PHILIPS

Statistical Analysis Plan

DCR4Contrast trial

Protocol Number: **XCY612-130576**

Protocol Title: **DCR4Contrast Clinical Evidence Study**

Protocol Date: **04 JUL 2019, revision 02**

Author(s):

[redacted]

Project Statistician

Philips Clinical Affairs

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
AIS	Acute Ischemic Stroke
AK	Air Kerma
AKI	Acute Kidney Injury
AKI-D	AKI requiring dialysis
AKIN	Acute Kidney Injury Network (definitions)
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
C(I)N	Contrast (Induced) Nephropathy
CABG	Coronary Artery Bypass Grafting
CE	Conformité Européenne (European Conformity)
CFR	Code of Federal Regulation
CI	Confidence Interval
CI-AKI	Contrast Induced AKI
CKD	Chronic Kidney Disease
CRF	Case Report Form
CRO	Contract Research Organization
DAP	Dose Area Product
DCR	Dynamic Coronary Roadmap
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HTA	Health Tech Assessment
ICH	International Conference on Harmonization
IDMS	Isotope Dilution Mass Spectrometry
iFR	instantaneous wave-Free Ratio
IQR	Interquartile Range
IRB	Institutional Review Board
ISO	International Organization for Standardization

IVUS	IntraVascular UltraSound
LMCA	Left Main Coronary Artery
LOCF	Last Observation Carried Forward
LSMEANS	Least-Squares Means
MACCE	Major Adverse Cardiovascular and Cerebral Events
MDD	Medical Device Directive
MDR	Medical Device Reporting
MEC	Medical Ethic Committee
MI	Myocardial Infarction
NYHA	New York Heart Association classification
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Interventions
RCA	Right Coronary Artery
SAS	Statistical Analysis Software
SCr	Serum Creatinine
SD	Standard Deviation
TIMI	Thrombolysis In Myocardial Infarction
UA	Unstable Angina
V/GFR ratio	Contrast Volume to GFR ratio

2 INTRODUCTION

The most common cardiovascular disease is Coronary Artery Disease (CAD) [Abubakar 2013] and can be treated (when severe) via minimally invasive Percutaneous Coronary Interventions (PCI) or Coronary Artery Bypass Grafting (CABG). Intraprocedural complication rate in PCI has been consistently low at around 1-2% over the past years [Meinertz 2013, Waldo 2018].

However, some risks still remain and are inevitable in PCI such as the use of toxic iodinated contrast agent used to visualize the coronary lumen patency and to assist when navigating devices through the coronary tree. Contrast is associated one of the risk factors for contrast induced Acute Kidney Injury (AKI), especially to patients with preprocedural renal impairment [Tehrani 2013]. AKI comes with economic burden (longer hospitalization and higher readmission rate) next to increased morbidity and mortality [Subramanian 2007, Tsai 2014, Koulouridis 2015].

Dynamic Coronary Roadmap provides automatic navigation guidance via a real-time and dynamic angiographic roadmap of the coronary arteries. Because of the continuous roadmap DCR has the potential to reduce for example the number contrast puffs (small contrast injections) normally required to help device navigation through the coronaries.

We designed this trial in order to confirm the initial pilot study results [Rajappan 2017, Yabe 2018] that showed that DCR can potentially lower the amount of iodinated contrast used during PCI procedures. To this end a randomized controlled investigation is required according to the clinical evaluation and post-market clinical follow-up Annex XIV of the EU Medical Device Regulation [MDR]. Furthermore, to be able to report out on generalizable results a multi-center approach is chosen. Therefore, the DCR4Contrast trial will be a post-market multi-center, prospective, unblinded, stratified 1:1 randomized controlled trial to assess whether using Dynamic Coronary Roadmap reduces the total iodinated contrast volume related to PCI compared to the control group without Dynamic Coronary Roadmap.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective of this clinical study is:

- To assess whether using Dynamic Coronary Roadmap reduces the total iodinated contrast volume related to PCI compared to the control group without Dynamic Coronary Roadmap.

The primary hypothesis is that using Dynamic Coronary Roadmap reduces the total iodinated contrast volume related to PCI compared to the control group without Dynamic Coronary Roadmap.

3.2 Secondary Objectives

The secondary objective is:

- To assess the total number of contrast enhanced cine angiographic X-ray runs (angiograms) related to PCI in the Dynamic Coronary Roadmap and control group

3.3 Exploratory Objectives

The exploratory objectives are:

- To assess the iodinated contrast volume used per vessel PCI in the Dynamic Coronary Roadmap and control group
- To assess the total iodinated contrast volume related to PCI per stratification group, i.e., 1 vessel PCI, 2 vessel PCI and 3 or more vessel PCI, in the Dynamic Coronary Roadmap and control group
- To assess the total iodinated contrast volume related to PCI in subgroups of simple, intermediate and complex PCI (where the SYNTAX score for the vessel(s) treated with PCI will be used as an index for complexity) in the Dynamic Coronary Roadmap and control group
- To assess the incidence of Acute Kidney Injury (AKI) in the Dynamic Coronary Roadmap and control group (at discharge following standard clinical care)
- To assess the variability of the total iodinated contrast volume related to PCI in the Dynamic Coronary Roadmap and control group
- To assess the total fluoroscopy & procedure time related to PCI in the Dynamic Coronary Roadmap and control group
- To assess the total X-ray dose (DAP, AK) related to PCI in the Dynamic Coronary Roadmap and control group
- To assess the procedural success in the Dynamic Coronary Roadmap and control group

- To register in-hospital Major Adverse Cardiovascular and Cerebral Events (MACCE) in the Dynamic Coronary Roadmap and control group

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

The DCR4Contrast trial is a post-market, multi-center, prospective, unblinded, stratified 1:1 randomized controlled trial to assess whether using Dynamic Coronary Roadmap reduces the total iodinated contrast volume related to PCI compared to the control group without Dynamic Coronary Roadmap.

4.2 Discussion of Study Design

We designed this trial in order to confirm the initial pilot study results [Rajappan 2017, Yabe 2018] that showed that DCR can potentially lower the amount of iodinated contrast used during PCI procedures. To this end a randomized controlled investigation is required according to the clinical evaluation and post-market clinical follow-up Annex XIV of the EU Medical Device Regulation [MDR].

Physician investigators participating in this study are expected to follow their normal clinical practice in treating and following up patients with Coronary Artery Disease (CAD). Patients randomized to the DCR group will undergo a PCI procedure during which DCR is used while those randomized to the control group will undergo PCI without the use of DCR. The preparation of the PCI procedure, the procedure itself and follow up will be performed following standard of care.

4.3 Selection of Study Population

The domain of the study is ad hoc and elective PCI patients:

- Patients scheduled for ad hoc PCI are patients potentially treated via PCI immediately following the diagnostic catheterization with diagnostic coronary angiography.
- Patients scheduled for elective PCI have recently undergone diagnostic catheterization with diagnostic coronary angiography that is still valid for the elective PCI and does not need to be redone. Elective PCI is not an emergency intervention and are often also

referred to as secondary PCI as opposed to primary PCI, which are emergency interventions.

Patients receiving a very straightforward PCI that does not require navigation guidance are not included based on the anticipated need for more than 25ml of iodinated contrast volume.

4.3.1 Inclusion Criteria

- Subject is undergoing Percutaneous Coronary Intervention (PCI) with a degree of complexity that anticipates the need for more than 25ml of iodinated contrast volume
- Subject has signed informed consent
- Subject is 18 years of age or older, or of legal age to give informed consent per state or national law

4.3.2 Exclusion Criteria

- Subject undergoing emergency PCI
- Subject with ST-segment Elevation Myocardial Infarction (STEMI)
- Subject with Chronic Total Occlusion (CTO)
- Subject undergoing PCI for isolated ostial disease of Left Main Coronary Artery (LMCA) or Right Coronary Artery (RCA)
- Subject undergoing PCI with Optical Coherence Tomography (OCT) support
- Subject undergoing PCI with rotational or orbital atherectomy
- Subject with Chronic Kidney Disease (CKD) stage V (eGFR < 15 ml/min/1.73 m^2)
- Subject with contrast allergy that cannot be adequately pre-medicated
- Subject participates in a potentially confounding drug or device trial during the course of the study.
- Subject is under 18 years of age, or pregnant woman, or breast feeding woman, or meets an exclusion criteria according to national law

4.4 Treatments

4.4.1 Treatment Groups

During the PCI procedure the Dynamic Coronary Roadmap study device will be used for the randomly selected subjects in the DCR group. For the randomly selected subjects in the control group Dynamic Coronary Roadmap will not be used in order to serve as the comparator to measure the effect of Dynamic Coronary Roadmap. Standard of care will be applied to all subjects.

