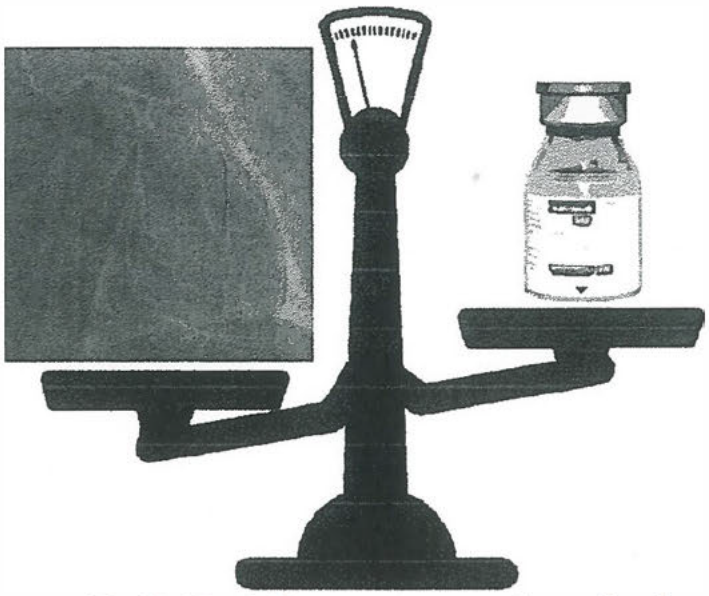


DCR4Contrast trial

Author: [redacted] velopment Scientist

Department: Clinical Science & Medical Affairs

Approval

Name	Role	Date (yyyy Mon dd)	Signature
[redacted]	GEN: Clinical Operations Lead	2019 Jul 09	[redacted]
	InCs: Study Leader	2019 Jul 09	
	Q&R: RA Officer	2019 JUL 09	
	GEN: Biostatistician	2019 JUL 05	

en all approvers have signed. Approval and effective date is the date of the latest signature.

Revision History

Revision	Revision Date	Author	Changes/Comments
00	2018 Apr 05	[redacted]	Initial version
01	2019 Jun 05		Protocol updated based on feedback from investigators and study coordinators at the potential sites: • Target patient population extended from elective PCI to elective + ad hoc PCI; rephrased inclusion/exclusion criteria, objectives, endpoints and study procedures to accommodate this change (see Summary section, Chapter 5, 6, and 7) • Chapter 9: Changed such that all (also non significant) changes of the clinical study protocol shall be notified to, or approved by the MEC and where appropriate regulatory authorities. • Appendix I: Updated list of investigators, sites, and third parties involved in the study • Appendix II: Updated list of monitors/clinical scientists, clinical study managers
02	2019 Jul 04		Protocol updated based on FDA pre-submission meeting feedback: • The secondary objective on the iodinated contrast volume used per vessel PCI has been moved to the Exploratory objectives. • Updated the sample size justification for the secondary objective resulting in 394 subjects required for the study (360 previously). • Added site effect analysis for the primary endpoint to assess poolability of data. • Added sensitivity analysis for the primary endpoint to perform worst-case analysis for missing data.

Open Issues

None

Table of Contents

1. Document Introduction

1.1. Purpose

This document is intended to be used as a template for the Post-Market Clinical Study Protocol for clinical studies. The document describes the minimum amount of information to be included in this clinical study protocol based on the regulations.

1.2. Scope

This post-market study protocol applies to the clinical evidence study Dynamic Coronary Roadmap for Contrast Reduction **(DCR4Contrast trial)**.

1.3. References

Reference	Identification	Title / additional remarks
[CER]	DHF287327	Clinical Evaluation Report Dynamic Coronary Roadmap
[IFU]	4522 203 59903	IFU Dynamic Coronary Roadmap R2.0
[FDA]	K172307	FDA 510(k) clearance Dynamic Coronary Roadmap R2.0
The following documents that are not controlled by Philips are referred to in this document:		
[MEDDEV]	MEDDEV 2.7/1	MEDDEV 2.7/1 rev 4 - Clinical Evaluation: a guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385 EEC
[MDD]	EU MDD 93/42/EEC	Council Directive 93/42/EEC concerning medical devices. Amended by Medical Device Directive as amended by 2007/47/EC
[MDR]	EU MDR 2017/745	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices
[ISO14155]	EN ISO 14155	EN ISO 14155:2011 – Clinical Investigation of medical devices

1.4. Definitions & Abbreviations

Term	Description
AF	Atrial Fibrillation
AK	Air Kerma
AKI	Acute Kidney Injury
AKI-D	AKI requiring dialysis
AKIN	Acute Kidney Injury Network (definitions)
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
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
GFR	Glomerular Filtration Rate
HTA	Health Tech Assessment
IDMS	Isotope Dilution Mass Spectrometry
iFR	instantaneous wave-Free Ratio
IFU	Instructions for Use
IQR	Interquartile Range
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	In-Stent Restenosis
IVUS	IntraVascular UltraSound
LMCA	Left Main Coronary Artery
MDD	Medical Device Directive
MDR	Medical Device Reporting
MEC	Medical Ethic Committee
MI	Myocardial Infarction
MVD	Multi Vessel Disease
NRD	Nephropathy requiring dialysis
NSTEMI	Non-ST segment Elevation Myocardial Infarction
NYHA	New York Heart Association classification
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Interventions
RCA	Right Coronary Artery
SCr	Serum Creatinine
SD	Standard Deviation
TIMI	Thrombolysis In Myocardial Infarction
UA	Unstable Angina

2. Summary

Identification of study device

The Dynamic Coronary Roadmap is a commercially available (CE labeled, FDA 510(k) cleared: K170130 for Dynamic Coronary Roadmap R1, and K172307 for Dynamic Coronary Roadmap R2) product developed by Philips Medical Systems, a Philips Healthcare company. Dynamic Coronary Roadmap is a software medical device intended to provide a real-time and dynamic angiographic roadmap of coronary arteries. The angiographic roadmap is automatically generated from previously acquired coronary angiograms during the same procedure. Dynamic Coronary Roadmap overlays the angiographic roadmap on live 2D fluoroscopic images, thereby assisting the physician in navigating devices, e.g. (guide) wires, catheters, through the coronary arteries.
Dynamic Coronary Roadmap is to be used in combination with a Philips interventional X-ray system.

