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## Complex Large-Bore Radial Percutaneous Coronary Intervention: Design and Rationale of the COLOR trial

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## Complex Large-Bore Radial Percutaneous Coronary Intervention: Design and Rationale of the COLOR trial

Thomas A. Meijers MD<sup>a\*</sup>, Adel Aminian MD<sup>b\*</sup>, Koen Teeuwen MD, PhD<sup>c</sup>, Marleen van Wely MD<sup>d</sup>, Thomas Schmitz MD, PhD<sup>e</sup>, Maurits T. Dirksen MD, PhD<sup>f</sup>, René J. van der Schaaf MD, PhD<sup>g</sup>, Juan F. Iglesias MD, PhD<sup>h</sup>, Pierfrancesco Agostoni MD, PhD<sup>i</sup>, Joseph Dens MD, PhD<sup>j</sup>, Paul Knaapen MD, PhD<sup>k</sup>, Sudhir Rathore MD, FRCP<sup>l</sup>, Jan Paul Ottervanger MD, PhD<sup>a</sup>, Jan Henk E. Dambrink MD, PhD<sup>a</sup>, Vincent Roolvink MD, PhD<sup>a</sup>, A.T. Marcel Gosselink MD, PhD<sup>a</sup>, Recinus S. Hermanides MD, PhD<sup>a</sup>, Niels van Royen MD, PhD<sup>d</sup>, Maarten A.H. van Leeuwen MD, PhD<sup>a</sup>

\* Both authors contributed equally.

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### Departments and institutions

<sup>a</sup> Department of Cardiology, Isala Heart Center, Zwolle, the Netherlands

<sup>b</sup> Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium

<sup>c</sup> Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

<sup>d</sup> Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

<sup>e</sup> Department of Cardiology, Elisabeth Krankenhaus, Essen, Germany

<sup>f</sup> Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands

<sup>g</sup> Department of Cardiology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the Netherlands

<sup>h</sup> Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

<sup>i</sup> Department of Cardiology, ZNA Middelheim, Antwerp, the Netherlands

<sup>j</sup> Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium

<sup>k</sup> Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands

<sup>l</sup> Department of Cardiology, Frimley Health NHS Foundation Trust, Surrey, United Kingdom

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### Conflict of interest

Maarten A.H. van Leeuwen, Adel Aminian and Juan F. Iglesias are consultants for Terumo corp., Juan F. Iglesias and Thomas Schmitz have received honoraria/speakers fee for Terumo corp., the other authors have no conflicts of interest to declare.

### Clinical trial registration

ClinicalTrials.gov identifier: NCT03846752.

### Address for correspondence

dr. M.A.H. van Leeuwen, Isala Heart Center, Dr. van Heesweg 2, 8025 AB Zwolle, The Netherlands. Email: m.a.h.van.leeuwen@isala.nl

## **Abstract**

### Introduction

The radial artery has become the standard access site for percutaneous coronary intervention (PCI) in stable coronary artery disease and acute coronary syndrome, because of less access site related bleeding complications. Patients with complex coronary lesions are underrepresented in randomized trials comparing radial with femoral access with regard to safety and efficacy. The femoral artery is currently the most applied access site in patients with complex coronary lesions, especially when large bore guiding catheters are required. With slender technology, transradial PCI may be increasingly applied in patients with complex coronary lesions when large bore guiding catheters are mandatory and might be a safer alternative as compared to the transfemoral approach.

### Methods and analysis

A total of 388 patients undergoing complex PCI will be randomized to radial 7 French access with Terumo Glidesheath Slender (Terumo Corp., Japan) or femoral 7 French access as comparator. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Procedural success and major adverse cardiovascular events up to 1 month will also be compared between both groups.

### Ethics and dissemination

Ethical approval for the study was granted by the local Ethics Committee at each recruiting center. The trial outcomes will be published in peer-reviewed journals of the concerned literature. The COLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

### **Strengths and limitations of this study**

- First randomized controlled trial comparing radial and femoral access for large bore complex PCI
- Patient enrollment at high-volume centers by operators with ample experience in complex PCI both through femoral and radial access
- Clinical Event Committee adjudicated primary endpoint
- First study assessing extremity dysfunction after complex large bore PCI
- May change daily clinical practice.

### **Keywords**

Complex percutaneous coronary intervention - Chronic total occlusion - Radial access - Femoral access - Slender

### **Abbreviations**

PCI = percutaneous coronary intervention

CTO = chronic total occlusion

CABG = coronary artery bypass grafting

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

MACE = major adverse cardiovascular events

AE = adverse event

SAE = serious adverse event

TR= transradial

TRA= transradial access

1  
2  
3 TF = transfemoral  
4 TFA = transfemoral access  
5 Fr = French  
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## Background

The radial artery has become the standard access site for percutaneous coronary interventions (PCI), driven not only by lower rates of major bleeding and vascular complications, but also by reduced mortality in patients presenting with acute coronary syndrome (ACS) (1–3). This has led the 2018 ESC/EACTS Guidelines on myocardial revascularization to recommend transradial access (TRA) over transfemoral access (TFA) as a class Ia indication in ACS patients undergoing invasive management (4). In patients with stable coronary artery disease, several small randomized trials comparing radial and femoral access have shown significantly less bleeding in favor of radial access but no mortality benefit (5–7). Of note, patients with complex coronary lesions were not included in these trials or not specifically described. PCI of chronic total occlusions (CTO), left main disease, heavily calcified or complex bifurcation lesions often require the use of large-bore guiding catheters (7 Fr or larger inner diameter). Indeed, large-bore guiding catheters provide more back-up and stability in addition to better materials' compatibility, leading to higher procedural success rates in more complex lesions (8,9). Because of potential radial artery-sheath mismatch, spasms or back-up problems, the femoral artery is still the most applied access site for complex PCI (10,11). In return, TFA with increased sheath size is associated with bleeding and vascular complications and adverse clinical outcome, including myocardial infarction (MI), stroke and death (12,13). The recent availability of modern slender technology, such as the thin-walled radial introducer sheath (Glidesheath Slender®, Terumo Corp., Japan), has the potential to expand the use of TRA for complex PCI. As compared to the average outer diameter of a standard sheath, the outer diameter of these slender sheaths has been reduced by approximately 1 Fr while maintaining the inner-diameter equivalent. In a prospective single-arm study it was recently shown that complex TR PCI with a 7 Fr Glidesheath Slender is safe and effective (14). Several observational studies have been published describing feasibility of large bore TRA for PCI of CTO's, left main disease, heavily calcified lesions and complex bifurcations without affecting procedural success rates (9,11,15–18). However, randomized data comparing TRA and TFA for percutaneous treatment of complex coronary lesions are lacking. Therefore, we have designed a randomized study, comparing the safety and efficacy of TRA and TFA for complex PCI using large-bore guiding catheters.

## Methods

### *Study design*

The Complex Large-Bore Radial PCI (COLOR) trial is an investigator-initiated international multi-center study with a prospective, randomized controlled design. Participating centers are the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-Krankenhaus (Essen, Germany), NorthWest Clinics (Alkmaar, the Netherlands), Onze Lieve Vrouwe Gasthuis Hospital (Amsterdam, the Netherlands), Centre Hospitalier Universitaire de Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-Limburg (Genk, Belgium), VU University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United Kingdom).