There are no additional devices or medications required for the study. Physician investigators participating in this study are expected to follow their normal clinical practice in treating and following up patients with Coronary Artery Disease (CAD). Patients randomized to the DCR group will undergo a PCI procedure during which DCR is used while those randomized to the control group will undergo PCI without the use of DCR. The preparation of the PCI procedure, the procedure itself and follow up will be performed following standard of care.

4.4.2 Randomization

The randomization will be performed via the Electronic Data Capture (EDC) system hosting the electronic Case Report Form.

In order to ensure balance of the treatment groups across subgroups, we stratified the randomization by site and within site by type of PCI (ad hoc or elective) and the number of vessels to be treated via PCI, i.e., 1, 2, or 3 or more vessel PCI. Within the subgroups we will perform a permutated block design. We will use a block size of 4 patients per block. There will be an equal allocation to the PCI procedure with DCR and the PCI procedure without the use of DCR (1:1 randomization).

In case of elective PCI, randomization will be done before the procedure and in case of ad hoc PCI randomization will be done upon decision to go for PCI right after diagnostics, so when the patient on the table still.

In enrolled subjects the investigator pre procedurally deemed no usage of OCT and/or the rotational or orbital atherectomy is required. During the PCI procedure usage of OCT and/or rotational or orbital atherectomy is left to the investigator's discretion.

In the case OCT and/or rotational or orbital atherectomy is used in enrolled subjects, these subjects will be replaced. When the decision is made to replace a subject this subject will not count for the required total number of subjects total, but will still be part of the Safety population. A new subject will be randomized to either of the arms.

Thus, the following subjects will be replaced:

- Subjects undergoing PCI supported by OCT will be replaced.
- Subjects undergoing PCI supported by rotational or orbital atherectomy will be replaced.

4.5 Control to Minimize Bias

Ideally the study should be blinded, because there is potential intrinsic bias (sometimes referred to as the Hawthorne Effect) due to the fact the participants know that they are participating in a clinical study and know which arm they are participating in. However, as the Dynamic Coronary Roadmap is a visualization tool the study cannot be blinded.

Only standard guiding catheters will be used in the study and devices that could potentially confound contrast usage (e.g. rotational or orbital atherectomy device) will be excluded.

The methods to check whether the PCI was successful can include angiography, Stent Boost, and/or IntraVascular UltraSound (IVUS). Some of these procedures can include contrast agent volume, whereas others specifically do not (e.g., Stent Boost is a software feature). Therefore, the choice for checking the PCI result could introduce a bias based on individual users' preferences. Some PCI check methods are potential confounders for contrast usage and we will investigate to take measures to reduce the risk of bias based on site differences and user preferences. During site initiation it has been communicated that the PCI check procedure is to be standardized in both arms, which is standard of practice. This will be checked via remote monitoring of the eCRFs.

Analyses to determine whether there is an effect based on e.g. intervention difficulty (measured by the SYNTAX score), lesion characteristics, patient demographics, physician experience, center effect etc. will be performed. If an effect is found applying adjustment analysis, i.e. analysis of covariance adjusting for relevant confounders will be considered as a sensitivity analysis.

5 EFFICACY AND SAFETY VARIABLES

5.1 Efficacy and Safety Measurements

The following efficacy and safety measurements will be performed:

Efficacy measurements

Total undiluted iodinated contrast volume (in ml) used per PCI procedure (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) measured by an automatic contrast injector. Any contrast use prior to getting access (e.g. for balloon preparation or contrast injector flushing) should not be counted in the total contrast volume, i.e., the contrast injector should be zeroed just prior to getting access if not zero already. Furthermore, during the PCI procedure any contrast use not injected into the patient, e.g. used for device preparation, should not be counted in the total PCI contrast volume.

Total number of contrast enhanced cine angiographic X-ray runs (angiograms) determined via visual assessment (e.g., on the Philips X-ray system) per PCI procedure (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure).

Incidence of Acute Kidney Injury (AKI) at discharge following standard clinical care. AKI is defined as [Parsh 2016, Bellomo 2004]:

- an absolute Serum Creatinine (SCr) increase >0.3 mg/dl within 48 hours post PCI or a relative SCr increase >50% within 7 days post PCI
  OR
- eGFR decrease >25% within 48 hours post PCI

The total fluoroscopy and procedure time per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure), where the fluoroscopy time is measured by the Philips X-ray system.

The total X-ray dose (DAP, AK) related to PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure). The total DAP and AK per PCI is measured by the Philips X-ray system.

Procedural success, defined as an open target vessel with a maximum of 30% residual stenosis and TIMI flow grade 3 (complete perfusion) [TIMI 1985], e.g. determined via visual inspection of Coronary Angiography.

In-hospital Major Adverse Cardiovascular and Cerebral Events (MACCE) are collected in the eCRF. MACCE is defined as one or more of the following events: All cause death, Acute Myocardial Infarction (AMI), Coronary Artery Bypass Grafting (CABG), Repeat Coronary Revascularization of the target lesion, Acute Ischemic Stroke (AIS) during hospitalization for the PCI procedure.

Safety Measurements

Serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay.

5.2 Appropriateness of Measurements

The endpoints are appropriate for measuring the stated efficacy and safety.

However the following restrictions for Serum Creatinine/EGFR and Acute Kidney Injury should be taken into account.

SCr/eGFR

According to [Guideline NVvR 2017] the measurement of SCr/eGFR is valid for:

- Maximally 7 days when the patient has an acute disease or an acute deterioration of a chronic disease;
- Maximally 3 months when the patient has a known chronic disease with stable renal function;
- Approximately 12 months in all other patients.

Acute Kidney Injury

The majority of PCI patients are discharged within 24 hours after the PCI procedure and consequently the SCr measurement is performed within 24 hours post PCI while the SCr levels might still be rising and diagnosis of AKI may be missed as a result.

5.3 Efficacy Variables

5.3.1 Primary Efficacy Variables

The primary efficacy variable is the total undiluted iodinated contrast volume (in ml) used per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) measured by an automatic contrast injector.

5.3.2 Secondary Efficacy Variables

The secondary efficacy variable is the total number of contrast enhanced cine angiographic X-ray runs (angiograms) per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) determined via visual assessment (e.g., on the Philips X-ray system).

5.3.3 Exploratory Efficacy Variables

The exploratory efficacy variables are:

- The average undiluted iodinated contrast volume (in ml) used per vessel PCI measured by an automatic contrast injector. For multi vessel PCI the iodinated contrast volume used per vessel PCI will be determined based on the total PCI contrast volume divided by the number of vessels treated by PCI.
- Total iodinated contrast volume (in ml) stratified by 1 vessel PCI, 2 vessel PCI and 3 or more vessel PCI.
- Total iodinated contrast volume (in ml) stratified by simple, intermediate and complex PCI (according to the SYNTAX score for the vessel(s) treated with PCI).
- Incidence of Acute Kidney Injury (AKI) at discharge following standard clinical care. AKI is defined as an absolute Serum Creatinine (SCr) increase >0.3 mg/dl within 48 hours post PCI or a relative SCr increase >50% within 7 days post PCI, or eGFR decrease >25% within 48 hours post PCI.
- Variability of the total iodinated contrast volume (in ml) used per PCI measured by an automatic contrast.
- The total fluoroscopy and procedure time per PCI, where the fluoroscopy time is measured by the Philips X-ray system.
- The total X-ray dose (DAP, AK) related to PCI. The total DAP and AK per PCI is measured by the Philips X-ray system.

- Procedural success, defined as an open target vessel with a maximum of 30% residual stenosis and TIMI flow grade 3 (complete perfusion) [TIMI 1985], e.g. determined via visual inspection of Coronary Angiography.
- In-hospital Major Adverse Cardiovascular and Cerebral Events (MACCE). MACCE is defined as one or more of the following events: All cause death, Acute Myocardial Infarction (AMI), Coronary Artery Bypass Grafting (CABG), Repeat Coronary Revascularization of the target lesion, Acute Ischemic Stroke (AIS) during hospitalization for the PCI procedure.

All parameters assessed during PCI are measured from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure.

5.4 Safety Variables

Adverse events and device deficiencies are reported through the Philips Vigilance Reporting System. MACCE, duration until discharge (in days) and laboratory assessments will be assessed in the CRF.

6 DEFINITIONS

Baseline is defined as last value prior to randomisation. Baseline values may be recorded at Screening if there is no other result prior to randomisation.

Duration (days) will be calculated as follows:

- Duration = last observation date – first observation date +1

Duration of procedure (minutes) will be calculated as stop date/time of PCI procedure minus the start date/time of the PCI procedure from first positioning the interventional guiding catheter in stable coronary position.