Study design

This is a 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. In the randomization process all subjects within each type of PCI (ad hoc or elective) will be stratified according to the number of vessels to be treated via PCI, i.e., 1, 2, or 3 or more vessel PCI.

Objectives

Primary objective:

- 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.

Secondary objective:

- 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

Exploratory objectives:

- 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

Primary and secondary endpoints

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.

Secondary endpoint:

- 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).

Main 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

Main 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

No. of subjects

In total 394 subjects will be enrolled in the study during an expected enrollment period of 9 months.

Study procedures

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.

Screening

Patients scheduled for PCI will be screened on inclusion and exclusion criteria by the principal investigator or delegated and trained study personnel. When a patient is eligible study information and the informed consent form is provided to the patient and after providing ample time to consider participation the patient is asked for signed consent.

PCI procedure

The investigator will perform PCI using standard of care procedures.

Standard of care PCI entails (deviations allowed up to investigator's discretion):

→ In case of elective PCI: Randomization before procedure

- Arterial access (femoral or radial; preferably perform femoral angiography of preclose device at this moment)
- In case of ad hoc PCI: Diagnostic Coronary Angiography
  → In case of ad hoc PCI: Randomization upon decision to go for PCI
- First positioning of interventional guiding catheter in stable coronary position
  → Record the contrast volume used up to that moment
- Coronary Angiography ***[DCR group: DCR started automatically]***
- Position guidewire

- Position balloon + inflate balloon
- Position stent + deploy stent
- Check PCI result by Coronary Angiography (potentially combined with e.g. Stent Boost, IVUS)
- Repeat above steps when necessary, e.g. post-dilate stent or perform PCI in different vessel
  → ***Record the total contrast volume used***

The principal investigator or his delegates on the study team will enter data in a pre-designed e-CRF. This will include patient demographics, relevant past medical history, specific target CAD data along with pre-procedural/screening imaging details, PCI procedure data and follow-up data until patient discharge.

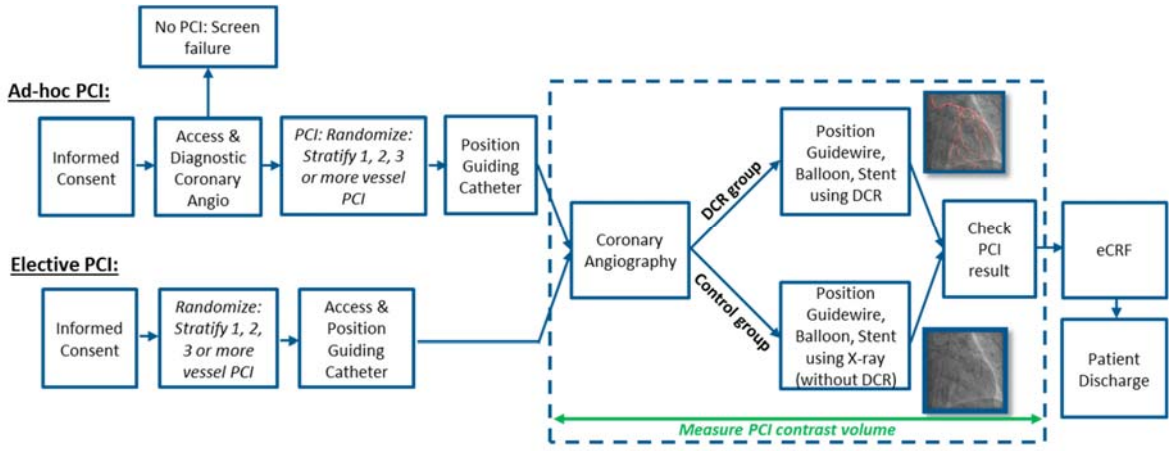


Figure 1 Clinical workflow of the DCR4Contrast trial following standard of care for PCI (ad hoc and elective)

Follow up

The subjects will be followed-up until discharge following standard clinical care.

Duration of the study

The total duration of the study is expected to take 9 months.

3. Device Description

3.1. Summary description of the study device

The Dynamic Coronary Roadmap is a commercially available (CE labeled, FDA 510(k) cleared: K170130 for Dynamic Coronary Roadmap R1, and K172307 for Dynamic Coronary Roadmap R2) product developed by Philips Medical Systems, a Philips Healthcare company. Dynamic Coronary Roadmap is a software medical device intended to provide a real-time and dynamic angiographic roadmap of coronary arteries. The angiographic roadmap is automatically generated from previously acquired coronary angiograms during the same procedure. Dynamic Coronary Roadmap overlays the angiographic roadmap on live 2D fluoroscopic images, thereby assisting the physician in navigating devices, e.g. (guide) wires, catheters, through the coronary arteries.
Dynamic Coronary Roadmap is to be used in combination with a Philips interventional X-ray system.