### *Trial organization*

The trial is approved by the appropriate ethics review board at each clinical site. Written informed consent will be obtained from all patients before enrollment. The trial was designed in accordance with the declaration of Helsinki. All data will be collected in an electronic data capturing system, the eDREAM (electronic case record form Diagnostic REsearch And Management). Diagram BV, Zwolle, the Netherlands will be responsible for overall trial and data management, as well as monitoring of the study. Evaluation of serious adverse events is

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3 being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical  
4 Events Committee (CEC) will review and adjudicate all end-point related adverse events. The  
5 COLOR trial has been administered in the ClinicalTrials.gov database, reference number:  
6 NCT03846752.  
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### 8 9 *Objectives*

10 The primary objective of this study is to investigate whether TR PCI is superior to TF PCI in  
11 complex coronary lesions with large-bore guiding catheters with respect to clinically relevant  
12 access site related bleeding and/or vascular complications.  
13

14 As secondary objectives, TR and TF large-bore access will be compared with regard to  
15 procedural success, procedural time, fluoroscopy time, contrast use, crossover rates, major  
16 adverse cardiovascular events (MACE) and non-access site related bleeding or vascular  
17 complications for complex PCI.  
18

19 For exploratory purposes extremity dysfunction and discomfort will be compared between TR  
20 and TF treated patients for complex PCI with large-bore guiding catheters.  
21  
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### 23 24 *Inclusion (figure 1)*

25 All patients of 18 years or older, presenting with stable coronary artery disease, unstable  
26 angina or non-ST elevation myocardial infarction and planned for complex PCI of CTO  
27 (defined as lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion  
28 duration of  $\geq 3$  months), left main, complex bifurcation or heavy calcification, in whom the  
29 operator anticipates that a 7 Fr guiding catheter is indicated, are screened for inclusion.  
30 Patients with ST elevation myocardial infarction or cardiogenic shock will be excluded.  
31 Patients with contraindications for femoral or radial access, such as occlusive peripheral  
32 artery disease, known severe spasm or known anatomical variants prohibiting radial or  
33 femoral access on both sides will be excluded as well.  
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### 36 37 *Randomization*

38 After providing written informed consent, eligible subjects are randomly assigned to receive  
39 one of the two study treatments in a 1:1 ratio. Treatment assignments are performed centrally  
40 through a dedicated website as part of the electronic Case Report Form (eCRF) according to a  
41 computer-generated random schedule in random permuted blocks with stratification by site  
42 (19). There will be no blinding of the randomization assignment.  
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### 45 46 *Endpoints*

47 Clinically relevant access site related bleeding or vascular complication requiring intervention  
48 of the randomized access site during hospitalization is defined as primary endpoint. Bleeding  
49 will be classified according to the Bleeding Academic Research Consortium (BARC) criteria  
50 (20), and considered clinically relevant when the score is  $\geq 2$  (CEC adjudicated)(21). Severity  
51 and type of intervention of vascular complications is specified in the CEC manual (Appendix  
52 I).

53 Secondary safety and efficacy endpoints are:

- 54 - Procedural success (defined as angiographic success without in-hospital MACE), procedural  
55 time, fluoroscopy time, contrast use and crossover rate (crossover is defined as conversion  
56 from TF to TR or vice versa; conversion to contralateral TR or TF access site is not  
57 considered crossover).
- 58 - Clinically relevant BARC bleedings or vascular complications (requiring intervention) that  
59 are not related to the randomized access (CEC adjudicated)  
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3 - MACE, defined as composite of death, MI and repeat revascularization, during  
4 hospitalization and at 1 month (CEC adjudicated)  
5

#### 6 *Index percutaneous coronary intervention and hospitalization*

7 Radial access will be performed according to the local protocol, using direct needle technique  
8 or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A  
9 standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial  
10 sheath placement. Femoral access will be performed using direct needle technique, followed  
11 by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will  
12 be left to the operator's discretion. A bolus of unfractionated heparin will be given after  
13 sheath placement, adapted to the patient's body weight. Activated clotting time (ACT)  
14 measurements will be performed during the procedure according to local protocol. Additional  
15 arterial access will be left to the discretion of the operator, i.e. in case of double arterial access  
16 for hybrid CTO treatment. PCI will be performed according to standard procedures with  
17 modern drug eluting stents. The applied technique for complex PCI will be left to the  
18 discretion of the operator. Patent hemostasis after radial access with the reverse Barbeau test  
19 is highly recommended (22). The type of femoral artery hemostasis will be left to the  
20 discretion of the treating interventional cardiologist; however the application of a closure  
21 device is advocated. The visual analogue scale (VAS) will be used to assess post-procedural  
22 pain of the access site(s). Before discharge the access site(s) will be checked for bleeding and  
23 vascular complications. Radial artery patency will be checked with the reverse Barbeau test  
24 (22). Additional ultrasound or doppler will be performed in those patients with suspected  
25 radial or femoral occlusion or the presence of other vascular complications.  
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#### 30 *Extremity dysfunction*

31 Two validated questionnaires will be used to assess the occurrence of upper and lower  
32 extremity dysfunction. Upper extremity function will be measured with the QuickDASH  
33 (Quick Disabilities of Arm, Shoulder and Hand) score (23) measured at baseline (before PCI)  
34 and at 1 month follow-up. Lower extremity function will be measured with the LEFS (Lower  
35 Extremity Functional Scale) (24). Both questionnaires are valid, reliable and responsive to  
36 monitor and assess pain and function of the extremities.  
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#### 40 *Follow-up*

41 Follow-up will be performed 1 month after index procedure discharge by either phone call or  
42 outpatient clinic visit. MACE and access site bleeding or vascular complications will be  
43 documented. Extremity function and discomfort will be assessed, using the aforementioned  
44 scores. Adverse Events (AE's) will be monitored from inclusion to one-month follow-up and  
45 will be assessed by an independent DSMB, composed of two experienced cardiologists and  
46 one statistician, reviewing patient safety and study integrity.  
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#### 49 *Sample size calculation and statistics*

50 Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the  
51 proportion of access site related bleeding or vascular complication to be 3.5% with radial  
52 access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1)  
53 will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients  
54 will be needed. Data will be analyzed according to the intention-to-treat analysis. All  
55 statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically  
56 significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago,  
57 Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-  
58 Square test will also be used for our secondary objectives with binary outcomes. For our  
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3 secondary objectives with continuous variables we will use the Student's t-test (normally  
4 distributed) or the Mann-Whitney U test (non-normally distributed). Statistical analysis will  
5 be performed by an independent contract research organization (Diagram BV, Zwolle, the  
6 Netherlands).  
7

### 8 *Patient and Public Involvement*

9 No patients were involved in the development of the research question or design of this study.  
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### 12 *Ethics and dissemination*

13 Ethical approval for the study was granted by the local Ethics Committee at each recruiting  
14 center. The trial outcomes will be published in peer-reviewed journals of the concerned  
15 literature.  
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### 18 **Discussion**

