reached an endpoint or are censored (~2.5 years). Figure 5 shows the expected distribution of patient follow-up at the time of the CMS pull. The bars in figure 5 show the percent and number of patients whose maximum follow-up fall within the interval on the x-axis. The line shows the percent and number of the cumulative follow-up for the patients that have at least the follow-up specified in the interval. The updated 1-year primary endpoint report will be submitted within 6 months after the CMS data pull. Using our current enrollment projection, 80% (N=697) of the patients will have at least 18 months of follow-up and 92% will have at least 15 months of follow-up(N=802).

However, for the Volcano primary endpoint, if the blinded assessment of the pooled event rates indicates the rates are lower than expected, the first submission of the 1-year primary endpoint clinical report will only include the Medtronic primary endpoint and Terumo observational endpoint analyses. The updated 1-year primary endpoint clinical

report submitted 6 months after the CMS data pull will include the Volcano primary endpoint using the event ascertainment process outlined in figure 4. In this process (figure 4) CMS will be used to ascertain and adjudicate any primary endpoint events that happen in the first year of follow-up for all patients as opposed to figure 3 which only uses CMS to ascertain events for patients that were LTFU. This will assure that all possible adjudicated primary endpoint events between index procedure and 1-year follow-up that have been identified using the CMS database will be included in the analysis. The updated 1-year primary endpoint clinical report using the event ascertainment process outlined in figure 4 will be submitted within 6 months after the CMS pull.