Dynamic Coronary Roadmap R1 and R2 are completely equivalent since Dynamic Coronary Roadmap R2 embodies the exact same algorithm as Dynamic Coronary Roadmap R1 and therefore no difference in the intended use [FDA]. Both versions R1 & R2 are commercially released products. The difference between R1 and R2 is the FFR/iFR Roadmap feature added to R2, which is not subject of the current study. The coronary roadmapping features of R1 and R2 are identical and the use of R1 and R2 in this study is not impacting study results. As a result both R1 and R2 of Dynamic Coronary Roadmap can be used for the purpose of this clinical evidence study.

The manufacturer of the study device is:
Philips Medical Systems Nederland B.V., *a Philips Healthcare company*
Veenpluis 6
5684 PC Best
The Netherlands

3.2. Intended Purpose

Since this study will be using the commercially available Dynamic Coronary Roadmap product also the related commercially available instruction for use [IFU] will be used. This manual contains safety precautions and handling of the study device and contains more features than the coronary roadmapping feature required for this study.

3.2.1. Indications for Use / Medical Purpose

Dynamic Coronary Roadmap is intended to assist the physician during percutaneous coronary interventions in correlating the device position to the coronary vasculature, by providing a motion compensated overlay of this coronary vasculature.

The FFR/iFR Roadmap feature[1] is intended to assist the physician during percutaneous coronary interventions in relating the intravascular blood pressure measurement to its anatomical location. FFR/iFR roadmap visualizes the position of the pressure wire and the coronary artery on an X-ray image at the moment that an intravascular blood pressure measurement was performed as well as the intravascular blood pressure measurement values themselves.

Dynamic Coronary Roadmap is suitable for use with the entire adult human population.

3.2.2. Intended operator profile

Dynamic Coronary Roadmap is intended to be used and operated by: adequately trained, qualified, and authorized healthcare professionals who have understanding of the safety information and emergency procedures as defined by local laws and regulations for radiation workers and staff.

[1] The FFR/iFR Roadmap feature is not subject of the current study and not to be used.

3.2.3. Clinical environment

Dynamic Coronary Roadmap is intended to be used in the catheterization laboratorium, interventional suite or hybrid operating room. The software medical device is connected to a Philips interventional X-ray system. Additionally it may also be connected to a compatible intravascular blood pressure measurement system.

3.2.4. General safety and effectiveness

To facilitate safe and effective operation of the system by a trained healthcare professional, instructions for use are provided as part of the device labeling.

Dynamic Coronary Roadmap is a software medical device and does not come in contact with a human subject.

3.2.5. Operating principle

The software medical device uses X-ray generated data as input data and image processing for medical imaging and/or pressure data from a compatible intravascular blood pressure measurement system. The software medical device provides visual feedback.

3.3. Necessary training and experience needed to use the research device

There will be no change in the normal operation of the study device/system. Therefore, minimal training is needed for the use of Dynamic Coronary Roadmap.

Operators that have no experience with Dynamic Coronary Roadmap should first familiarize themselves with the tool for at least 10 interventions before participating in the study.

3.4. Materials that will be in contact with tissues or body fluids

No materials of the study device will be in contact with tissue or body fluids.

3.5. Device Traceability

The study device includes a name, including software version and accessories to permit full identification. Device traceability will be maintained by Philips. Records shall be kept to document when the device is received, installed or uninstalled at the hospital.

4. Justification for the design of the study

4.1. Clinical background

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.

4.2. Clinical study results

The clinical evaluation of Dynamic Coronary Roadmap has been covered by the Clinical Evaluation Report [CER], including a review of the relevant scientific literature published.

Pilot studies [Dannenberg 2016, Piayda 2018] using DCR in PCI confirmed safety and performance. Other recent pilot studies also indicated the potential of DCR to reduce iodinated contrast use:

- [Rajappan 2017]: Single center, non-randomized, prospective study showed a contrast reduction of 26% after introduction of DCR in elective PCI (n=84). The number of contrast enhanced cine runs (angiograms) per procedure was reduced by 26% in this study.
- [Yabe 2018]: Single center, non-randomized, retrospective study showed to achieve 21.9% contrast reduction using Dynamic Coronary Roadmap in PCI (n=43 DCR group, n=103 control group).

Both pilot studies reported that contrast usage is potentially reduced by Dynamic Coronary Roadmap as continuously showing the automatic dynamic coronary roadmap reduces:

- the need to perform small contrast injections (“puffs”);
- the need to perform redo contrast enhanced cine runs (angiograms) to refresh the mental map of the coronary arteries;
- the need to perform contrast enhanced angiograms when returning to earlier angiogram positions by automatically showing the earlier created angiographic roadmap.

4.3. DCR4Contrast trial justification

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 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 (see Figure 2).