Duration until discharge (days)

Duration until discharge= discharge date – PCI procedure date +1

Study Day is defined as follows:

- If study date < randomisation date then study day = study date – randomisation date
- If study date >= randomisation date then study day = study date – randomisation date + 1

Physician Experience is defined as the number of years of experience post-fellowship.

Body Mass Index (BMI)

$$\text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\text{Weight (kg)}}{\text{Height(m)}^2}$$

Incidence of Acute Kidney Injury (AKI) is defined as

- an absolute Serum Creatinine (SCr) increase >0.3 mg/dl within 48 hours post PCI or a relative SCr increase >50% within 7 days post PCI

OR

- or eGFR decrease >25% within 48 hours post PCI

Procedural success is defined as an open target vessel with a maximum of 30% residual stenosis and TIMI flow grade 3 (complete perfusion) [TIMI 1985], e.g. determined via visual inspection of Coronary Angiography.

Estimated Glomerular Filtration Rate

Using the SCr measurement often the estimated GFR (eGFR) is determined as a measure of kidney function, which can be calculated according to the Modification of Diet in Renal Disease (MDRD) equation or its successor the Chronic Kidney Disease epidemiology (CKD-EPI) equation [Levey 1999, Bellomo 2004, Levey 2006, Levey 2009, Van den Brand 2011, Nyman 2014]. The CKD-EPI equation to estimate the glomerular filtration rate reads [Levey 2009]:

The Chronic Kidney Disease epidemiology (CKD-EPI) equation to estimate the glomerular filtration rate reads [Levey 2009]:

$$eGFR = 141 * \min(SCr/K, 1)^{\alpha} * \max(SCr/K, 1)^{-1.209} * 0.993^{Age} * 1.018 \text{ [if female]} \times 1.159 \text{ [if black]},$$

with K=0.7 and α=-0.329 if female;

with K=0.9 and α=-0.411 if male.

In which SCr is Serum Creatinine. Here min indicates the minimum of SCr/K or 1, and max indicates the maximum of SCr/K or 1.

Based on the eGFR calculation Chronic Kidney Disease (CKD) can be classified in 5 stages [Tsai 2014a].

CKD classification	eGFR (ml/min/1.73m^2)
Stage I (normal renal function)	>=60
Stage II (mild – moderate reduction)	45 – < 60
Stage III (moderate – severe reduction)	30 – < 45
Stage IV (severe reduction)	15 - < 30
Stage V (renal failure)	<15

Table 1 CKD classification based on eGFR

Contrast volume (V) to creatinine clearance GFR ratio

The contrast volume (V)/eGFR ratio will be calculated by dividing the volume of contrast volume (in ml) received by the patients' eGFR (in ml/min/1.73m^2).

MACCE

In-hospital Major Adverse Cardiovascular and Cerebral Events (MACCE). MACCE is defined as one or more of the following events: All cause death, Acute Myocardial Infarction (AMI), Coronary Artery Bypass Grafting (CABG), Repeat Coronary Revascularization of the target lesion, Acute Ischemic Stroke (AIS) during hospitalization for the PCI procedure.

The **SYNTAX score** [Sianos 2005, Neumann 2018] will be determined for each vessel treated with PCI as an index for anatomical complexity of the PCI, see Figure below and Appendix 1.

The vessel SYNTAX score calculates a point value for each vessel treated with PCI. The patients' overall SYNTAX score will be derived as the maximum value across all treated vessels.

The patients' overall SYNTAX score will be divided into tertiles as an index for complexity of the PCI procedure. We will label these groups as Complexity 1st Tertile, Complexity 2nd Tertile and Complexity 3rd Tertile.

Step 1 Dominance: determine right or left coronary artery dominance
Step 2 Coronary segment: each diseased coronary segment is assigned a weight depending on its location

Segment No		Right dominance	Left dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	n.a.
16	Posterolateral branch from RCA	0.5	n.a.
16a	Posterolateral branch from RCA	0.5	n.a.
16b	Posterolateral branch from RCA	0.5	n.a.
16c	Posterolateral branch from RCA	0.5	n.a.
5	Left Main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9a	First diagonal[a]	1	1
10	Second diagonal	0.5	0.5
10a	Second diagonal[a]	0.5	0.5
11	Proximal circumflex artery	1.5	2.5
12	Intermediate/ anterolateral artery	1	1
12a	Obtuse marginal[a]	1	1
12b	Obtuse marginal[b]	1	1
13	Distal circumflex artery	0.5	1.5
14	Left posterolateral	0.5	1
14a	Left posterolateral[a]	0.5	1
14b	Left posterolateral[b]	0.5	1
15	Posterior descending	n.a.	1

Step 3	Diameter stenosis	The score of each diseased coronary segment is multiplied by two in case of a stenosis 50-99% and by five in case of total occlusion. In case of total occlusion, additional points will be added as follows: – Age >3 months or unknown +1 – Blunt stump +1 – Bridging +1 – First segment visible distally +1 per non-visible segment – Side branch at the occlusion +1 if <1.5 mm diameter +1 if both <1.5 mm and >1.5 mm diameter +0 if ≥1.5 mm diameter (i.e. bifurcation lesion)
Step 4	Trifurcation lesion	The presence of a trifurcation lesion adds additional points based on the number of diseased segments: – 1 segment +3 – 2 segments +4 – 3 segments +5 – 4 segments +6
Step 5	Bifurcation lesion	The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification:126 – Medina 1,0,0-0,1,0-1,1,0 +1 – Medina 1,1,1-0,0,1-1,0,1-0,1,1 +2 Moreover, the presence of a bifurcation angle <70° adds one additional point
Step 6	Aorto-ostial lesion	The presence of aorto-ostial lesion segments adds one additional point
Step 7	Severe tortuosity	The presence of severe tortuosity proximal of the diseased segment adds two additional points
Step 8	Lesion length	Lesion length >20 mm adds one additional point
Step 9	Calcification	The presence of heavy calcification adds two additional points
Step 10	Thrombus	The presence of thrombus adds one additional point
Step 11	Diffuse disease/ small vessels	The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter <2 mm) adds one point per segment number
SYNTAX: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery		

Figure 1 Steps to determine SYNTAX score as an index for anatomical complexity of the PCI [from Neumann 2018]

7 DATA QUALITY ASSURANCE

An independent angiographic committee of experts may be consulted to blindly analyze cases to check for validity of exclusion and inclusion criteria and other relevant aspects of the study.

8 STATISTICAL METHODS

8.1 Sample Size

We plan to include 394 subjects in the study, the maximum number of subjects needed for the analysis of the primary and secondary endpoint. We target to limit the enrollment duration of the 394 subjects to a 9 months maximum, which translates to minimally 10 subject inclusions per week overall. Based on a typical PCI procedure volume and the inclusion and exclusion criteria it is feasible to enroll at least 2 subjects per week per center, i.e., at least 5 centers are required.

8.1.1 Sample Size Justification Primary Endpoint

A recent single center, non-randomized, retrospective study [Yabe 2018] has shown to achieve 21.9% contrast reduction when using Dynamic Coronary Roadmap compared to the control group without using Dynamic Coronary Roadmap, see Table 2.

	Control group	**DCR group**
Number of patients	103	43
Iodinated contrast volume (ml) average ± standard deviation	152.1 ± 73.0	118.8 ± 49.7

Table 2 Results of a recent pilot study [Yabe 2018]

To determine the sample size for the primary endpoint of this study we used the Yabe study outcomes as input with a margin of 7% for the contrast reduction, i.e., the sample size calculation is performed to reliably show a 15% contrast reduction in the DCR group compared to the control group not using Dynamic Coronary Roadmap.

For the sample size and power calculations we have set:

- Estimated mean for the Control group = 152.1 (based on [Yabe 2018])
- Estimated mean for the DCR group = 129.3 (15% reduction)
- Estimated standard deviation = 73.0 (based on [Yabe 2018])
- Effect size (standardized difference): (152.1 – 129.3)/73.0 = 0.3123
- Significance: one-sided $\alpha = 0.025$ (the type I error, i.e., probability of rejecting a true null hypothesis)

- Power (1-β) = 80%

Sample sizes of 162 for each group achieves 80% power to reject the null hypothesis of equal means when the population mean difference is 15% with a standard deviation of 73.0 for both groups and with a significance level (alpha) of 0.025 using a one-sided two-sample equal-variance t-test (calculated by PASS 16.0.3 software).

Finally the percentage of subjects that are expected to be lost at random during the course of the study (drop-out rate) and for whom no response data will be collected (i.e., will be treated as "missing") needs to be taken into account. A drop-out rate of 10% (DR=0.1) is assumed, meaning that 162/(1-DR)=180 patients are needed in each group totaling 360 patients for the primary endpoint.