Figure 6: Submission Timeline

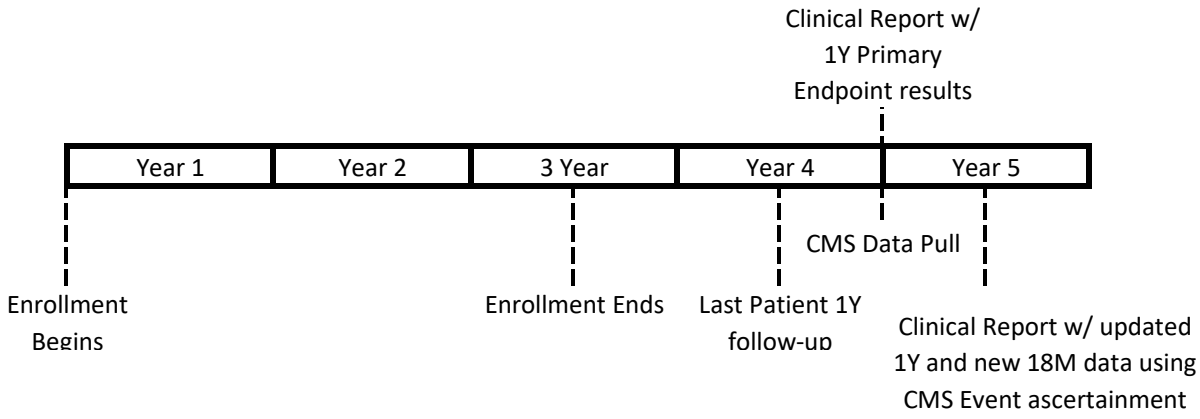


Figure 7: Events Ascertainment process for 1 year Clinical Report

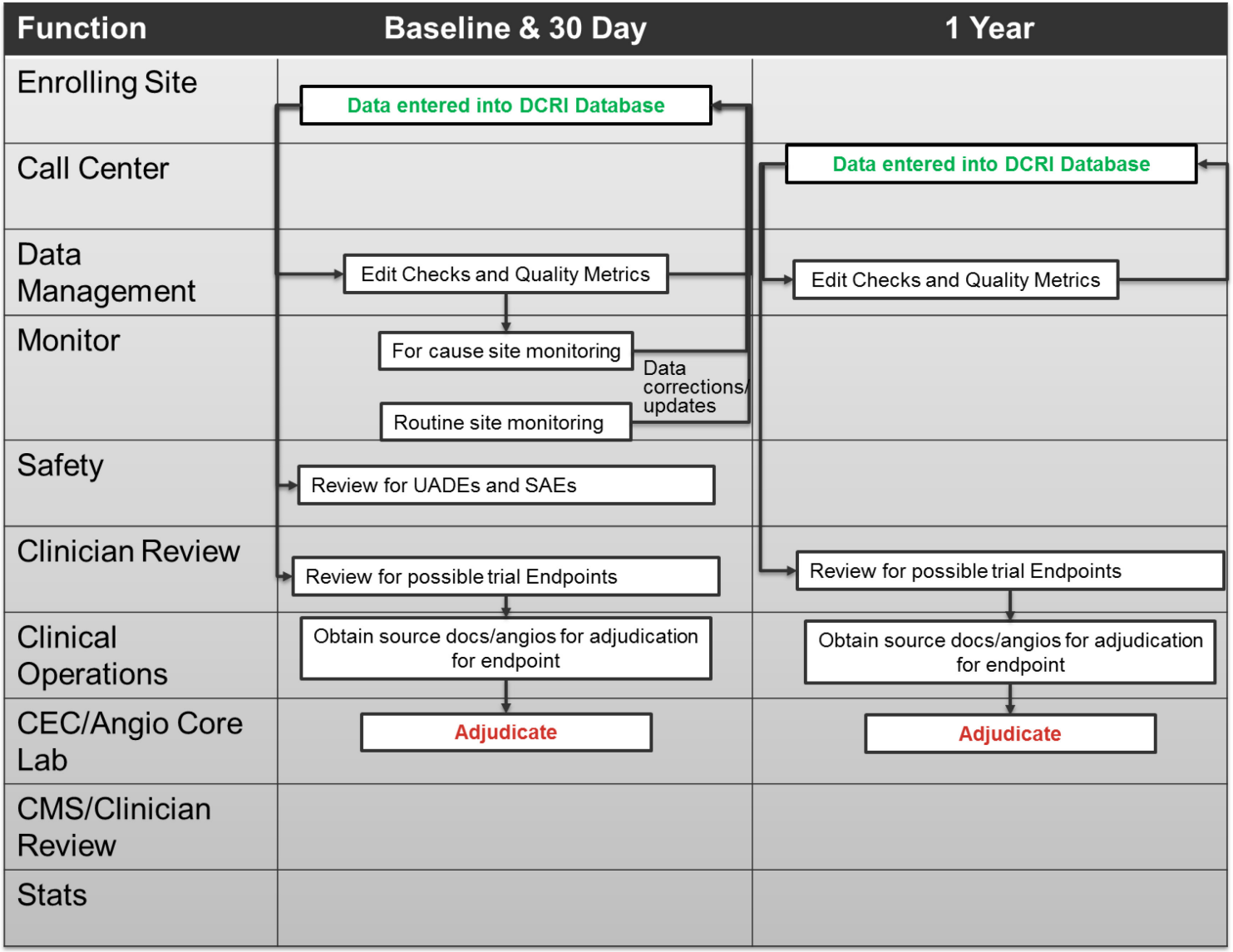


Figure 8: Event Ascertainment process for the Updated One Year Primary Endpoint Clinical Report (updated after CMS pull)