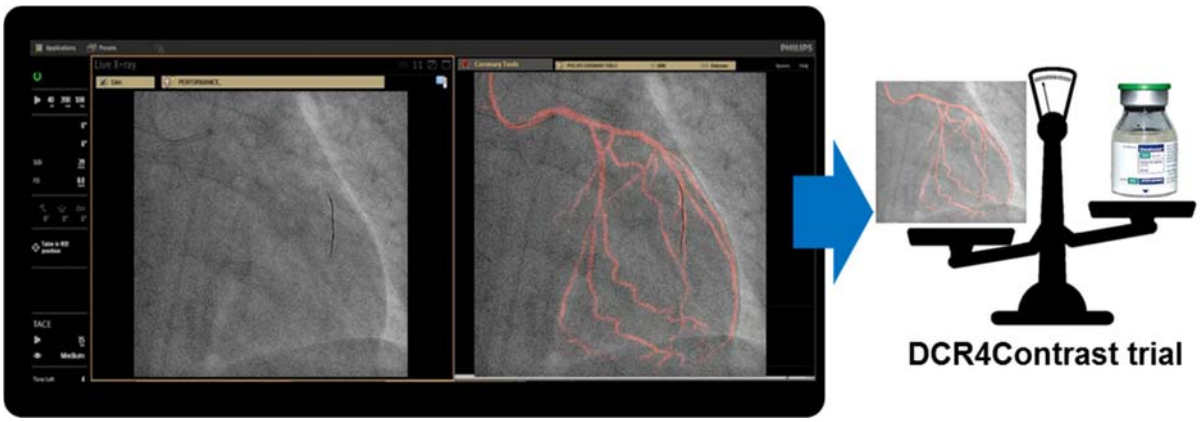


Figure 2 DCR provides a real-time motion compensated coronary roadmap on fluoro for PCI guidance. The DCR4Contrast trial aims to assess whether using DCR reduces the total iodinated contrast volume related to PCI compared to the control group without Dynamic Coronary Roadmap.

5. Objectives and hypotheses

5.1. Primary objective

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.

5.2. Secondary objective

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

5.3. 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

6. Study Design

6.1. General

This is a 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. In the randomization process all subjects within each type of PCI (ad hoc or elective) will be stratified according to the number of vessels to be treated via PCI, i.e., 1, 2, or 3 or more vessel PCI.

A prospective multi-center study has been chosen to observe standard of care with the study device, see Figure 3 for the DCR4Contrast trial flow.

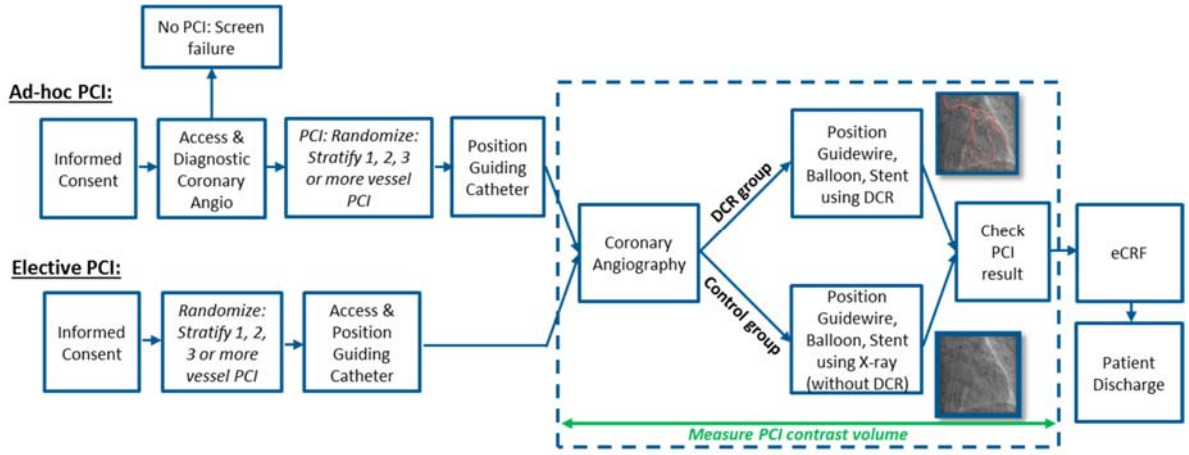


Figure 3 Clinical workflow of the DCR4Contrast trial following standard of care for PCI (ad hoc and elective)

6.2. Maintenance and calibration

The equipment relevant for the assessment of the clinical study is the Dynamic Coronary Roadmap study device and automatic contrast injector for accurate iodinated contrast volume measurement. Maintenance and calibration of this equipment will be monitored if this is appropriately performed and documented. The contrast agents used within the study will be used according to the legally approved dosing and intended use.

6.3. Study device exposure and comparators

During the PCI procedure the Dynamic Coronary Roadmap study device will be used for the randomly selected subjects in the DCR group, see Figure 3. 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.

6.4. Subjects

6.4.1. In- and exclusion criteria

Subjects participating in the study will be carefully selected based on the next inclusion and exclusion criteria.

6.4.1.1. *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

6.4.1.2. 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

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. This threshold has been determined based on standard PCI practice: In PCI typically one contrast enhanced angiogram run is performed at the start of the intervention to confirm the C-arm working position and typically two contrast injected runs are performed after stent placement to check wall apposition and for documentation purposes. Each run typically accounts for 7ml of iodinated contrast, therefore a very straightforward PCI not requiring navigation guidance will be performed under 25ml total.

6.4.2. Duration

The total duration of the study is expected to take 9 months.

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.

6.4.3. Enrollment

Subjects are considered to be enrolled in the study after they have signed the informed consent form and met all the inclusion and exclusion criteria. No study procedures will be performed before this moment.

The subjects will be followed-up until discharge following standard clinical care.

6.4.4. Number of subjects

In total 394 subjects will be enrolled in the study during an expected enrollment period of 9 months.

See section 7 Statistical considerations for more detail on the number of sample size calculation.

6.4.5. Procedure for the replacement of subjects

In enrolled subjects the investigator preprocedurally 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.
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.

6.4.6. Subject withdrawal or discontinuation

Subjects can withdraw informed consent at any time during the study.

6.5. Procedures

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.

Screening
Patients scheduled for PCI will be screened on inclusion and exclusion criteria by the principal investigator or delegated and trained study personnel. When a patient is eligible study information and the informed consent form is provided to the patient and after providing ample time to consider participation the patient is asked for signed consent.

PCI procedure
The investigator will perform PCI using standard of care procedures.