The study will be a multi-center trial in which per center a maximum of three investigators will be participating and each investigator is required to include at least 20 patients in the study, which indirectly sets the minimum number of subjects to be included per center.

8.1.2 Sample Size Justification Secondary Endpoint

A recent single center, non-randomized, prospective study [Rajappan 2017] showed a 25.6% reduction in the median number of cine X-ray runs after introduction of Dynamic Coronary Roadmap, see Table 3.

	Enrollment group 1	**Enrollment group 4**
Number of patients	21	21
Number of cine X-ray runs	Average: 46.2 SD: 22.4 Median: 43.0 IQR: 31-54	Average: 34.6 SD: 21.2 Median: 32.0 IQR: 20-43
Number of stents	Average: 1.76 SD: 0.89	Average: 1.67 SD: 0.86

Table 3 Results of a recent pilot study [Rajappan 2017]

For the sample size and power calculations we have set based on [Rajappan 2017]:

- Estimated mean for the Control group = 46.2
- Estimated mean for the DCR group = 34.6

- Estimated median for the Control group = 43.0
- Estimated median for the DCR group = 32.0
- Significance: one-sided $\alpha = 0.025$ (the type I error, i.e., probability of rejecting a true null hypothesis)
- Power $(1-\beta) = 80\%$

Sample sizes of 177 for each group achieves 80% power to reject the null hypothesis of equal population distributions with a significance level (alpha) of 0.025 using a one-sided Wilcoxon-Mann-Whitney test, since the number of angiographic X-ray runs is discrete and is likely to be not normally distributed (calculated by SAS software).

This means for the secondary endpoint on Number of Angiograms that 177/(1-DR)=197 patients are needed in each group, so 394 in total which is higher than the total number of patients (360) required for the primary endpoint, so **a total of 394 subjects are required for this study.**

8.2 General Considerations

All results will be summarized by treatment group using the following descriptive statistics: n, mean with 95% confidence intervals, standard deviation (SD), median, interquartile range (IQR), minimum and maximum. Categorical data will be summarised for each treatment group as the number and percentage of subjects in each category (including the category 'missing' if applicable). Generally, percentages will be calculated for missing categories and all percentages will be based on total number of subjects in the population (denoted by N on the summary tables and figures) Statistical analysis will be performed using SAS (SAS® Life Science Analytics Framework 5.1.2) and/or R statistical software (https://www.r-project.org/).

All data will be listed for the enrolled population. The data will be sorted by treatment group, subject number and date of assessment (if applicable).

All hypotheses will be tested at a 2.5% level of significance using a one-sided test unless otherwise specified.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., SD) will be displayed to two decimal places greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Percentages will be displayed to 1 decimal place. P-values will be reported to three decimal places; p-values less than 0.001 will be reported as $p<0.001$.

Summary tables will have treatment columns labelled as 'Dynamic Coronary Roadmap' or 'Control'. The main data will also be presented per clinical site.

8.2.1 Analysis Population

The following analysis populations will be defined in this study.

Enrolled Population
The enrolled population is defined as all subjects who signed informed consent.

Randomized population
The randomised population is defined as all randomised subjects, defined as any subject with a randomisation result as recorded in the eCRF.
Analysis of data using the randomised population will consider allocation of subjects to treatment groups as randomised.

Full Analysis Population
The full analysis population (FAP) is defined as all randomised subjects who underwent a PCI in at least one vessel without the use of OCT and/or rotational or orbital atherectomy of which the primary endpoint and/or the secondary endpoint is available.
Analysis of data using the Full analysis population will consider allocation of subjects to treatment groups as randomised.

Safety population
The safety analysis population (SAF) is defined as all randomised subjects who underwent a(n) attempt to PCI or another procedure (for example CABG).
Analysis of data using the Safety population will consider allocation of subjects to treatment groups as treated (i.e. will be based on the actual treatment a subject has received regardless of which treatment they were randomised to receive).
In case the safety population is equal to the full analysis population, only the results of the full analysis population will be presented.

Per Protocol population
The Per Protocol population is defined as all FAP subjects without major protocol violations. Protocol violations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be divided into major protocol violations and minor protocol violations. Major protocol violations are those that are considered to have a significant effect on the treatment efficacy and hence would exclude the subject from the PP population. Minor protocol violations are those that are not considered to significantly affect the efficacy evaluation and

hence do not warrant subjects' exclusion from the PP population. Major protocol violations will be identified by a Data Review Meeting prior to database lock.
The following criteria might be considered as major protocol violations:

(1) Violation of any inclusion or exclusion criteria
(2) Errors in treatment assignment (i.e. actual treatment differs from the randomised treatment)

Analysis of data using the Per Protocol population will consider allocation of subjects to treatment groups as randomised.

8.2.2 Handling of Dropouts or Missing Data

We will perform a missing value analysis to check the volume of missing data and whether the missing data shown patterns across subgroups. In case the missing values are non-ignorable, methods to correct for missing data will be used like, e.g., worst case scenario analysis, multiple imputation methods [Rubin 2004].

For the primary endpoint a worst-case analysis will be considered as a sensitivity analysis. For missing outcomes for the control group, the lower bound of the 95% confidence interval around the control mean will be imputed. For missing outcomes for the DCR group, the upper bound of the 95% confidence interval around the DCR mean will be imputed. The primary analysis will be repeated using the imputed values.

8.2.3 Efficacy Subset

As exploratory efficacy analyses subgroup analyses we will analyze the primary endpoint by 1, 2, 3 or more vessel PCI and by tertiles of the patients' SYNTAX score as approximation of the complexity of the PCI procedure.

8.3 Patient Disposition

Subject disposition, including the total number of subjects evaluated will be presented for the enrolled population. In addition, a listing will be provided with the reasons for why the subject was not evaluated.

For the randomized population the number and percentage of randomized subjects will be presented by site.

A listing will present the randomized treatment for the randomized population.

A listing will present study population flags, study completion data, including the primary reason for study discontinuation for the enrolled population.

8.4 Demographics and Baseline Characteristics

Demographic and baseline variables will be summarized by treatment group for subjects in the Full Analysis Population (FAP). Age (years), height (cm), weight (kg) and body mass index (BMI) (kg/m^2) will be summarized as continuous data. Gender (Male/Female) and race (African American (Black), Non-African American, Unknown) will be summarized as categorical data.

We will perform statistical tests to compare the baseline characteristics of the two groups to check that the control and Dynamic Coronary Roadmap groups are similar at the start of the study. For categorical variables, we will perform a Chi-2 or Fisher Exact test, and for continuous variables a t-test or Wilcoxon-Mann-Whitney test as appropriate. When the groups are not comparable regarding baseline characteristics, adjustment for covariates will be applied as a sensitivity analysis (see section 8.14).

8.5 Medical History

Medical history will be summarized in categories by treatment group for subjects in the FAP and the SAF. A subject can have a medical condition in more than one category.

8.6 Medication use

Medication use will be summarized in categories by treatment group for subjects in the FAP and the SAF. A subject can have a medication use in more than one category. Also iodine contrast administration less than 1 week before the current PCI procedure will be summarized in this table.

8.7 Screening information

Left ventricular ejection fraction (LVEF) (%), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) at screening will be summarized for subjects in the FAP and the SAF.

8.8 Compliance

NA

8.9 Concomitant Therapy

NA

8.10 Procedure characteristics

Type of PCI (ad hoc PCI or elective (scheduled) PCI) and number of vessels treated by PCI (1 vessel PCI, 2 vessel PCI, 3 or more vessel PCI) will be summarized by treatment group for the FAP and the SAF. In addition, the SYNTAX score will be presented for the vessel(s) treated with PCI as an index for anatomical complexity. The SYNTAX score will be summarized in categories and as a continuous variable.

Also pre-procedural hydration (Y/N) and discontinuation of any renal drugs (e.g. ACE inhibitors) (Y/N) will be summarized in this table.

The access method (Transfemoral, Transradial, Other) and whether Femoral angiography was performed (if Transfemoral=Yes) and the timing of the Femoral angiography will be presented as categorical variables. Contrast usage details such as contrast injector (ml) at skin incision, generic name of iodine contrast used and contrast injector speed (ml/s) will be summarized.