19 TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and  
20 vascular complications compared to TFA, with even a mortality benefit in ACS patients  
21 (2,3,25,26). Randomized data in patients with stable coronary artery disease are limited and  
22 more heterogeneous, and show less beneficial effect of radial over femoral access (1,27,28).  
23 Moreover, complex coronary lesions are absent or at least not specifically described in most  
24 trials supporting current guidelines on myocardial revascularization. Currently, the femoral  
25 artery is still considered the preferred access site for complex PCI by many operators  
26 (11,16,29–31), despite the increased risk of bleeding and vascular complications, especially  
27 when large bore guiding catheters ( $\geq 7$  Fr) are required (11,32–34). During CTO-PCI, the use  
28 of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a  
29 higher procedural success rate (9,16). Large-bore guiding catheters have better materials'  
30 compatibility, especially when using guide extensions and microcatheters. The use of  
31 CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-  
32 entry technique is only possible with large-bore guiding catheters (35). When performing PCI  
33 of heavily calcified lesions with rotational atherectomy using large burr sizes, large-bore  
34 guiding catheters will be needed as well (36). Application of large-bore guiding catheters for  
35 complex PCI of left main and true bifurcations is advocated by experts, though efficacy and  
36 safety data are lacking. Limited data show comparable feasibility of TRA versus TFA for left  
37 main as well as bifurcation PCI with a tendency towards less bleeding complications(11,37).  
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43 The most important argument to refrain from TR PCI for complex coronary lesions is the  
44 limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer  
45 diameter of 2.97-3.19 mm (38). As such, the percentage of patients with a radial artery  
46 smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and  
47 between 60% up to 85% in women (39). This suggests that using a standard 7 Fr sheath for  
48 TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing  
49 the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent  
50 complication after radial access, with increasing RAO rates with increasing sheath size (40).  
51 In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO  
52 may require intervention because of extremity dysfunction or ischemia (41,42). Moreover,  
53 RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as  
54 conduit for CABG or creating a hemodialysis shunt (43). Other arguments to use the femoral  
55 artery for complex PCI have been suggested, such as improved back-up with potential higher  
56 procedural success rates and shorter procedural time and lower radiation dose. However, this  
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3 is not supported by observational data showing similar effectiveness, procedural success rates,  
4 cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).  
5

6  
7 Several technologies have been developed to facilitate large bore access through the radial  
8 artery (44). A sheathless approach for example was shown to be a feasible alternative for  
9 large bore radial access (45). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc,  
10 Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer  
11 diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr)  
12 compared with a standard 7 Fr sheath (46). However, PCI with sheathless guiding catheters  
13 requires specific experience due to the highly hydrophilic coating, and limited evidence exists  
14 regarding the true impact on RAO (47,48). Miniaturization of TR equipment can also be  
15 achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness  
16 (“slender technology”), thin-walled sheaths have reduced their outer diameter while  
17 maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the  
18 first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm,  
19 compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent  
20 prospective multicenter study has shown the feasibility and safety of using the 7 Fr  
21 Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural  
22 success and low rate of vascular complications (14).  
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26  
27 In the literature, several outcome measures have been used to evaluate access site related  
28 bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(49), the  
29 Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary  
30 arteries (GUSTO)(50) or BARC (20). Access site hematoma size has also been used as an  
31 outcome measure in studies comparing radial with femoral access. BARC bleeding  $\geq 2$  has  
32 shown to independently predict 1-year mortality and capture more clinically significant  
33 bleeding than TIMI minor/major and GUSTO moderate/severe criteria (20,21). Importantly,  
34 hematoma size alone, not meeting criteria for other bleeding outcome measures, has not  
35 shown any association with clinically relevant endpoints (51). The current trial will use the  
36 BARC bleeding score for the primary outcome measure to detect a clinically relevant  
37 difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC.  
38 Besides bleeding and vascular complications, vascular access may also have a potential effect  
39 on extremity function (52,53). Although upper extremity dysfunction is present in a small  
40 proportion of patients after TRA, it can lead to important morbidity for the affected patients  
41 (52–55). Extremity dysfunction may be more pronounced in patients with large-bore access.  
42 In addition, current literature does not provide an insight around prevalence and significance  
43 of lower extremity function after TFA (53). Therefore, we will assess the occurrence of  
44 extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be  
45 valuable information for both patients and doctors.  
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50 In conclusion, The COLOR trial is the first prospective multicenter randomized trial  
51 comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290  
52 patients are randomized. The results of this trial will provide important insights about the  
53 safety and efficacy of large-bore TRA and TFA for complex PCI, with a potential impact on  
54 daily practice.  
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## Appendix I

### *CEC manual for adjudicating bleeding and vascular complications*

#### Classification and Definition

#### **Bleeding**

##### BARC 0

No bleeding or hematoma.

##### BARC 1

Every bleeding or hematoma not meeting the criteria for BARC 2 or higher.

##### BARC 2

Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, (prolonged) hospitalization, or treatment by a health care professional. Specified for radial access and femoral access in this appendix

##### BARC 3a

Overt bleeding + Hb drop of 3-5 g/dl (1.9 – 3.1 mmol/L), or any transfusion with overt bleeding (independent of Hb)

##### BARC 3b

Overt bleeding + Hb drop >5g/dl (>3.1 mmol/L), or cardiac tamponade, or bleeding requiring surgical intervention and/or IV vasoactive agents

##### BARC 3c

Intracranial hemorrhage or intraocular bleedings

##### BARC 4

CABG related bleeding

##### BARC 5

Fatal bleeding

#### **Vascular complications**

Retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention. Specified for radial access and femoral access in this appendix

#### Radial access

##### *Specification of BARC 2 bleedings*

##### 1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital

- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

##### 2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis

- Bleeding after removal of first TR band and additional compression bandage or TR band is needed

Ongoing bleeding with first TR band and additional compression therapy is needed

- Adding 1 or 2cc of air in the first TR band due to slight oozing should not be scored as BARC 2

##### 3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

#### 4. Additional therapy

Any additional or change of therapy related to bleeding/hematoma

- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation of medical therapy (i.e. vitamin K, hematological products)
- Percutaneous intervention (i.e. coiling)

#### *Specification of vascular complications*

Vascular complications requiring intervention: percutaneous, surgical, medical

- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
- Infection (i.e. antibiotics)
- Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
- Radial artery occlusion (percutaneous intervention, heparin therapy)
- Dissection (i.e. percutaneous or surgical intervention)
- Compartment syndrome (i.e. percutaneous or surgical intervention)

#### Femoral access

##### *Specification BARC 2 bleeding*

#### 1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital
- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

#### 2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis:

- New compression therapy after removal of the first bandage, or additional compression after closure device
- Prolonging compression bandage due to slight oozing should not be scored BARC 2, when this will not lead to prolonged hospitalization (one or more days).

#### 3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, angiography or CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

#### 4. Additional therapy

Any additional or change of therapy related to bleeding/hematoma

- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation medical therapy (i.e. vitamin K, hematological products)
- Percutaneous intervention (i.e. coiling or stenting of peripheral arteries)

#### *Specification of vascular complications*

Vascular complications requiring intervention: percutaneous, surgical, medical:

- Retroperitoneal hematoma (i.e. coiling, surgery)
- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
- Infection (i.e. antibiotics)
- Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
- Femoral artery occlusion or severe stenosis (percutaneous or surgical intervention)
- Dissection (i.e. percutaneous or surgical intervention)
- Compartment syndrome (i.e. percutaneous or surgical intervention)