Standard of care PCI entails (deviations allowed up to investigator's discretion):

→ ***In case of elective PCI: Randomization before procedure***

- Arterial access (femoral or radial; preferably perform femoral angiography of preclose device at this moment)
- In case of ad hoc PCI: Diagnostic Coronary Angiography
  → ***In case of ad hoc PCI: Randomization upon decision to go for PCI***
- First positioning of interventional guiding catheter in stable coronary position
  → ***Record the contrast volume used up to that moment***
- Coronary Angiography ***[DCR group: DCR started automatically]***
- Position guidewire
- Position balloon + inflate balloon
- Position stent + deploy stent
- Check PCI result by Coronary Angiography (potentially combined with e.g. Stent Boost, IVUS)
- Repeat above steps when necessary, e.g. post-dilate stent or perform PCI in different vessel
  → ***Record the total contrast volume used***

The principal investigator or his delegates on the study team will enter data in a pre-designed e-CRF. This will include patient demographics, relevant past medical history, specific target CAD data along with pre-procedural/screening imaging details, PCI procedure data and follow-up data until patient discharge.

6.6. Monitoring Plan

A detailed plan for monitoring arrangement will be separate from this Clinical Protocol.

Monitoring will be performed by a trained person appointed by Philips to ensure compliance with the clinical study protocol, applicable national regulations and international standards, patient safety and data validity. The Sponsor may designate one or more individuals to monitor the progress of a clinical study. The Sponsor may also delegate the monitoring responsibilities to a third party. However, the Sponsor remains ultimately responsible for the conduct of the study. The Institution is responsible for the appropriate de-identification of subject data. The investigational site should provide access to the source data of the subjects.

All regulatory documents (e.g. MEC/IRB approval, contracts, etc.) will be reviewed for each actively participating center.

In accordance to ISO 14155 Clinical investigation of medical devices for human subjects standard before, during and after the clinical investigation on-site monitoring is required. After site initiation the first visit will occur as soon as possible after the first subject is enrolled at each study site. The monitoring schedule is based on the following considerations: enrollment rate, study compliance at the center, magnitude of data corrections required, complexity of the study, IRB/MEC request, audit/inspection.

The monitor activities include:

- Check that the study is conducted, recorded and reported in compliance with this clinical study protocol, and applicable regulations. Acts to oversee the progress of the study.
- Check signed and dated informed consent of the subjects and check that this is signed before any study-related procedures are undertaken.
- Ensure that essential documents (e.g. contract, MEC approval) are maintained in the Site Regulatory File.
- Ensure recording of deviations from protocol and store in Site Regulatory File or CRF.
- Ensure that all adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay.
- Ensure that adverse events and device deficiency are reported to the MEC/IRB, if required.
- Ensure that the principal investigator is informed and knowledgeable of all relevant document updates concerning the clinical study (e.g. clinical study protocol).
- Ensure that amendments to the protocol are provided to the MEC/IRB by the principal investigator.
- Ensure device accountability.
- Verification of source data.

Critical data and processes will be monitored for this study prior to clinical report completion based on a risk based monitoring approach. Dependent on the risk a high or lower sample will be monitored.
The monitor will review critical clinical data that affect study endpoints. Data collection for reasons other than to support the protocol-defined endpoints will not be monitored.

A close-out visit for sites that have enrolled subjects will be conducted once the site has completed collecting data for the study.

Names of the monitor(s) can be found in Appendix II. List of Monitors of this protocol. An update of this list can be provided to the site under separate cover.

7. Statistical considerations

Any deviation from the planned analysis described below will be documented with justification in the final clinical end report.

7.1. 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 1.

	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 1 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 α = 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.

7.1.1. Sample Size Justification Secondary Endpoint

A recent single center, non-randomized, prospective study [Rajappan 2017] showed a 25.6% reduction in the total number of cine X-ray runs after introduction of Dynamic Coronary Roadmap, see Table 2.

	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 2 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 α = 0.025 (the type I error, i.e., probability of rejecting a true null hypothesis)
- Power (1-β) = 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.**

7.2. General Considerations

All results will be summarized using descriptive statistics, i.e., using frequencies and percentages or summary statistics like averages and medians (including confidence intervals and interquartile ranges).

Subgroup analyses (e.g., for 1, 2, 3 or more vessel PCI, and anatomical complexity via SYNTAX score) will be performed and presented. Methods to correct for missing data will be used like, e.g., worst case scenario analysis, multiple imputation methods [Rubin 2004]. Analyses to determine whether there is an effect based on e.g. intervention difficulty, lesion characteristics, patient demographics, physician experience, center effect etc. will be performed. If an effect is found applying adjustment analysis will be considered. 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, and potential adjustment analysis will be considered. Statistical analysis will be performed using SAS (SAS Institute, Cary, North Carolina) and/or R statistical software (https://www.r-project.org/).

7.3. Poolability

A site effect analysis will be conducted on the primary endpoint to assess poolability of data. Adjustment analysis will be considered if sites are not homogeneous.