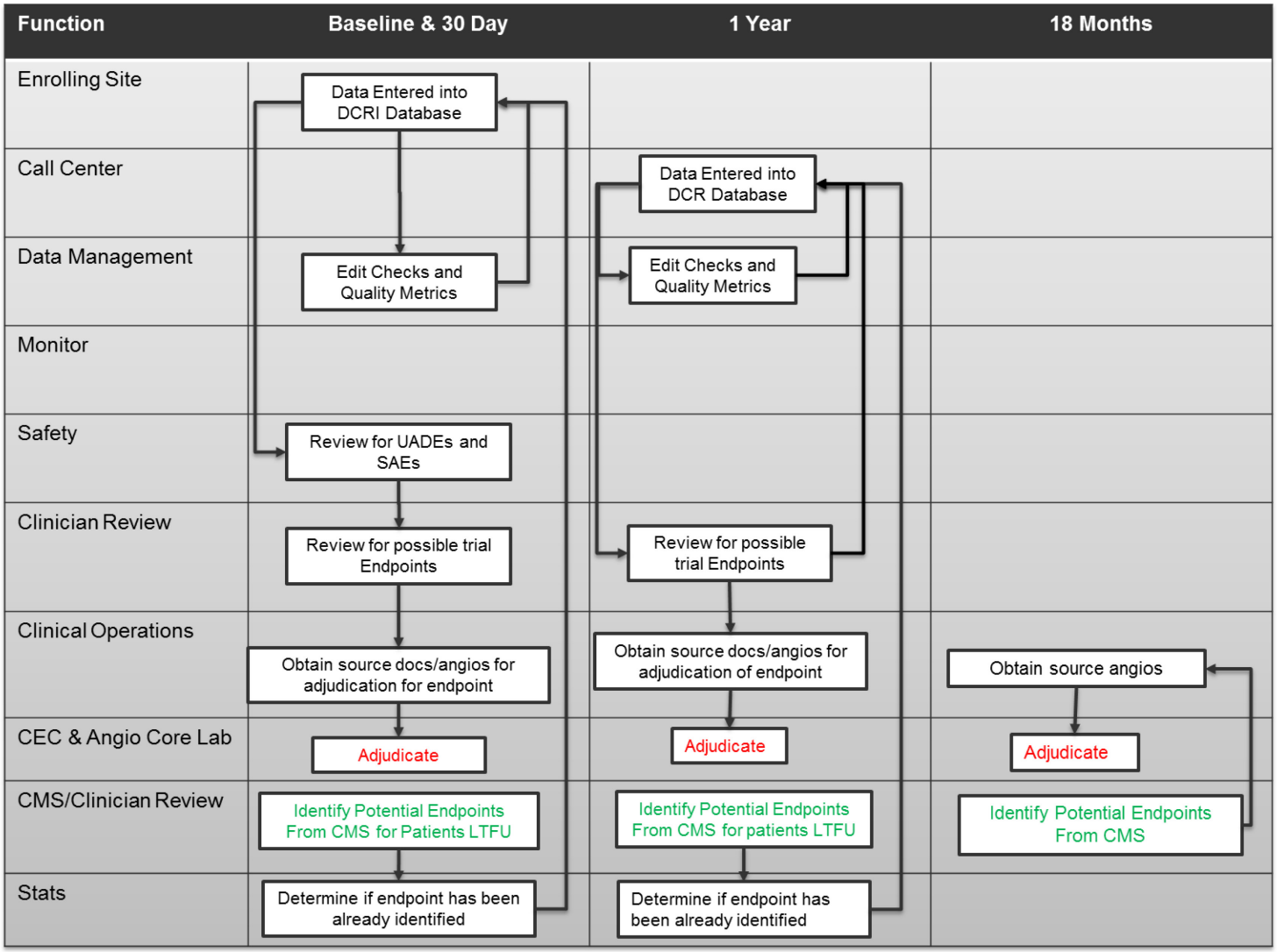


Figure 9: Alternative Event Ascertainment process for the Updated One Year Primary Endpoint Clinical Report For Volcano (updated after CMS pull)