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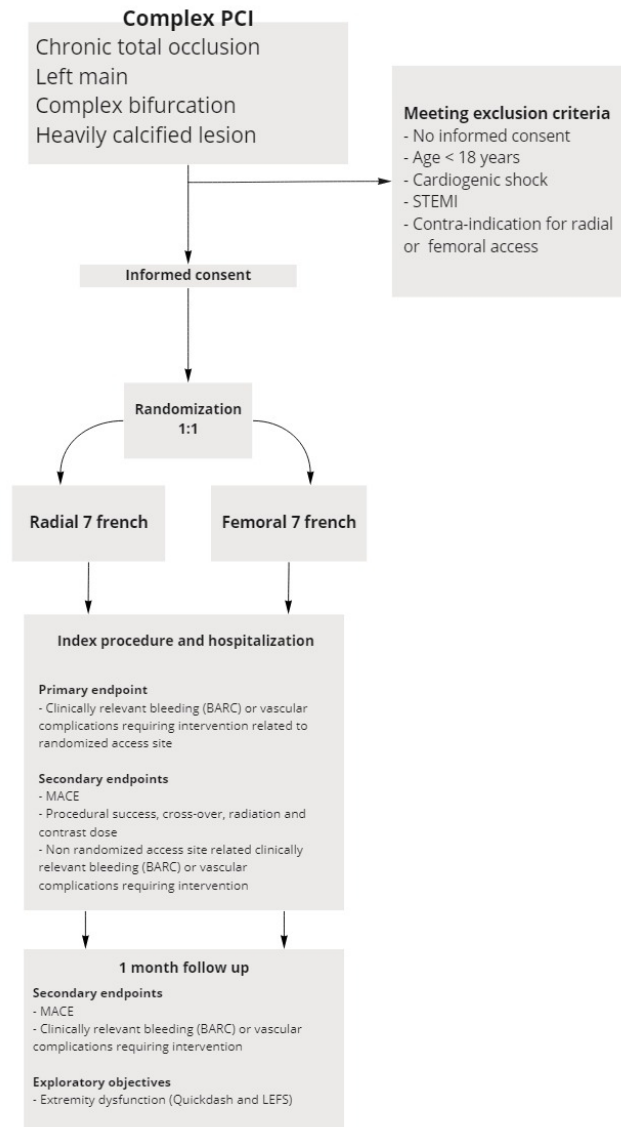
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Figure 1: enrollment flowchart of the COLOR trial

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P
	2b	All items from the World Health Organization Trial Registration Data Set	P 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	P 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1
	5b	Name and contact information for the trial sponsor	P 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P 4
	6b	Explanation for choice of comparators	P 4
Objectives	7	Specific objectives or hypotheses	P 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P 4

## Methods: Participants, interventions, and outcomes

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4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
5			P 4
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8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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13	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
14			P 6
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16		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
17			N/A
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19			
20		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
21			N/A
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25		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
26			N/A
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28	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
29			P 5
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36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
37			Fig. 1
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41	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
42			P 6
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45	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
46			P 6
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## Methods: Assignment of interventions (for controlled trials)

### Allocation:

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53	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
54			P 6
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
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7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	N/A
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	N/A
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
14			procedure for revealing a participant's allocated intervention during	
15			the trial	
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20	<b>Methods: Data collection, management, and analysis</b>			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P11-12
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27		18b	Plans to promote participant retention and complete follow-up,	P 6
28			including list of any outcome data to be collected for participants who	
29			discontinue or deviate from intervention protocols	
30	Data	19	Plans for data entry, coding, security, and storage, including any	P 6
31	management		related processes to promote data quality (eg, double data entry;	
32			range checks for data values). Reference to where details of data	
33			management procedures can be found, if not in the protocol	
34	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P 6
35	methods		Reference to where other details of the statistical analysis plan can be	
36			found, if not in the protocol	
37		20b	Methods for any additional analyses (eg, subgroup and adjusted	N/A
38			analyses)	
39		20c	Definition of analysis population relating to protocol non-adherence	N/A
40			(eg, as randomised analysis), and any statistical methods to handle	
41			missing data (eg, multiple imputation)	
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52	<b>Methods: Monitoring</b>			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	N/A
54			and reporting structure; statement of whether it is independent from	
55			the sponsor and competing interests; and reference to where further	
56			details about its charter can be found, if not in the protocol.	
57			Alternatively, an explanation of why a DMC is not needed	
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	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 7
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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# BMJ Open

## Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR trial study protocol

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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	Coronary intervention < CARDIOLOGY, CARDIOLOGY, Coronary heart disease < CARDIOLOGY

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5 2 Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR  
6 3 trial study protocol  
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9 6 Thomas A. Meijers MD<sup>a\*</sup>, Adel Aminian MD<sup>b\*</sup>, Koen Teeuwen MD, PhD<sup>c</sup>, Marleen van  
10 7 Wely MD<sup>d</sup>, Thomas Schmitz MD, PhD<sup>e</sup>, Maurits T. Dirksen MD, PhD<sup>f</sup>, René J. van der  
11 8 Schaaf MD, PhD<sup>g</sup>, Juan F. Iglesias MD, PhD<sup>h</sup>, Pierfrancesco Agostoni MD, PhD<sup>i</sup>, Joseph  
12 9 Dens MD, PhD<sup>j</sup>, Paul Knaapen MD, PhD<sup>k</sup>, Sudhir Rathore MD, FRCP<sup>l</sup>, Jan Paul Ottervanger  
13 10 MD, PhD<sup>a</sup>, Jan Henk E. Dambrink MD, PhD<sup>a</sup> Vincent Roolvink MD, PhD<sup>a</sup>, A.T. Marcel  
14 11 Gosselink MD, PhD<sup>a</sup>, Renicus S. Hermanides MD, PhD<sup>a</sup>, Niels van Royen MD, PhD<sup>d</sup>,  
15 12 Maarten A.H. van Leeuwen MD, PhD<sup>a</sup>

16 13  
17 14  
18 14 \* Both authors contributed equally.  
19 15

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22 18 Departments and institutions

23 19 <sup>a</sup> Department of Cardiology, Isala Heart Center, Zwolle, the Netherlands

24 20 <sup>b</sup> Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi,  
25 21 Belgium

26 22 <sup>c</sup> Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

27 23 <sup>d</sup> Department of Cardiology, Radboud University Medical Center, Nijmegen, the  
28 24 Netherlands

29 25 <sup>e</sup> Department of Cardiology, Elisabeth Krankenhaus, Essen, Germany

30 26 <sup>f</sup> Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands

31 27 <sup>g</sup> Department of Cardiology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the  
32 28 Netherlands

33 29 <sup>h</sup> Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

34 30 <sup>i</sup> Department of Cardiology, ZNA Middelheim, Antwerp, the Netherlands

35 31 <sup>j</sup> Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium

36 32 <sup>k</sup> Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands

37 33 <sup>l</sup> Department of Cardiology, Frimley Health NHS Foundation Trust, Surrey, United  
38 34 Kingdom  
39 35

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51 47

52 48 Address for correspondence

53 49 dr. M.A.H. van Leeuwen, Isala Heart Center, Dr. van Heesweg 2, 8025 AB Zwolle, The  
54 50 Netherlands. Email: m.a.h.van.leeuwen@isala.nl  
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**Abstract****Introduction**

The radial artery has become the standard access site for percutaneous coronary intervention (PCI) in stable coronary artery disease and acute coronary syndrome, because of less access site related bleeding complications. Patients with complex coronary lesions are underrepresented in randomized trials comparing radial with femoral access with regard to safety and efficacy. The femoral artery is currently the most applied access site in patients with complex coronary lesions, especially when large bore guiding catheters are required. With slender technology, transradial PCI may be increasingly applied in patients with complex coronary lesions when large bore guiding catheters are mandatory and might be a safer alternative as compared to the transfemoral approach.

**Methods and analysis**

A total of 388 patients undergoing complex PCI will be randomized to radial 7 French access with Terumo Glidesheath Slender (Terumo Corp., Japan) or femoral 7 French access as comparator. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Procedural success and major adverse cardiovascular events up to 1 month will also be compared between both groups.

**Ethics and dissemination**

Ethical approval for the study was granted by the local Ethics Committee at each recruiting center. The trial outcomes will be published in peer-reviewed journals of the concerned literature. The COLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

**Strengths and limitations of this study**

- The design as a randomized 1:1 open label study (radial 7 Fr versus femoral 7) and the vast experience with complex PCI of the participating centers
- Clinical Event Committee adjudicated and clinically relevant primary endpoint
- First study assessing extremity dysfunction after complex large bore PCI
- As a limitation, bias could be derived from the unblinded nature of the study for the treating interventional cardiologist
- As a limitation, use of secondary access sites for hybrid approach of CTO lesions will influence efficacy outcomes, although it will not influence the primary endpoint.