7.4. Subject Disposition

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

7.5. Demographics and Baseline Characteristics

Basic subject characteristics such as age, gender, height and weight will be summarized. In addition, the SYNTAX score [Sianos 2005, Neumann 2018] will be determined for the vessel(s) treated with PCI as an index for anatomical complexity, the number of lesions treated in the PCI, the location of the lesion, etc., see Figure 4:

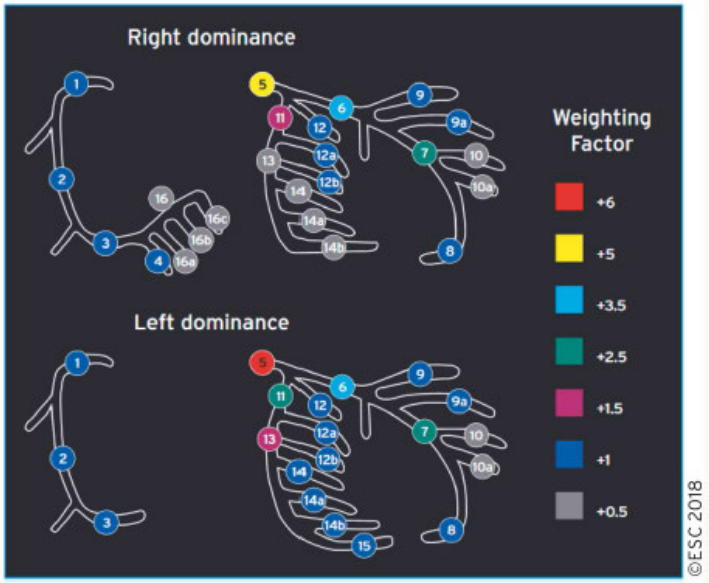
Steps	Variable assessed	Description
Step 1	Dominance	The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.
Step 2	Coronary segment	The diseased coronary segment directly affects the score as each coronary segment is assigned a weight depending on its location, ranging from 0.5 (i.e. the posterolateral branch) to 6 (i.e. left main in case of left dominance). 
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 4 Steps to determine SYNTAX score as an index for anatomical complexity of the PCI [from Neumann 2018]

7.6. Primary objective

Objective
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.

Endpoint
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.

H_0: $\mu_{Control1} - \mu_{DCR1} \leq 0$
H_a: $\mu_{Control1} - \mu_{DCR1} > 0$

Where $\mu_{Control1}$ is the average total iodinated contrast volume usage per PCI for the Control group, and μ_{DCR1} is the average total iodinated contrast volume usage per PCI for the DCR group.

Rationale for choice of hypothesis
Based on pilot study results and the working mechanism of DCR this hypothesis is chosen to measure the reducing effect of DCR on the total iodinated contrast volume usage in PCI.

Analysis
The objective will be evaluated using a one-sided two-sample equal-variance t-test. The relative impact of the analysis results will be made in comparison to the maximum ratio of contrast volume (in ml) to the glomerular filtration rate (in ml/min/1.73m^2) being 3.7 for severe CKD (eGFR<30) as recommended by the ESC/EACTS Guidlines [Laskey 2007, Neumann 2018].

All subjects will be included in this analysis.

7.7. Secondary objective

7.7.1. Secondary objective: Number of Angiograms

Objective
- 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

Endpoint
- 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).

Hypothesis
Dynamic Coronary Roadmap reduces the total number of contrast enhanced cine angiographic X-ray runs (angiograms) acquired on average per PCI.

H_0: $Pop_{Control2} \leq Pop_{DCR2}$
H_a: $Pop_{Control2} > Pop_{DCR2}$ (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.

Rationale for choice of hypothesis
Based on pilot study results and the working mechanism of DCR this hypothesis is chosen to measure the effect of DCR on the number of contrast enhanced cine angiographic X-ray runs (angiograms) acquired in PCI.

Analysis
The number of angiographic X-ray runs is discrete and is likely to be not normally distributed, so the objective will be evaluated using a one-sided Wilcoxon-Mann-Whitney test.

All subjects will be included in this analysis.

7.8. Exploratory objectives

7.8.1. Exploratory objective: Contrast Volume per Vessel PCI

Objective
- To assess the iodinated contrast volume used per vessel PCI in the Dynamic Coronary Roadmap and control group

Endpoint
- 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) 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 (from first positioning the interventional guiding catheter in stable coronary position till end of PCI procedure) divided by the number of vessels treated by PCI.

Analysis
The objective will be evaluated using a two-sample equal-variance t-test and cluster analysis.

All subjects will be included in this analysis.

7.8.2. Exploratory objective: Contrast Volume per Stratification Group (1, 2, 3 or more vessel PCI)

Objective
- 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

Endpoint
- 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 in each stratification group, i.e., 1 vessel PCI, 2 vessel PCI and 3 or more vessel PCI.

Analysis
The objective will be evaluated using a two-sample equal-variance t-test and cluster analysis.

All subjects will be included in this analysis.

7.8.3. Exploratory objective: Contrast Volume per Simple, Intermediate, Complex PCI subgroup

Objective
- 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

Endpoint

- 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 injector in subgroups of simple, intermediate and complex PCI. The SYNTAX score for the vessel(s) treated with PCI will be calculated to be used as an index for the anatomical complexity of the PCI [Sianos 2005].

Analysis

The objective will be evaluated using a two-sample equal-variance t-test and cluster analysis.

The iodinated contrast volume usage and related contrast volume usage difference will be binned according to the anatomical complexity of the PCI procedure using the SYNTAX score for the vessel(s) treated with PCI as index for anatomical complexity.

All subjects will be included in this analysis.

7.8.4. Exploratory objective: AKI Incidence

Objective

- To assess the incidence of Acute Kidney Injury (AKI) in the Dynamic Coronary Roadmap and control group (at discharge following standard clinical care)

Endpoint

- The total number and percentage of subjects in which AKI, (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) is diagnosed after PCI.

Analysis

Multiple AKI definitions exist, which are all based on measuring serum creatinine (SCr, measured via isotope dilution mass spectrometry (IDMS) [Meyers 2006]) or urine output:

- RIFLE (Risk, Injury, Failure, Loss, End stage renal disease) [Bellomo 2004],
- Acute Kidney Injury Network (AKIN) [Mehta 2007], and
- Kidney Disease Improving Global Outcomes (KDIGO) guidelines [KDIGO guidelines AKI 2012].