The following information measured at the end of the PCI procedure will be summarized by treatment group for the FAP and the SAF:

- Procedure time (min)
- Total procedural contrast volume read-out of contrast injector (ml)
- Total number of stent(s) placed
- Total size of stent(s) placed (mm)
- Total number of balloon inflations
- Physiology assessment (instantaneous wave-Free Ratio (iFR) or Fractional Flow Reserve (FFR)) (Y/N)
- IVUS (Y/N)
- Any complication(s) during procedure (Y/N)
- Procedural success (Y/N)
- Total fluoroscopy time (mm)
- Total Air Kerma (mGy)

- Total Dose Area Product (DAP; Gy*cm^2)
- Total Exposure DAP (Gy*cm^2)
- Total Fluoroscopy DAP (Gy*cm^2)
- Total number of exposure series (runs)
- Total number of exposure images
- Total number of contrast enhanced angiograms
- Total number of Stent Boost (runs)
- Post-procedural hydration (Y/N)
- Dynamic Coronary Roadmap used (Y/N)
- Overall quality and accuracy of roadmap (very good/ good/ fair/ poor/ very poor)

8.11 Efficacy Analysis

All efficacy outcomes will be presented for the Full Analysis Population and the Per Protocol Population.

8.11.1 Primary Efficacy Analysis

The primary endpoint of the study is the average total undiluted iodinated contrast volume (in ml) used per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) measured by an automatic contrast injector.

Hypothesis

Dynamic Coronary Roadmap reduces the total iodinated contrast volume used on average per PCI. The null and alternative hypotheses are as follows:

H_0: $\mu_{Control} - \mu_{DCR} \leq 0$

H_a: $\mu_{Control} - \mu_{DCR} > 0$

Where $\mu_{Control}$ is the average total iodinated contrast volume usage per PCI for the Control group, and μ_{DCR} is the average total iodinated contrast volume usage per PCI for the DCR group.

Analysis

Descriptive summaries of the total undiluted iodinated contrast volume will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), mean with 95% confidence interval, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values.

The primary endpoint will be evaluated using a one-sided two-sample t-test. We will test for assumptions, e.g. normality and equal variances. Normality will be checked using histograms and Q-Q plots. If there are strong indications of non-normality, the data will be (log)transformed, and the back transformed results will be presented. Levene's test for equality of variances will be applied. When the p-value of this test is greater than 0.05, then we assume the variances are equal and we will used the arithmetic mean of the variances in calculating the standard error. When the p-value is less than or equal to 0.05, then we assume the variances are unequal and then we will calculate the standard error from the weighted average of the two variances.

All subjects in the full analysis population will be included in this analysis.

The results of the t-test will be displayed as estimates of the between treatment group difference (with 95% confidence intervals) and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

The primary analysis will be repeated for the PP population.

In addition and for sensitivity purposes a worst-case analysis will be considered for the primary endpoint. For missing outcomes for the control group, the lower bound of the 95% confidence interval around the control mean will be imputed. For missing outcomes for the DCR group, the upper bound of the 95% confidence interval around the DCR mean will be imputed. The primary endpoint will be re-assessed with a complete dataset for the FAP population.

As a descriptive analysis, the (V) to creatinine clearance GFR ratio will be calculated. Assuming a contrast volume reduction by DCR, the contrast volume/GFR ratio will give information on how clinically meaningful this contrast reduction is. The ratio will be calculated by dividing the volume of contrast volume (in ml) received by the patients' GFR (in ml/min/1.73m2).

The CKD-EPI equation to estimate the glomerular filtration rate reads [Levey 2009]:

$eGFR = 141 * \min(SCr/K, 1)^{\alpha} * \max(SCr/K, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]

with K=0.7 and α=-0.329 if female

with K=0.9 and α=-0.411 if male

Here min indicates the minimum of SCr/K or 1, and max indicates the maximum of SCr/K or 1. In case the race is unknown we will use 1 as multiplication factor.

As recommended by the ESC/EACTS Guidelines, the total contrast volume/GFR ratio should not exceed 3.7, because when the ratio is larger than 3.7 the risk for severe CKD (eGFR<30) increases significantly [Laskey 2007, Neumann 2018].

The average V/GFR ratio (with 95% CI) and the proportion of patients with a V/GFR ratio > 3.7 (with 95% exact CI) will be presented by treatment group for the FAP.

8.11.2 Secondary Efficacy Analysis

The secondary endpoint is the average total number of contrast enhanced cine angiographic X-ray runs (angiograms) per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) determined via visual assessment (e.g., on the Philips X-ray system To assess the total number of contrast enhanced cine angiographic X-ray runs (angiograms) related to PCI in the Dynamic Coronary Roadmap and control group

Hypothesis

Dynamic Coronary Roadmap reduces the total number of contrast enhanced cine angiographic X-ray runs (angiograms) acquired on average per PCI. The null and alternative hypotheses are as follows:

H_0: $Pop_{Control2} \leq Pop_{DCR2}$

H_a: $Pop_{Control2} > Pop_{DCR2}$ (Distribution of Control is shifted to the right of DCR)

Where $Pop_{Control2}$ is the population distribution for the number of contrast enhanced cine angiographic X-ray runs (angiograms) acquired per PCI for the Control group, and Pop_{DCR2} is the population distribution for the number of contrast enhanced cine angiographic X-ray runs (angiograms) acquired per PCI for the DCR group.

Analysis

Descriptive summaries of the total number of contrast enhanced cine angiographic X-ray runs (angiograms) will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), frequency distributions, median, interquartile range (IQR) and minimum and maximum values.

The number of angiographic X-ray runs is discrete and is likely to be not normally distributed, so the endpoint will be evaluated using a one-sided Wilcoxon-Mann-Whitney test. The results of the Wilcoxon-Mann-Whitney will be displayed as the rank sum and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

All subjects in the full analysis population will be included in this analysis. The secondary analysis will be repeated for the PP population.

8.11.3 Exploratory Efficacy Analysis

8.11.3.1 Contrast Volume per Vessel PCI

The average undiluted iodinated contrast volume (in ml) used per vessel PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) by treatment group. For multi vessel PCI the iodinated contrast volume used per vessel PCI will be determined based on the total PCI contrast volume (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) divided by the number of vessels actually treated by PCI.

Descriptive summaries of the total undiluted iodinated contrast volume divided by the actual number of vessels treated by PCI will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), mean with 95% confidence interval, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values.

The endpoint will be evaluated using a one-sided two-sample t-test. We will test for assumptions, e.g. normality and equal variances. Normality will be checked using histograms and Q-Q plots. If there are strong indications of non-normality, the data will be (log)transformed, and the back transformed results will be presented. Levene's test for equality of variances will be applied. When the p-value of this test is greater than 0.05, then we assume the variances are equal and we will used the arithmetic mean of the variances in calculating the standard error. When the p-value is less than or equal to 0.05, then we assume

the variances are unequal and then we will calculate the standard error from the weighted average of the two variances.

The results of the t-test will be displayed as estimates of the between treatment group difference (with 95% confidence intervals) and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.2 Contrast Volume per Stratification Group (1, 2, 3 or more vessel PCI)

The total undiluted iodinated contrast volume (in ml) used per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) in each stratification group, i.e., 1 vessel PCI, 2 vessel PCI and 3 or more vessel PCI.

Descriptive summaries of the total undiluted iodinated contrast volume will be presented by treatment group and by stratification group (1 vessel PCI, 2 vessel PCI and 3 or more vessel PCI)

for the FAP and the PP population and will include the number of subjects with non-missing data (n), mean with 95% confidence interval, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values.

The endpoint will be evaluated per subgroup (1 vessel PCI, 2 vessel PCI and 3 or more vessel PCI) using a one-sided two-sample t-test. We will test for assumptions, e.g. normality and equal variances. Normality will be checked using histograms and Q-Q plots. If there are strong indications of non-normality, the data will be (log)transformed, and the back transformed results will be presented. Levene's test for equality of variances will be applied. When the p-value of this test is greater than 0.05, then we assume the variances are equal and we will used the arithmetic mean of the variances in calculating the standard error. When the p-value is less than or equal to 0.05, then we assume the variances are unequal and then we will calculate the standard error from the weighted average of the two variances.

The results of the t-test will be displayed as estimates of the between treatment group difference (with 95% confidence intervals) and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.3 Contrast Volume per Simple, Intermediate, Complex PCI subgroup

The total undiluted iodinated contrast volume (in ml) used per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) in subgroups of simple, intermediate and complex PCI.

Descriptive summaries of the total undiluted iodinated contrast volume will be presented by treatment group and by complexity in tertiles for the FAP and the PP population and will include the number of subjects with non-missing data (n), mean with 95% confidence interval, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values.

The endpoint will be evaluated per subgroup using a one-sided two-sample t-test. We will test for assumptions, e.g. normality and equal variances. Normality will be checked using histograms and Q-Q plots. If there are strong indications of non-normality, the data will be (log)transformed, and the back transformed results will be presented. Levene's test for equality of variances will be applied. When the p-value of this test is greater than 0.05, then we assume the variances are equal and we will used the arithmetic mean of the variances in calculating the standard error. When the p-value is less than or equal to 0.05, then we assume the variances are unequal and then we will calculate the standard error from the weighted average of the two variances.