**Keywords**

Complex percutaneous coronary intervention - Chronic total occlusion - Radial access - Femoral access - Slender

**Abbreviations**

PCI = percutaneous coronary intervention

CTO = chronic total occlusion

CABG = coronary artery bypass grafting

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

MACE = major adverse cardiovascular events

AE = adverse event

SAE = serious adverse event

TR= transradial

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2  
3 101 TRA= transradial access  
4 102 TF = transfemoral  
5 103 TFA = transfemoral access  
6 104 Fr = French  
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For peer review only

## 151 **Background**

152 The radial artery has become the standard access site for percutaneous coronary interventions  
153 (PCI), driven not only by lower rates of major bleeding and vascular complications, but also  
154 by reduced mortality in patients presenting with acute coronary syndrome (ACS) (1–3). This  
155 has led the 2018 ESC/EACTS Guidelines on myocardial revascularization to recommend  
156 transradial access (TRA) over transfemoral access (TFA) as a class Ia indication in ACS  
157 patients undergoing invasive management (4). In patients with stable coronary artery disease,  
158 several small randomized trials comparing radial and femoral access have shown significantly  
159 less bleeding in favor of radial access but no mortality benefit (5–7). Of note, patients with  
160 complex coronary lesions were not included in these trials or not specifically described. PCI  
161 of chronic total occlusions (CTO), left main disease, heavily calcified or complex bifurcation  
162 lesions often require the use of large-bore guiding catheters (7 Fr or larger inner diameter).  
163 Indeed, large-bore guiding catheters provide more back-up and stability in addition to better  
164 materials' compatibility, leading to higher procedural success rates in more complex lesions  
165 (8,9). Because of potential radial artery-sheath mismatch, spasms or back-up problems, the  
166 femoral artery is still the most applied access site for complex PCI (10,11). In return, TFA  
167 with increased sheath size is associated with bleeding and vascular complications and adverse  
168 clinical outcome, including myocardial infarction (MI), stroke and death (12,13). The recent  
169 availability of modern slender technology, such as the thin-walled radial introducer sheath  
170 (Glidesheath Slender®, Terumo Corp., Japan), has the potential to expand the use of TRA for  
171 complex PCI. As compared to the average outer diameter of a standard sheath, the outer  
172 diameter of these slender sheaths has been reduced by approximately 1 Fr while maintaining  
173 the inner-diameter equivalent. In a prospective single-arm study it was recently shown that  
174 complex transradial (TR) PCI with a 7 Fr Glidesheath Slender is safe and effective (14).  
175 Several observational studies have been published describing feasibility of large bore TRA for  
176 PCI of CTO's, left main disease, heavily calcified lesions and complex bifurcations without  
177 affecting procedural success rates (9,11,15–18). However, randomized data comparing TRA  
178 and TFA for percutaneous treatment of complex coronary lesions are lacking. Therefore, we  
179 have designed a randomized study, comparing the safety and efficacy of TRA and TFA for  
180 complex PCI using large-bore guiding catheters.

## 181 **Methods**

### 182 *Study design*

183 The Complex Large-Bore Radial PCI (COLOR) trial is an investigator-initiated international  
184 multi-center study with a prospective, randomized controlled design. Participating centers are  
185 the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the  
186 Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-  
187 Krankenhaus (Essen, Germany), NorthWest Clinics (Alkmaar, the Netherlands), Onze Lieve  
188 Vrouwe Gasthuis Hospital (Amsterdam, the Netherlands), Centre Hospitalier Universitaire de  
189 Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-  
190 Limburg (Genk, Belgium), Geneva University Hospital (Geneva, Switzerland), VU  
191 University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United  
192 Kingdom). All centers have been selected based on their high volumes and experience with  
193 complex PCI and large bore access. For CTO, each center has a dedicated program for an  
194 average of 6 years, with 1-3 dedicated CTO operators and an average of 110 procedures per  
195 year (spreading from 55 to 200 procedures per year). 83% of CTO procedures are done with  
196 dual arterial access, with biradial access in 20%, bifemoral access in 24% and radial/femoral  
197 (hybrid) access in the remaining 49% of cases. Large bore access is used in 89% of cases. For  
198 non-CTO complex PCI, the participating centers have a dedicated program for an average of  
199 11 years, performing an average of 245 procedures per year with 3-5 complex PCI operators.

201 76% of these cases are done with TRA and 24% with TFA. Large bore access is used in 62%  
202 of all complex non CTO PCI.

203

### 204 *Trial organization*

205 The trial is approved by the appropriate ethics review board at each clinical site. Written  
206 informed consent will be obtained from all patients before enrollment. The trial was designed  
207 in accordance with the declaration of Helsinki. All data will be collected in an electronic data  
208 capturing system, the eDREAM (electronic case record form Diagnostic REsearch And  
209 Management). Diagram BV, Zwolle, the Netherlands will be responsible for overall trial and  
210 data management, as well as monitoring of the study. Evaluation of serious adverse events is  
211 being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical  
212 Events Committee (CEC) will review and adjudicate all end-point related adverse events. The  
213 COLOR trial has been administered in the ClinicalTrials.gov database, reference number:  
214 NCT03846752.

215

### 216 *Objectives*

217 The primary objective of this study is to investigate whether TR PCI is superior to  
218 transfemoral (TF) PCI in complex coronary lesions with large-bore guiding catheters with  
219 respect to clinically relevant access site related bleeding and/or vascular complications.

220

221 As secondary objectives, TR and TF large-bore access will be compared with regard to  
222 procedural success, procedural time, fluoroscopy time, contrast use, crossover rates, major  
223 adverse cardiovascular events (MACE) and non-access site related bleeding or vascular  
224 complications for complex PCI.

225

226 For exploratory purposes extremity dysfunction and discomfort will be compared between TR  
227 and TF treated patients for complex PCI with large-bore guiding catheters.

228

### 229 *Inclusion*

230 All patients of 18 years or older, presenting with stable coronary artery disease, unstable  
231 angina or non-ST elevation myocardial infarction and planned for complex PCI of CTO  
232 (defined as lesion exhibiting TIMI 0-1 flow in a native coronary artery with an occlusion  
233 duration of  $\geq 3$  months), left main, complex bifurcation or heavy calcification, in whom the  
234 operator anticipates that a 7 Fr guiding catheter is indicated, are screened for inclusion.  
235 Patients with ST elevation myocardial infarction or cardiogenic shock will be excluded.  
236 Patients with contraindications for femoral or radial access, such as occlusive peripheral  
237 artery disease, known severe spasm or known anatomical variants prohibiting radial or  
238 femoral access on both sides will be excluded as well. See also Figure 1 for graphic  
239 representation of study inclusion.

240

### 241 *Randomization*

242 After providing written informed consent, eligible subjects are randomly assigned to receive  
243 one of the two study treatments in a 1:1 ratio. Treatment assignments are performed centrally  
244 through a dedicated website as part of the electronic Case Report Form (eCRF) according to a  
245 computer-generated random schedule in random permuted blocks with stratification by site  
246 (19). There will be no blinding of the randomization assignment.

247

### 248 *Endpoints*

249 Clinically relevant access site related bleeding or vascular complication requiring intervention  
250 of the randomized access site during hospitalization is defined as primary endpoint. Bleeding

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3 251 will be classified according to the Bleeding Academic Research Consortium (BARC) criteria  
4 252 (20), and considered clinically relevant when the score is  $\geq 2$  (CEC adjudicated)(21). Severity  
5 253 and type of intervention of vascular complications is specified in the CEC manual  
6 254 (Supplementary file I).