A recent study [Parsh 2016] showed that the combination of 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 might be the most optimal definition for AKI.

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]:

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

with K=0.7 and α=-0.329 if female;
with K=0.9 and α=-0.411 if male.

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 CKD can be classified in 5 stages as indicated in Table 3.

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 3 CKD classification based on eGFR [Tsai 2014a]

New AKI biomarkers are being investigated such that both renal function and renal damage can be diagnosed early, but even the most promising ones (cystatin C and neutrophil gelatinase-associated lipocalin (NGAL)) are rarely routinely used in the hospital [Ostermann 2016]. Serum creatinine measurement and eGFR calculation are still most commonly used to diagnose AKI, which we will also adopt using the following definition for AKI [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

Note that 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;
- Approx. 12 months in all other patients

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.

Furthermore 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.

As AKI prevention method adequate pre- and post-hydration with isotonic saline (NaCl 0.9%) should be applied to patients with GFR<60 ml/min/1.73m^2 as recommended by the ESC/EACTS Guidelines: 1 ml/kg/h 12 h before and continued for 24 h after the procedure (0.5 ml/kg/h if LVEF ≤35% or NYHA >2) [Neumann 2018].

The objective will be evaluated using a two-sample equal-variance t-test.

All subjects will be included in this analysis.

7.8.5. Exploratory objective: Contrast Usage Variability

Objective

- To assess the variability of the total iodinated contrast volume related to PCI in the Dynamic Coronary Roadmap and control group

Endpoint

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

Analysis
The objective will be evaluated using a Brown-Forsythe test to test for equal variances in both groups and cluster analysis.

All subjects will be included in this analysis.

7.8.6. Exploratory objective: Fluoro & Procedure Time

Objective
- To assess the total fluoroscopy & procedure time related to PCI in the Dynamic Coronary Roadmap and control group

Endpoint
- The average 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.

Analysis
The objective will be evaluated using a two-sample equal-variance t-test.

All subjects will be included in this analysis.

7.8.7. Exploratory objective: X-ray Dose

Objective
- To assess the total X-ray dose (DAP, AK) related to PCI in the Dynamic Coronary Roadmap and control group

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

Analysis
The objective will be evaluated using a two-sample equal-variance t-test.

All subjects will be included in this analysis.

7.8.8. Exploratory objective: Procedural Success

Objective
- To assess the procedural success in the Dynamic Coronary Roadmap and control group

Endpoint
- The total number and percentage of subjects treated with procedural success. 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.

Analysis
Since DCR is a tool assisting the physician in navigating devices through the coronary arteries it is not likely this trial will find a significant difference in procedural success in the DCR group compared to the control group.

The objective will be evaluated using a two-sample equal-variance t-test.

All subjects will be included in this analysis.

7.8.9. Exploratory objective: In-hospital MACCE

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

Endpoint

- The total number and percentage of in-hospital. MACCE is defined as all-cause death, acute myocardial infarction, coronary artery bypass surgery, repeat coronary revascularization of the target lesion, or acute ischemic stroke during hospitalization for the PCI procedure.

Analysis
Since DCR is a tool assisting the physician in navigating devices through the coronary arteries it is not likely this trial will find a significant difference in in-hospital MACCE in the DCR group compared to the control group.

The objective will be evaluated using a frequencies and percentages.

All subjects will be included in this analysis.

7.8.10. Sensitivity Analysis for the Primary Endpoint

A worst-case analysis will be considered for the primary endpoint [the average total undiluted iodinated contrast volume (in ml) used per PCI]. 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.

8. Data management

An e-CRF will be used to collect medical history, subjects demographics, procedure related information, protocol deviations, adverse events and device deficiencies.

The e-CRF will be used for data review, data cleaning and issuing and resolving queries. This e-CRF is a web-based e-CRF which is password protected and is 21 CFR part 11 compliant. At the end of the study the data will be stored as a frozen dataset and will be retained. Interview can be performed separately from the e-CRF.

The e-CRF data from the subjects will be key-coded (pseudonomyzed). The information related to the subjects (like name) is kept separately in the enrollment log at the hospital. Date and time of the procedure and date of discharge will be collected.

All exported (image) data will be de-identified and this data will be collected and stored in a secure location.

8.1. Retention period

The investigator shall maintain the records related to this study during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application in the US or a notice of completion of a product development protocol. Or longer if national regulation requires this.
Philips will maintain the records for the same period as the investigator or for a period of device End of Life (EoL) plus 15 years, whichever is later.

The sponsor and principal investigator shall take measures to prevent accidental or premature destruction of these documents.

9. Amendments to the Clinical Study Protocol

Amendment to the Clinical Study Protocol shall be notified to, or approved by the MEC and where appropriate regulatory authorities. The version number and date of amendments shall be documented. Significant changes (such as device modifications, study procedures) shall be discussed with the coordinating investigator and principal investigator prior approval. All changes will be documented with a justification and described in the latest version of the clinical study protocol.

10. Deviations from the Clinical Study Protocol

The Investigator is not allowed to deviate from the clinical study protocol or to enroll subjects that do not comply with all inclusion and exclusion criteria. Under emergency circumstances, deviations from the clinical study protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the MEC. Such deviations shall be documented and reported to the sponsor and the MEC as soon as possible.
All deviations from the clinical study protocol will be documented with date, subject, reason, actions taken and if the deviation affects subject's rights, safety and well being or the scientific integrity of the clinical study. The deviation shall be notified to the Sponsor as soon as possible via the e-CRF. Deviations will be reviewed by the sponsor and in case of serious or repetitive deviations a corrective action plan may represent a need to initiate a corrective action plan with the principal investigator. In some cases, necessitate suspension of enrollment at the site or ultimately the principal investigator will be disqualified.