The results of the t-test will be displayed as estimates of the between treatment group difference (with 95% confidence intervals) and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.4 Acute Kidney Injury (AKI) Incidence

The total number and percentage of subjects in which Acute Kidney Injury (AKI) diagnosed after PCI. AKI is defined as an absolute SCr increase >0.3 mg/dl within 48 hours post PCI or a relative SCr increase >50% within 7 days post PCI, or eGFR decrease >25% within 48 hours post PCI.

Descriptive summaries of AKI incidence will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), percentages and 95% exact confidence intervals.

The between treatment group difference in AKI incidence will be tested using a Chi-square test. If a Chi square analysis is not possible (i.e. >20% of the expected cell frequencies less than 5), then a Fisher's exact test will be performed instead. The two-sided p-value of this test will be presented. When the p-value is lower than the significance level of 5% (alpha) we will reject the null hypothesis of equal procedural success in both treatment groups.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

When considering the incidence of AKI in the patient population of this trial (7.1% incidence, but reported from 3% to 19% [Tsai 2014a]) and taking into account the sample size of 394 patients it is not likely this trial will find a significant difference in AKI incidence in the DCR group compared to the control group.

8.11.3.5 Contrast Usage Variability

The following variability parameters of the total undiluted iodinated contrast volume (in ml) used per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) will be presented by treatment group for the FAP and the PP population:

- standard deviation
- interquartile Range (IQR)
- quartile coefficient of dispersion ((Q3-Q1)/(Q3+Q1), where Q1 and Q3 are the first and third quartiles)
- relative standard deviation (SD divided by the average, also known as coefficient of variation).

We will test for a difference between variances in both groups using the Brown-Forsythe test. The p-value of the test will be presented. When the p-value is lower than the significance level of 5% (alpha) we will reject the null hypothesis of equal variances between groups.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.6 Fluoroscopy and Procedure Time

The fluoroscopy and procedure time per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) by treatment group.

Descriptive summaries of the fluoroscopy and procedure time in minutes will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), mean with 95% confidence interval, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values. The analysis will be repeated for the PP population.

The endpoints will be evaluated separately using one-sided two-sample t-tests. We will test for assumptions, e.g. normality and equal variances. Normality will be checked using histograms and Q-Q plots. If there are strong indications of non-normality, the data will be (log)transformed, and the back transformed results will be presented. Levene's test for equality of variances will be applied. When the p-value of this test is greater than 0.05, then we assume the variances are equal and we will used the arithmetic mean of the variances in calculating the standard error. When the p-value is less than or equal to 0.05, then we assume the variances are unequal and then we will calculate the standard error from the weighted average of the two variances.

The results of the t-test will be displayed as estimates of the between treatment group difference (with 95% confidence intervals) and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.7 X-ray Dose

The total DAP and AK per PCI (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) by treatment group.

Descriptive summaries of the total DAP (Gy*cm^2) and AK (mGy) per PCI will be presented by treatment group for the FAP and will include the number of subjects with non-missing data (n), mean with 95% confidence interval, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values.

The total DAP and AK will be evaluated separately using one-sided two-sample t-tests. We will test for assumptions, e.g. normality and equal variances. Normality will be checked using histograms and Q-Q plots. If there are strong indications of non-normality, the data will be (log)transformed, and the back transformed results will be presented. Levene's test for equality of variances will be applied. When the p-value of this test is greater than 0.05, then we assume the variances are equal and we will used the arithmetic mean of the variances in

calculating the standard error. When the p-value is less than or equal to 0.05, then we assume the variances are unequal and then we will calculate the standard error from the weighted average of the two variances.

The results of the t-test will be displayed as estimates of the between treatment group difference (with 95% confidence intervals) and the (one-sided) p-value for the between treatment group difference. When the p-value is lower than the significance level of 2.5% (alpha) we will reject the null hypothesis.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.8 Procedural Success

The total number and percentage of subjects treated with procedural success by treatment group. Procedural success is defined as an open target vessel with a maximum of 30% residual stenosis and TIMI flow grade 3 (complete perfusion) [TIMI 1985], e.g. determined via visual inspection of Coronary Angiography.

Descriptive summaries of procedural success will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), percentages and 95% exact confidence intervals.

The between treatment group difference in procedural success will be tested using a Chi-square test. If a Chi square analysis is not possible (i.e. >20% of the expected cell frequencies less than 5), then a Fisher's exact test will be performed instead. The two-sided p-value of this test will be presented. When the p-value is lower than the significance level of 5% (alpha) we will reject the null hypothesis of equal procedural success in both treatment groups.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.11.3.9 In-hospital MACCE

The total number and percentage of in-hospital MACCE. MACCE is defined as one or more of the following events: All cause death, Acute Myocardial Infarction (AMI), Coronary Artery Bypass Grafting (CABG), Repeat Coronary Revascularization of the target lesion, Acute Ischemic Stroke (AIS) during hospitalization for the PCI procedure.

Descriptive summaries of MACCE will be presented by treatment group for the FAP and the PP population and will include the number of subjects with non-missing data (n), percentages and 95% exact confidence intervals.

The between treatment group difference in MACCE will be tested using a Chi-square test. If a Chi square analysis is not possible (i.e. >20% of the expected cell frequencies less than 5), then a Fisher's exact test will be performed instead. The two-sided p-value of this test will be presented. When the p-value is lower than the significance level of 5% (alpha) we will reject the null hypothesis of equal in-hospital MACCE in both treatment groups.

All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.

8.12 Safety Analysis

All safety analysis will be performed on the Safety Population. The percentages will be calculated using the number of subjects in the Safety Population as the denominator.

8.12.1 In-hospital MACCE

The number and percentage of subjects with MACCE will be summarized for the Safety population. Also number and percentage of subjects in each of the subcategories of MACCE will be presented, i.e. All cause death, Acute Myocardial Infarction (AMI), Coronary Artery Bypass Grafting (CABG), Repeat Coronary Revascularization of the target lesion, Acute Ischemic Stroke (AIS) during hospitalization for the PCI procedure. In addition, the number of reported cases of MACCE will be summarised.

All deaths and in-hospital MACCE will be listed.

8.12.2 Duration until discharge

Duration until discharge will be calculated and summarized by actual treatment group for the Safety population.

8.12.3 Device deficiencies

Device deficiencies will be listed and summarized for the DCR group for the Safety population.

8.12.4 Laboratory measurements

Hemoglobin value (g/dl), serum creatinine (SCr) baseline measurements (mg/dl) and highest post-PCI serum creatinine (SCr) measurement (mg/dl) will be summarized by treatment group for the Safety Population. Estimated eGFR (ml/min/1.73m2) at baseline and post PCI will be summarized as continuous variables and in categories (Stage I normal renal function/Stage II mild – moderate reduction/ Stage III moderate – severe reduction/ Stage IV severe reduction/ Stage V renal failure).

8.13 Subgroup Analysis

As exploratory analyses the primary endpoint will be analyzed by 1, 2, 3 or more vessel PCI and by anatomical complexity as derived from SYNTAX score in tertiles (see Section 6).

We will also analyze the primary and secondary endpoint in the DCR arm of the PP population by overall quality and accuracy of the roadmap divided into 3 groups: very good or good, fair and poor or very poor, also comparing 1 vessel PCI vs. multi vessel (2 or more vessel) PCI. We will also assess the overall quality and accuracy of the roadmap for 1 vessel PCI vs multi vessel (2 or more vessel) PCI. Here "very good" or "good" is indicated when the roadmap shows the coronary artery tree correctly (no missing relevant arteries and no significant artefacts in the roadmap) and the roadmap overlay location is in the correct location during vast majority of the PCI (comparing roadmap location with e.g. interventional guiding catheter, guidewire and device location). The score "fair" is indicated when the roadmap misses some arteries but is still useful (showing the overall artery tree correctly) and/or the roadmap overlay location is not always correct but is correct sufficiently to provide navigation guidance during the PCI. The roadmap is scored "poor" or "very poor" when the roadmap misses relevant arteries and not providing a correct overall artery tree overview and/or the roadmap overlay location is not correct majority of the PCI and not usable for PCI navigation guidance. Scoring the overall quality and accuracy of the roadmap during PCI is left to investigator discretion.