7 255 Secondary safety and efficacy endpoints are:

- 8 256 - Procedural success (defined as successful PCI of the target lesion with a residual stenosis of  
9 257 less than 20%, without in-hospital MACE), procedural time, fluoroscopy time, contrast use  
10 258 and crossover rate (crossover is defined as conversion from TF to TR or vice versa;  
11 259 conversion to contralateral TR or TF access site is not considered crossover).  
12 260 - Clinically relevant BARC bleedings or vascular complications (requiring intervention) that  
13 261 are not related to the randomized access (CEC adjudicated)  
14 262 - MACE, defined as composite of death, MI and repeat revascularization, during  
15 263 hospitalization and at 1 month (CEC adjudicated)  
16 264

### 17 265 *Index percutaneous coronary intervention and hospitalization*

18 266 Radial access will be performed according to the local protocol, using direct needle technique  
19 267 or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A  
20 268 standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial  
21 269 sheath placement. Femoral access will be performed using direct needle technique, followed  
22 270 by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will  
23 271 be left to the operator's discretion. A bolus of unfractionated heparin will be given after  
24 272 sheath placement, adapted to the patient's body weight. Activated clotting time (ACT)  
25 273 measurements will be performed during the procedure according to local protocol. Additional  
26 274 arterial access will be left to the discretion of the operator, i.e. in case of double arterial access  
27 275 for hybrid CTO treatment. PCI will be performed according to standard procedures with  
28 276 modern drug eluting stents. The applied technique for complex PCI will be left to the  
29 277 discretion of the operator. Patent hemostasis after radial access with the reverse Barbeau test  
30 278 is highly recommended (22). The type of femoral artery hemostasis will be left to the  
31 279 discretion of the treating interventional cardiologist; however the application of a closure  
32 280 device is advocated. The visual analogue scale (VAS) will be used to assess post-procedural  
33 281 pain of the access site(s). Before discharge the access site(s) will be checked for bleeding and  
34 282 vascular complications. Radial artery patency will be checked with the reverse Barbeau test  
35 283 (22). Additional ultrasound or doppler will be performed in those patients with suspected  
36 284 radial or femoral occlusion or the presence of other vascular complications.  
37 285

### 38 286 *Extremity dysfunction*

39 287 Two validated questionnaires will be used to assess the occurrence of upper and lower  
40 288 extremity dysfunction. Upper extremity function will be measured with the QuickDASH  
41 289 (Quick Disabilities of Arm, Shoulder and Hand) score (23) measured at baseline (before PCI)  
42 290 and at 1 month follow-up. Lower extremity function will be measured with the LEFS (Lower  
43 291 Extremity Functional Scale) (24). Both questionnaires are valid, reliable and responsive to  
44 292 monitor and assess pain and function of the extremities.  
45 293

### 46 294 *Follow-up*

47 295 Follow-up will be performed 1 month after index procedure discharge by either phone call or  
48 296 outpatient clinic visit. MACE and access site bleeding or vascular complications will be  
49 297 documented. Extremity function and discomfort will be assessed, using the aforementioned  
50 298 scores. Adverse Events (AE's) will be monitored from inclusion to one-month follow-up and  
51 299 will be assessed by an independent DSMB, composed of two experienced cardiologists and  
52 300 one statistician, reviewing patient safety and study integrity.

### 301 *Sample size calculation and statistics*

302 Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the  
303 proportion of access site related bleeding or vascular complication to be 3.5% with radial  
304 access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1)  
305 will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients  
306 will be needed. Data will be analyzed according to the intention-to-treat analysis. All  
307 statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically  
308 significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago,  
309 Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-  
310 Square test will also be used for our secondary objectives with binary outcomes. For our  
311 secondary objectives with continuous variables we will use the Student's t-test (normally  
312 distributed) or the Mann-Whitney U test (non-normally distributed). A pre-specified battery  
313 of sub-group analyses will be performed as well, including several independent risk factors  
314 for clinically significant bleeding and vascular complications. For demographics and baseline  
315 characteristics, these sub-groups consist of age  $\geq 75$  years, female sex, low body weight  
316 (Body Mass Index  $< 18.5$ ), hypertension, peripheral arterial disease, left ventricular ejection  
317 fraction  $< 30\%$ , severe renal dysfunction (Modification of Diet in Renal Disease (MDRD)  $<$   
318  $30\text{ml}/1.73\text{m}^2$ ) and pre-existent anemia (hemoglobin  $< 6.8$  mmol/l) (13,25–30). For procedural  
319 characteristics, sub-group analyses will be performed for use of secondary access site,  
320 ultrasound guided puncture, ACT  $> 150$  seconds right before sheath removal and use of  
321 closure device (31–34). In addition, primary and secondary endpoints will be specified for the  
322 entire population as well as for each group of complex lesions separately (CTO, left main  
323 disease, complex bifurcation and heavy calcification). Statistical analysis will be performed  
324 by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

### 325 *Ethics and dissemination*

326 Ethical approval for the study was granted by the local Ethics Committee ('Medisch Ethische  
327 Toetsing Commissie Isala Zwolle' for all Dutch sites, 'Commissie voor medische ethiek  
328 ZNA' for ZNA Middelheim, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for  
329 Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi – ISPPC' for Centre Hospitalier  
330 Universitaire de Charleroi, 'Commission cantonale d'éthique de la recherche CCER –  
331 Republique et Canton de Geneve' for Geneva University Hospital, 'Ethik Kommission de  
332 Ärztekammer Nordrhein' for Elisabeth-Krankenhaus and 'Riverside Research Ethics  
333 Committee' for Frimley NHS) after reviewing the protocol, site-  
334 specific informed consentforms (local language and English versions, see also supplementary  
335 file II), participant education and recruitment materials, other requested documents and any  
336 subsequent modifications. Trained research nurses or physicians directly involved in the trial  
337 will introduce the trial to eligible patients. Patients will also receive patient information  
338 form (PIF). The research nurse or physician will discuss the trial with patients in light of the  
339 information provided in the PIF and will obtain written consent from patients willing to  
340 participate in the trial. No reimbursement is provided to study participants. All study-related  
341 information will be stored securely at the study site. All participant information will be stored  
342 in locked file cabinets in areas with limited access. All reports, data collection, process, and  
343 administrative forms will be identified by a coded identification-number only to maintain  
344 participant confidentiality. All records that contain names or other personal identifiers, such  
345 as locator forms and informed consent forms, will be stored separately from study records  
346 identified by code number. All local databases will be secured with password-protected  
347 access systems. Safety and progress reports to the EC's will be made at least annually and  
348 within three months of study termination or completion. These reports will include the total  
349 number of participants enrolled and summaries of the DSMB. Any modifications to the  
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3 351 protocol which may have impact on the conduct of the study, potential benefit of the patient  
4 352 or may affect patient safety, including changes of study objectives, study design, patient  
5 353 population, sample sizes, study procedures, or significant administrative aspects will require a  
6 354 formal amendment to the protocol. Such amendment will have to be approved by the Ethics  
7 355 Committee prior to implementation. The study findings will be disseminated via publication  
8 356 of peer-reviewed manuscripts and presentations at international conferences, as well as  
9 357 through media publications. Results will be published irrespective of whether the findings are  
10 358 positive or negative.