11. Device accountability

A device that is market released is used in this study, therefore no device accountability (e.g documented return and disposal) will be performed.

12. Statements of compliance

This clinical study shall be conducted in accordance with the clinical study protocol, and with the ethical principles that have their origin in the Declaration of Helsinki and all applicable regional and/or national regulations. Furthermore, in Europe this clinical study shall be in accordance with the International Standards ISO 14155 Clinical investigation of medical devices for human subjects - Good clinical practice [ISO14155], and the Medical Device Directive [MDD] and in accordance with [MEDDEV] Clinical Evaluation guidance. Furthermore all investigators will complete financial disclosures, as outlined in the CFR 21 part 54 and will also comply with part 11. Investigators located in the US shall follow: 21 CFR part 50, 56 and 812.

This study shall not be started prior to obtaining a favorable opinion from a Medical Ethics Committee (MEC)/Institutional Review Board (IRB), if required. Any additional requirements imposed by the MEC/IRB shall be followed.

Insurance shall be provided for the subjects participating in this clinical trial according to local law.

13. Informed consent process

Informed consent will be obtained from every subject in writing by the Investigator or his authorized designee before any research related procedures are started is started.
The subject will be informed both orally and in writing about all aspects that are relevant to the subject's decision to participate in the clinical study, including the clinical study procedures. Ample time should be provided for the subject to read and understand the informed consent form and to consider participation. The informed consent will include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process. A copy of the signed and dated informed consent form and any other written information will be provided to the subject.

Subjects who are unwilling to provide informed consent will not be included in the Research.

If new information becomes available that might significantly affect the subject's future health and medical care, it shall be provided to the subjects in written form. If relevant, subject shall be asked to reconfirm their continuing informed consent in writing.

14. Safety reporting

The following event should be reported to Philips for Medical Device Reporting (MDR) according to 21 CFR part 803: Deaths and serious injuries that a device has or may have caused or contributed to, Caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of: (1) Failure; (2) Malfunction; (3) Improper or inadequate design; (4) Manufacture; (5) Labeling; or (6) User error.
Medical Device Reporting shall be reported to the regular Philips Healthcare customer feedback system, i.e. contact the local Helpdesk to report these events. Also report these to the Clinical Study Manager (see Appendix II. List of Monitors).

The following incident should be reported to Philips for Vigilance Reporting:
Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health.
A serious deterioration in state of health can include according to the definition:
a) life-threatening illness,
b) permanent impairment of a body function or permanent damage to a body structure,
c) a condition necessitating medical or surgical intervention to prevent a) or b).
Examples: - clinically relevant increase in the duration of a surgical procedure,
- a condition that requires hospitalization or significant prolongation of existing hospitalization.
d) any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic test results when used within manufacturer's instructions for use.
e) foetal distress, foetal death or any congenital abnormality or birth defects.
Vigilance Reporting shall be reported to the regular Philips Healthcare customer feedback system, i.e. contact the local Helpdesk to report these events. Also report these to the Clinical Study Manager (see Appendix II. List of Monitors).

15. Early termination or suspension of the Clinical study

There are no provisions or interim analyses planned that can result in an early termination of the trial. Serious or repetitive occurrence of deviations from study protocol or non-compliance with regulations may also be reason for early termination or suspension of a study site.

16. Publication policy

It is the intention of the investigator and sponsor to submit the clinical study data for publication. Prior to submission, claims on intellectual property will be assessed.

This study will also be registered on clinicaltrial.gov before first enrollment.

17. Bibliography

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Appendix I. List of Investigators and Sites

Update of this list can be provided to the study site under separate cover.

Table 4: Principal Investigator of the study (Clinical Coordinating Investigator)

Name Principal Investigator of the study	Name and address investigation site
Prof. Javier Escaned [redacted]	Hospital Clinico San Carlos Calle del Prof Martín Lagos s/n Madrid 28040 Spain

Table 5: List of Investigators

Name Investigators	Name and address investigation sites
Dr. Manish Parikh *(Co-Principal Investigator of the study)* [redacted]	New York Presbyterian - Columbia University Irving Medical Center 630 West 168th Street, New York, NY 10032 USA
Prof. John Messenger [redacted]	University of Colorado Hospital 12605 E 16th Ave, Aurora, CO 80045 USA
Dr. Frédéric De Vroey [redacted]	Grand Hôpital de Charleroi Saint-Joseph Rue Marguerite Depasse 6, Charleroi, 6060 Belgium
Prof. Haim Danenberg [redacted]	Hadassah Medical Center שכונת, Jerusalem Israël

Table 6: Third parties/other institutions involved in the Clinical study

Name and address other Institution(s)
CRO: TRIUM Baron Opsomerlaan 32 2500 Lier Belgium

Appendix II. List of Monitors/Clinical Scientists/Clinical Study Manager

Update of this list can be provided to the Investigational sites under separate cover.

Table 7: List of Monitors/Clinical Scientists

Name Monitors/Clinical Scientists	Contact Information of Monitors/Clinical Scientists
[redacted] Clinical Trial Manager	Best, The Netherlands [redacted]
[redacted] Clinical Scientist	Boston, MA, USA [redacted]
[redacted] Clinical Scientist	Boston, MA, USA [redacted]
[redacted] Clinical Scientist	Denver, CO, USA [redacted]

Table 8: List of Clinical Study Manager

Name Clinical Study Manager	Contact Information of Study Manager
[redacted] Clinical Trial Manager Emergency contact	Best, The Netherlands [redacted]