8.14 Adjustment for Covariates

Analyses to determine whether there is an effect based on e.g. intervention difficulty (as measured by the SYNTAX score), lesion characteristics, patient demographics, physician experience, center etc. will be performed. If an effect on the primary of secondary endpoint is found, applying adjustment analysis will be considered. As a sensitivity analysis, we will then perform an analysis

of covariance (ANCOVA) for the primary and/or the secondary endpoint adjusting for covariates which are deemed important. The results of the ANCOVA will be displayed through Least-Squares Means (LSMEANS) estimates of the between treatment group difference (with 95% confidence intervals) and the p-value for the between treatment group difference adjusted for covariates.

To investigate whether there is a center effect on the primary outcome, we will calculate the Intra Class Correlation coefficient (ICC) of the total iodinated contrast volume between centers. The ICC is the ratio of the variability between centers to the total variance. The ICC measures to what extent the proportion of the total variability of the primary outcome is accounted for by the clustering of patients within centers. If the ICC is higher than 0.10 we will perform a random effects model on the primary outcome with center as a random effect and treatment as a fixed effect. We will also check the distribution of baseline characteristics between centers. If the centers differ in characteristics, which may influence the primary outcome, such as intervention difficulty, lesion characteristics, patient demographics, physician experience etc, we will perform a random effects model on the primary outcome with center as a random effect and treatment and other covariates as fixed effects (ANCOVA) as a sensitivity analysis. The results of the ANCOVA will be displayed through Least-Squares Means (LSMEANS) estimates of the between treatment group difference (with 95% confidence intervals) and the p-value for the between treatment group difference adjusted for covariates.

8.15 Multiple Comparison and Multiplicity

No adjustments for multiplicity will be made. The primary and secondary endpoint will be tested with a one-sided alpha of 2.5%.

9 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

9.1 Changes in the Conduct of the Study

No changes in the conduct of the study are foreseen.

9.2 Changes in the Planned Analysis

We will check for violation of assumptions of the two-sample t-test instead of using a two-sample equal-variance t-test routinely. As appropriate, we will (log)transform the scores in case of non-normality or perform a test for unequal variances in case of unequal variances between

groups. For AKI and Procedural success, we will perform a Chi-square test or Fisher exact test as appropriate. We removed the cluster analysis from the study.

The protocol states that we will define subgroups of simple, intermediate and complex PCI, in which the patients' SYNTAX score for the vessel(s) treated with PCI will be used as an index for complexity. We will define 3 subgroups based in the patients' SYNTAX score divided into tertiles and label them as Complexity 1st Tertile, Complexity 2nd Tertile and Complexity 3rd Tertile instead of using the labels Simple, Intermediate and Complex PCI.

In the protocol is stated for that for the primary, secondary and exploratory endpoints all subjects will be included in the analysis. In the SAP this is specified as 'All subjects in the FAP population will be included in this analysis. The analysis will be repeated for the PP population.'

10 REFERENCES

[Abubakar 2013]	Abubakar, I. I., T. Tillmann, and A. Banerjee. "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." Lancet 385.9963 (2015): 117-171.
[Bellomo 2004]	Bellomo, Rinaldo, et al. "Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group." Critical care 8.4 (2004): R204.
[Guideline NVvR 2017]	Safe Use of Contrast Media - Part 1 (September 2017), Nederlandse Vereniging voor Radiologie (Radiological Society of the Netherlands)
[Koulouridis 2015]	Koulouridis, Ioannis, et al. "Hospital-acquired acute kidney injury and hospital readmission: a cohort study." American Journal of Kidney Diseases 65.2 (2015): 275-282.
[Laskey 2007]	Laskey, Warren K., et al. "Volume-to-creatinine clearance ratio: a pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention." Journal of the American College of Cardiology 50.7 (2007): 584-590.

[Levey 1999]	Levey, Andrew S., et al. "A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation." Annals of internal medicine 130.6 (1999): 461-470.
[Levey 2006]	Levey, Andrew S., et al. "Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate." Annals of internal medicine 145.4 (2006): 247-254.
[Levey 2009]	Levey, Andrew S., et al. "A new equation to estimate glomerular filtration rate." Annals of internal medicine 150.9 (2009): 604-612.
[MDR]	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.
[Neumann 2018]	Neumann, Franz-Josef, et al. "2018 ESC/EACTS guidelines on myocardial revascularization." European heart journal 40.2 (2018): 87-165.
[Nyman 2014]	Nyman, Ulf, et al. "The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in
[Rajappan 2017]	Rajappan, Anil Kumar. "PILOT STUDY OF DYNAMIC CORONARY ROADMAP DURING CORONARY ANGIOPLASTY." Journal of the American College of Cardiology 69.11 Supplement (2017): 1079.
[Rubin 2004]	Rubin, Donald B. Multiple imputation for nonresponse in surveys. Vol. 81. John Wiley & Sons, 2004.
[Sianos 2005]	Sianos, Georgios, et al. "The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease." EuroIntervention 1.2 (2005): 219-227.
[Subramanian 2007]	Subramanian, Sujha, et al. "Economic burden of contrast-induced nephropathy: implications for prevention strategies." Journal of medical economics 10.2 (2007): 119-134.

[Tehrani 2013]	Tehrani, Shana, et al. "Contrast-induced acute kidney injury following PCI." European journal of clinical investigation 43.5 (2013): 483-490.
[TIMI 1985]	TIMI Study Group*. "The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings." New England Journal of Medicine 312.14 (1985): 932-936.
[Tsai 2014a]	Tsai, Thomas T., et al. "Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry." JACC: Cardiovascular Interventions 7.1 (2014): 1-9.
[Tsai 2014b]	Tsai, Thomas T., et al. "Validated contemporary risk model of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the National Cardiovascular Data Registry Cath-PCI Registry." Journal of the American Heart Association 3.6 (2014): e001380.
[Van den Brand 2011]	van den Brand, Jan AJG, et al. "Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population." Nephrology Dialysis Transplantation 26.10 (2011): 3176-3181.
[Waldo 2018]	Waldo, Stephen W., et al. "Temporal Trends in Coronary Angiography and Percutaneous Coronary Intervention: Insights From the VA Clinical Assessment, Reporting, and Tracking Program." JACC: Cardiovascular Interventions 11.9 (2018): 879-888.
[Yabe 2018]	Yabe, Takayuki, et al. "THE IMPACT OF PERCUTANEOUS CORONARY INTERVENTION USING THE NOVEL DYNAMIC CORONARY ROADMAP SYSTEM." Journal of the American College of Cardiology 71.11 (2018): A1103.

11 TABLES

STUDY PATIENTS		
Disposition of patients		
Table 1	Enrolment by Site	ENROLLED
Table 2	Randomized Population by Site	RAND
Table 3	Stratification Factors by Randomized Treatment	RAND
Table 4	Screen Failures	SCREENED
Table 5	Disposition by Randomized Treatment	RAND
Table 6	Reason for Non-completion by Randomized Treatment	RAND
Table 7	Analysis Populations	SCREENED
Table 8	Analysis Populations by Randomized Treatment	RAND
BASELINE EVALUATION		
Demographics and other baseline characteristics		
Table 9-10	Demographics	RAND, FAP
Table 11-12	Medical History	SAF ,FAP
Table 13/15	Medication Used	SAF, FAP
Table 14/16	Iodine Contrast Administration	SAF, FAP
PCI PROCEDURE		
Table 17/19	PCI Procedure	SAF, FAP
Table 18/20	Complications during Procedure	SAF, FAP
Table 21/23	SYNTAX score per vessel	SAF, FAP
Table 22/24	Total SYNTAX score	SAF, FAP
EFFICACY EVALUATION		
Analysis of efficacy		
Table 25/26	Primary Outcome - Total Undiluted Iodinated Contrast Volume (ml) - Descriptive Statistics	FAP, PP
Table 27/28	Secondary and Exploratory Outcomes - Descriptive Statistics	FAP, PP
Table 29/30	Primary Efficacy Analysis on Log-transformed Total Undiluted Iodinated Contrast Volume (ml)	FAP, PP
Table 31/32	Secondary Efficacy Analysis	FAP, PP
Table 33/34	Exploratory Efficacy Analysis	FAP, PP
Table 35/36	Exploratory Outcomes	FAP, PP

Table 37/38	Exploratory Efficacy : Total Iodinated Contrast Volume by Number of vessels treated	FAP, PP
Table 39/40	Exploratory Efficacy : Total Iodinated Contrast Volume by Complexity of PCI procedure	FAP, PP
Table 41/42	Total Iodinated Contrast Volume by Roadmap Quality	FAP, PP
Table 43/44	Exploratory Efficacy : Variability of Total iodinated Contrast Volume by Randomized Treatment	FAP, PP
SAFETY		
Vital Signs		
Table 45	Vital Signs	SAF
Clinical laboratory evaluation		
Table 46/47	Serum Creatinine	SAF, FAP
Table 48/40	Acute Kidney Injury	SAF, FAP
Major Adverse Cardiovascular and Cerebral Events		
Table 50/51	In-Hospital MACCE	SAF, FAP
STUDY DEVIATIONS		
Table 52	Major Protocol Deviations	FAP
Table 53	Study Deviations	FAP