11 359

12 360 *Patient and Public Involvement*

13 361 No patient involved

14 362

15 363 **Discussion**

16 364 TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and  
17 365 vascular complications compared to TFA, with even a mortality benefit in ACS patients  
18 366 (2,3,35,36). Randomized data in patients with stable coronary artery disease are limited and  
19 367 more heterogeneous, and show less beneficial effect of radial over femoral access (1,37,38).  
20 368 Moreover, complex coronary lesions are absent or at least not specifically described in most  
21 369 trials supporting current guidelines on myocardial revascularization. Currently, the femoral  
22 370 artery is still considered the preferred access site for complex PCI by many operators  
23 371 (11,16,39–41), despite the increased risk of bleeding and vascular complications, especially  
24 372 when large bore guiding catheters ( $\geq 7$  Fr) are required (11,42–45). During CTO-PCI, the use  
25 373 of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a  
26 374 higher procedural success rate (9,16). Large-bore guiding catheters have better materials'  
27 375 compatibility, especially when using guide extensions and microcatheters. The use of  
28 376 CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-  
29 377 entry technique is only possible with large-bore guiding catheters (46). Although registries  
30 378 show increased temporal adoption of TRA for PCI of heavily calcified lesions with use of  
31 379 rotational atherectomy with similar procedural success rates and less bleeding, TFA is still  
32 380 used in a large proportion of these procedures, which often mandate large bore guiding  
33 381 catheters especially for accommodating larger burr sizes (47,48). Application of large-bore  
34 382 guiding catheters for complex PCI of left main and true bifurcations is advocated by experts,  
35 383 though efficacy and safety data are lacking. Limited data show comparable feasibility of TRA  
36 384 versus TFA for left main as well as bifurcation PCI with a tendency towards less bleeding  
37 385 complications (11,49–55).

38 386

39 387 The most important argument to refrain from TR PCI for complex coronary lesions is the  
40 388 limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer  
41 389 diameter of 2.97-3.19 mm (56). As such, the percentage of patients with a radial artery  
42 390 smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and  
43 391 between 60% up to 85% in women (57). This suggests that using a standard 7 Fr sheath for  
44 392 TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing  
45 393 the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent  
46 394 complication after radial access, with increasing RAO rates with increasing sheath size (58).  
47 395 In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO  
48 396 may require intervention because of extremity dysfunction or ischemia (59,60). Moreover,  
49 397 RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as  
50 398 conduit for CABG or creating a hemodialysis shunt (61). Other arguments to use the femoral  
51 399 artery for complex PCI have been suggested, such as improved back-up with potential higher

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3 400 procedural success rates and shorter procedural time and lower radiation dose. However, this  
4 401 is not supported by observational data showing similar effectiveness, procedural success rates,  
5 402 cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).  
6 403 Several technologies have been developed to facilitate large bore access through the radial  
7 404 artery (62). A sheathless approach for example was shown to be a feasible alternative for  
8 405 large bore radial access (63). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc,  
9 406 Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer  
10 407 diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr)  
11 408 compared with a standard 7 Fr sheath (64). However, PCI with sheathless guiding catheters  
12 409 requires specific experience due to the highly hydrophilic coating, and limited evidence exists  
13 410 regarding the true impact on RAO (65,66). Miniaturization of TR equipment can also be  
14 411 achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness  
15 412 (“slender technology”), thin-walled sheaths have reduced their outer diameter while  
16 413 maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the  
17 414 first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm,  
18 415 compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent  
19 416 prospective multicenter study has shown the feasibility and safety of using the 7 Fr  
20 417 Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural  
21 418 success and low rate of vascular complications (14).  
22 419

23 420 In the literature, several outcome measures have been used to evaluate access site related  
24 421 bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(67), the  
25 422 Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary  
26 423 arteries (GUSTO)(68) or BARC (20). Access site hematoma size has also been used as an  
27 424 outcome measure in studies comparing radial with femoral access. BARC bleeding  $\geq 2$  has  
28 425 shown to independently predict 1-year mortality and capture more clinically significant  
29 426 bleeding than TIMI minor/major and GUSTO moderate/severe criteria (20,21). Importantly,  
30 427 hematoma size alone, not meeting criteria for other bleeding outcome measures, has not  
31 428 shown any association with clinically relevant endpoints (69). The current trial will use the  
32 429 BARC bleeding score for the primary outcome measure to detect a clinically relevant  
33 430 difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC.  
34 431 Besides bleeding and vascular complications, vascular access may also have a potential effect  
35 432 on extremity function (70,71). Although upper extremity dysfunction is present in a small  
36 433 proportion of patients after TRA, it can lead to important morbidity for the affected patients  
37 434 (70–73). Extremity dysfunction may be more pronounced in patients with large-bore access.  
38 435 In addition, current literature does not provide an insight around prevalence and significance  
39 436 of lower extremity function after TFA (71). Therefore, we will assess the occurrence of  
40 437 extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be  
41 438 valuable information for both patients and doctors.  
42 439

43 440 In conclusion, The COLOR trial is the first prospective multicenter randomized trial  
44 441 comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290  
45 442 patients are randomized. The results of this trial will provide important insights about the  
46 443 safety and efficacy of large-bore TRA and TFA for complex PCI, with a potential impact on  
47 444 daily practice.  
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### Contributorship statement

Maarten van Leeuwen and Adel Aminian substantially contributed to conception and design of the study protocol. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely, Thomas Schmitz, Rene van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco Agostoni, Joseph Dens, Paul Knaapen, Sudhir Rathore and Maarten van Leeuwen contributed to acquisition of data. Thomas Meijers, Adel Aminian and Maarten van Leeuwen contributed to analysis of data. Thomas Meijers, Adel Aminian, Maarten van Leeuwen and Niels van Royen contributed to interpretation of data. Thomas Meijers, Adel Aminian and Maarten van Leeuwen reviewed the literature, contributed to the design and wrote the draft of the manuscript. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely, Thomas Schmitz, René van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco Agostoni, Joseph Dens, Paul Knaapen, Sudhir Rathore, Jan Paul Ottervanger, Jan Henk Dambrink, Vincent Roolvink, Marcel Gosselink, Renicus Hermanides, Niels van Royen and Maarten van Leeuwen contributed to refinement of the study protocol and approved the final manuscript.

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### 11 707 **Figure legend**

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13 709 Figure 1: Inclusion flowchart for the COLOR trial.

14 710 **Caption:** *Graphic representation of inclusion for the COLOR trial. STEMI = ST elevation*  
15 711 *myocardial infarction, BARC = Bleeding Academic Research Group, MACE = Major*  
16 712 *Adverse Cardiovascular Events.*  
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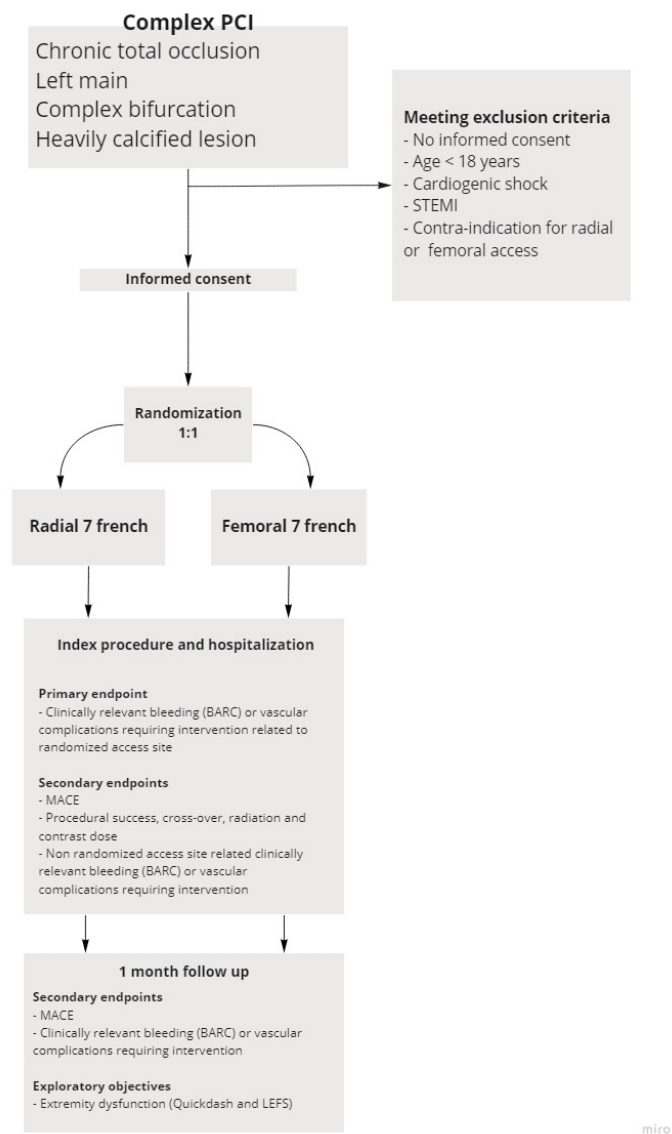