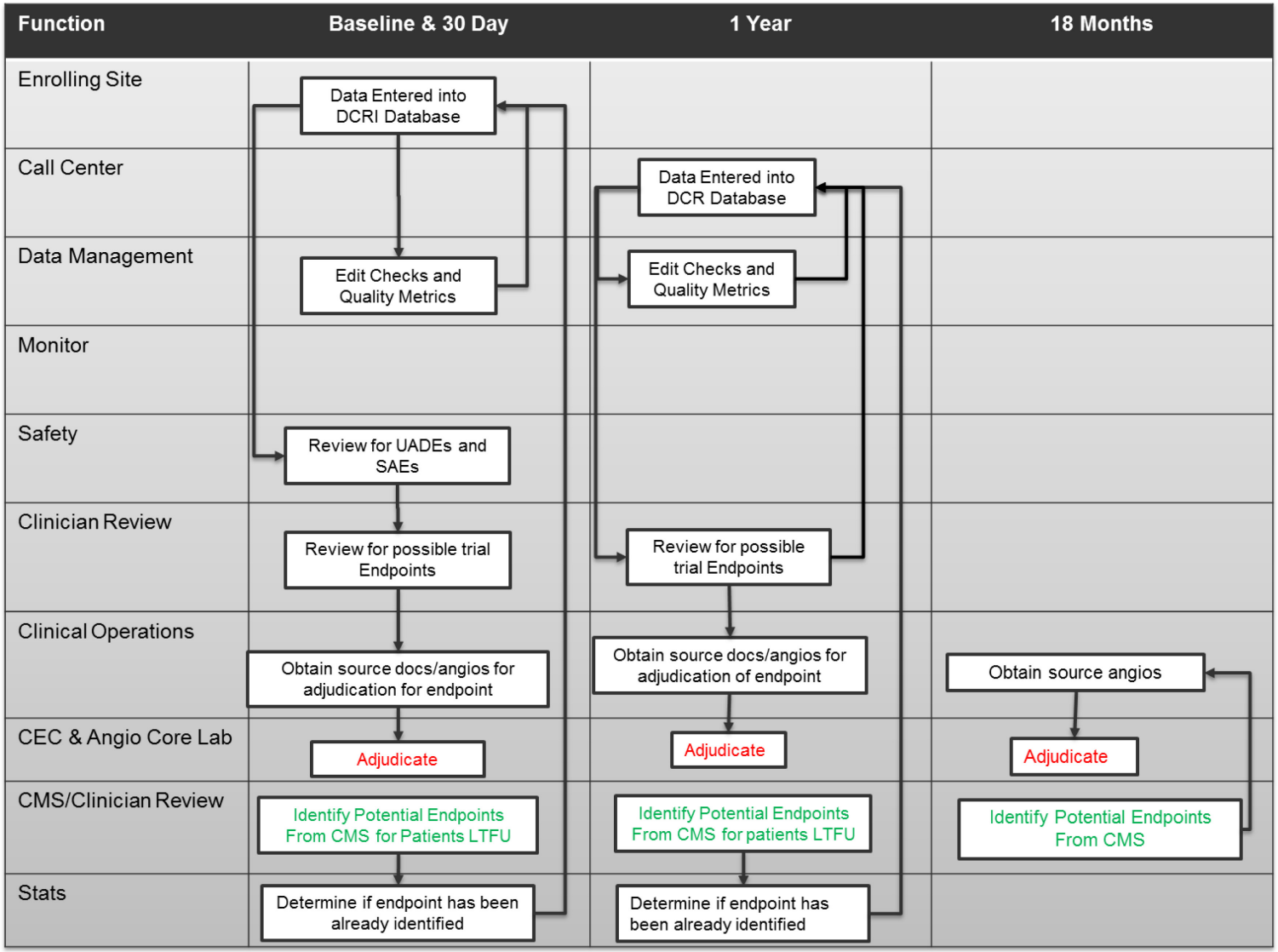
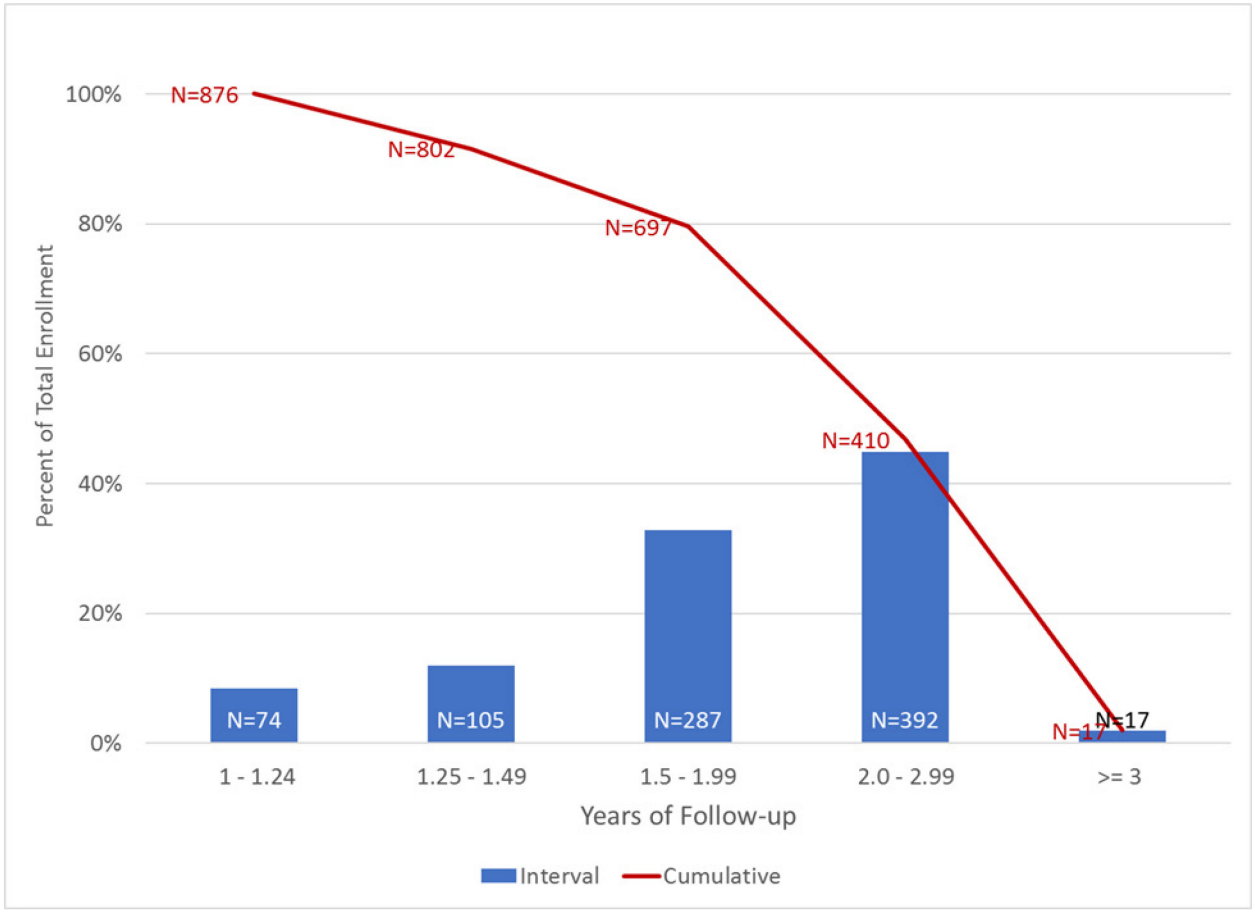


Figure 10: Distribution of patient follow-up at the time of the CMS data pull



15.3 Appendix C: Medtronic Stent IFU

15.4 Appendix D: Volcano Verrata PGW IFU

15.5 Appendix E: Volcano PremeWire Ptrstige PLUS PGW IFU

15.6 Appendix F: Terumo Guidesheath Slender IFU

15.7 Appendix G: Terumo TR Band IFU