12 INDIVIDUAL SUBJECT DATA LISTINGS

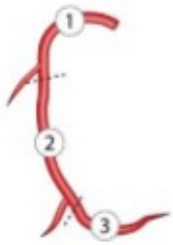
STUDY PATIENTS		
Disposition of Patients		
Listing 1	List of Inclusion and Exclusion Criteria	
Listing 2	In- and exclusion criteria	ENROLLED
Listing 3	Randomization results	RAND
Listing 4	Visit Dates	ENROLLED
Listing 5	Study Discontinuation	ENROLLED
Listing 6	Study Completion	ENROLLED
Listing 7	Subjects Analysis Set	SCREENED
BASELINE EVALUATION		
Demographics and Baseline Values		
Listing 8	Demographics	ENROLLED
Listing 9	Medical history	ENROLLED
Listing 10	Medication	ENROLLED
PCI PROCEDURE		
Listing 11	Procedure information	SAF
Listing 12	Procedure and Fluoroscopy time	SAF
Listing 13	Procedure: Contrast Usage	SAF
Listing 14	Procedure parameters	SAF
Listing 15	Procedure: number of runs	SAF
Listing 16	End of procedure information	SAF
Listing 17	Procedural complications	SAF
Listing 18	Procedural comments	SAF
Listing 19	Treated vessel SYNTAX questions	SAF
Listing 20	Number of Vessels treated with PCI and SYNTAX score	SAF
Listing 21	Hospital Discharge	SAF
EFFICACY EVALUATION		
Analysis of efficacy		
Listing 22	Primary and Secondary Efficacy Parameters	FAP
SAFETY		

Listing 23	Vital Signs	ENROLLED
Listing 24	Clinical Laboratory Tests	ENROLLED
Listing 25	Major Adverse Cardiovascular and Cerebral Events	ENROLLED
STUDY DEVIATIONS		
Listing 26	Study Deviations	ENROLLED

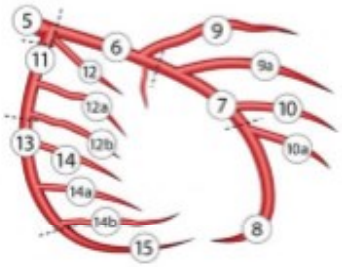
13 APPENDIX 1 CALCULATION OF SYNTAX SCORES

First assess dominance coronary system (Left/Right dominance) of the treated vessel.

If left dominance, treated vessel segment:

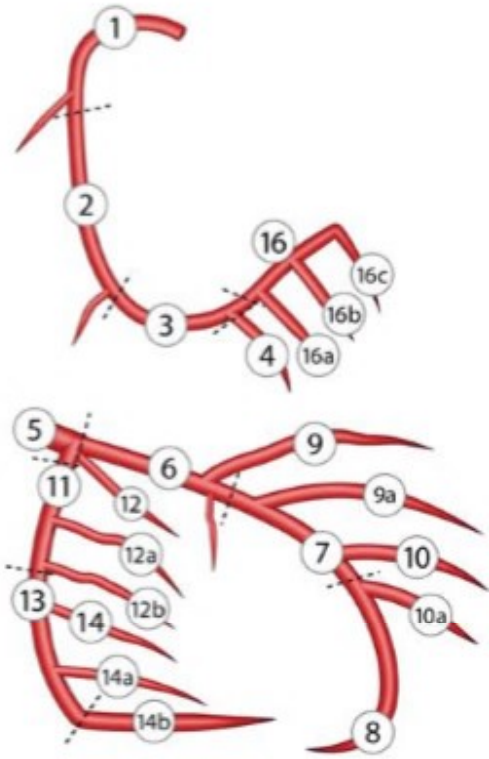


- RCA
  - RCA proximal — 1 [+0]
  - RCA mid — 2 [+0]
  - RCA distal — 3 [+0]
- LM Left main — 5 [+6]
- LAD
  - LAD proximal — 6 [+3.5]
  - LAD mid — 7 [+2.5]
  - LAD apical — 8 [+1]
  - First diagonal — 9 [+1]
  - Add. first diagonal — 9a [+1]
  - Second diagonal — 10 [+0.5]
  - Add. second diagonal — 10a [+0.5]



- LCX
  - Proximal circumflex — 11 [+2.5]
  - Intermediate/anterolateral — 12 [+1]
  - First obtuse marginal — 12a [+1]
  - Add. second obtuse marginal — 12b [+1]
  - Distal circumflex — 13 [+1.5]
  - Left posterolateral — 14 [+1]
  - Add. first left posterolateral — 14a [+1]
  - Add. second left posterolateral — 14b [+1]
  - Posterior descending — 15 [+1]

If right dominance, treated vessel segment:



RCA
- RCA proximal — 1 [+1]
- RCA mid — 2 [+1]
- RCA distal — 3 [+1]
- Posterior descending — 4 [+1]
- Posterolateral from RCA — 16 [+0.5]
- First posterolateral from RCA — 16a [+0.5]
- Second posterolateral from RCA — 16b [+0.5]
- Third posterolateral from RCA — 16c [+0.5]

LM Left main — 5 [+5]

LAD
- LAD proximal — 6 [+3.5]
- LAD mid — 7 [+2.5]
- LAD apical — 8 [+1]
- First diagonal — 9 [+1]
- Add. first diagonal — 9a [+1]
- Second diagonal — 10 [+0.5]
- Add. second diagonal — 10a [+0.5]

LCX
- Proximal circumflex — 11 [+1.5]
- Intermediate/anterolateral — 12 [+1]
- Obtuse marginal — 12a [+1]
- Obtuse marginal — 12b [+1]
- Distal circumflex — 13 [+0.5]
- Left posterolateral — 14 [+0.5]
- Left posterolateral — 14a [+0.5]
- Left posterolateral — 14b [+0.5]

Significant lesion (diameter stenosis >50%)? Y/N [Y: diseased segment score x2]

If RCA proximal (1), Left main (5), LAD proximal (6) or LCX proximal circumflex (11), Aorto-ostial stenosis? [Y: +1]

Total occlusion? Y/N (Y: diseased segment score x5)

If, total occlusion

- Age >3 months or unknown [+1]
- Blunt stump [+1]
- Bridging [+1]
- Side branch
  -Yes, all sidebranches <1.5mm [+1]
  -Yes, both sidebranches <1.5mm and ≥1.5mm are involved [+1]

Trifurcation? Y/N

If yes, specify:

- 1 diseased segment involved [+3]
- 2 diseased segments involved [+4]
- 3 diseased segments involved [+5]
- 4 diseased segments involved [+6]

Bifurcation? Y/N

If yes, specify type of bifurcation lesion:

- Medina 1,0,0 [+1]
- Medina 0,1,0 [+1]
- Medina 1,1,0 [+1]
- Medina 1,1,1 [+2]
- Medina 0,0,1 [+2]
- Medina 1,0,1 [+2]
- Medina 0,1,1 [+2]

If bifurcation, bifurcation angulation (between distal main vessel and side branch) < 70°? [Y: +1]

Severe tortuosity? Y/N [Y: +2]

Length >20mm? Y/N [Y: +1]

Heavy calcification? Y/N [Y: +2]

Thrombus? Y/N [Y: +1]

Diffusely diseased and narrowed segment? Y/N [Y: +1 per segment]

If yes, specify

- LAD proximal 6
- LAD mid 7
- LAD apical 8
- First diagonal 9
- Add. first diagonal 9a
- Second diagonal 10
- Add. second diagonal 10a

SYNTAX score per vessel: Add the above scored points.

Overall SYNTAX Score per patient: Take the maximum of the scored points across the vessels.

Document Revision History

Version	Date	Author	Reason for Change
Final 1.0	03FEB2020	[redacted]	NA
Final 2.0	14MAR2023	[redacted]	Updated definition of FAP, updated cut-off points for CKD classification, updated definition of overall syntax score, used tertiles of the SYNTAX score as index of complexity of PCI procedure, added subgroup analysis of roadmap quality, updated list of TLFs, minor textual changes.
Final 3.0	11MAY2023	[redacted]	Added total occlusion to calculation of SYNTAX score in Appendix1, added analysis populations to summary of changes from the protocol.

Document Approval History

Approved by	Role / Function	Signature & Date
[redacted]	Project Statistician (SAP author)	[redacted]
	Project Manager or Business Leader	
	Clinical Study Manager or Clinical Operations Lead	
	Director of Biostatistics	