Figure 1: enrollment flowchart of the COLOR trial

300x413mm (72 x 72 DPI)

## Supplementary file I: CEC manual for adjudicating bleeding and vascular complications

### Classification and Definition

#### **Bleeding**

##### BARC 0

No bleeding or hematoma.

##### BARC 1

Every bleeding or hematoma not meeting the criteria for BARC 2 or higher.

##### BARC 2

Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, (prolonged) hospitalization, or treatment by a health care professional.

Specified for radial access and femoral access in this appendix

##### BARC 3a

Overt bleeding + Hb drop of 3-5 g/dl (1.9 – 3.1 mmol/L), or any transfusion with overt bleeding (independent of Hb)

##### BARC 3b

Overt bleeding + Hb drop >5g/dl (>3.1 mmol/L), or cardiac tamponade, or bleeding requiring surgical intervention and/or IV vasoactive agents

##### BARC 3c

Intracranial hemorrhage or intraocular bleedings

##### BARC 4

CABG related bleeding

##### BARC 5

Fatal bleeding

#### **Vascular complications**

Retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention. Specified for radial access and femoral access in this appendix

### Radial access

#### *Specification of BARC 2 bleedings*

##### 1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital

- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

##### 2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis

- Bleeding after removal of first TR band and additional compression bandage or TR band is needed

- Ongoing bleeding with first TR band and additional compression therapy is needed

- Adding 1 or 2cc of air in the first TR band due to slight oozing should not be scored as BARC 2

##### 3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as

BARC 2. This includes imaging (i.e. ultrasound, CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

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#### 4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation of medical therapy (i.e. vitamin K, hematological products)
  - Percutaneous intervention (i.e. coiling)

#### *Specification of vascular complications*

- Vascular complications requiring intervention: percutaneous, surgical, medical
- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
  - Infection (i.e. antibiotics)
  - Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
  - Radial artery occlusion (percutaneous intervention, heparin therapy)
  - Dissection (i.e. percutaneous or surgical intervention)
  - Compartment syndrome (i.e. percutaneous or surgical intervention)

#### Femoral access

#### *Specification BARC 2 bleeding*

##### 1. Prolonged hospitalization

- Any bleeding that leads to one or more extra hospitalization day(s)
- Based on standard discharge policy of hospital
  - For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

##### 2. Additional compression therapy

- Any additional compression therapy after successful primary hemostasis:
- New compression therapy after removal of the first bandage, or additional compression after closure device
  - Prolonging compression bandage due to slight oozing should not be scored BARC 2, when this will not lead to prolonged hospitalization (one or more days).

##### 3. Additional investigations

- Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, angiography or CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

##### 4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation medical therapy (i.e. vitamin K, hematological products)
  - Percutaneous intervention (i.e. coiling or stenting of peripheral arteries)

#### *Specification of vascular complications*

- Vascular complications requiring intervention: percutaneous, surgical, medical:
- Retroperitoneal hematoma (i.e. coiling, surgery)
  - (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
  - Infection (i.e. antibiotics)
  - Arteriovenous-fistula (i.e. percutaneous or surgical intervention)

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- Femoral artery occlusion or severe stenosis (percutaneous or surgical intervention)
  - Dissection (i.e. percutaneous or surgical intervention)
  - Compartment syndrome (i.e. percutaneous or surgical intervention)

For peer review only

## Supplementary file II

# Participation Information Sheet and Consent Form

Centre Number: \_\_\_\_\_ Patient Number: \_\_\_\_\_

**Study Title: COLOR study** - Comparative study of complex Percutaneous Coronary Intervention (PCI) procedures with large catheters through the radial artery or femoral artery.

**Principle Investigator:** Site specific

**Name and Address:** Site specific

**Telephone:** Site specific

**Sponsor:** ISALA Heart Centre, Zwolle, Netherlands.

## 1. Introduction

We would like to invite you to take part in this study. Participation is voluntary. If you would like to participate, we need your written consent. Before you decide whether to participate in the study or not, you should know what the study entails. Read this information carefully and ask the researcher for an explanation if you have any questions. If you would like more information, you can also consult the independent expert listed at the end of this letter. You can also discuss it with your partner, friends or family.

## 2. General information

This study was initiated by the cardiology partnership of the Isala hospital in

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3 Zwolle, and is being conducted by multiple cardiologists in the Netherlands,  
4 Belgium, Germany, Switzerland and England. The study requires 388 subjects  
5 from different countries.  
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8 All research is looked at by an independent group of people called Research Ethics  
9 Committee to protect your safety, rights, wellbeing and dignity. This study has been  
10 reviewed and given favorable opinion by the local Ethics Committee.  
11  
12

### 13 14 **3. Background of the study**

15  
16 The radial artery (artery in the arm) is smaller than the femoral artery (artery in the leg).  
17 Cardiac catheterization and PCI are already often performed through the radial artery. If  
18 the PCI procedure required a thicker catheter because the cardiologist needed more  
19 sturdiness to complete it, the groin was often used as the access site due to the larger  
20 artery. With the development of a thin-walled radial artery sheath, complex PCI  
21 procedures with thicker catheters can now also be performed through the radial artery. A  
22 complex PCI procedure through the radial artery may lead to fewer access-site  
23 complications than through the femoral artery, while providing a similar PCI result, but  
24 this has not yet been properly researched.  
25  
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31

### 32 33 **4. What your participation will entail**

34 If you wish to participate, we will first check whether both the groin and the wrist can  
35 be used for the PCI procedure.  
36

37  
38 Before the procedure, we will ask you questions regarding whether or not you can use  
39 your arms and legs properly. We will ask you the same questions again one month  
40 after the procedure. You will also be asked to complete 2 questionnaires.  
41

42  
43 If both the radial and femoral arteries can be used, we will randomly assign you,  
44 - to determine whether you will be treated through the wrist or the groin.  
45

46  
47 If you are selected for the wrist procedure, we will use the modern sheath. If you are  
48 selected for the groin procedure, we will use the standard sheath.  
49

50  
51 Aside from the potential difference in sheath, the treatment you will receive will be  
52 exactly the same as if you did not participate in the study. The procedure may  
53 sometimes require the use of a 2<sup>nd</sup> catheter. In that case, the cardiologist will  
54 determine where the access site for the second catheter will be.  
55  
56

57  
58 The examinations you receive before and after the treatment are also exactly the same  
59 as if you did not participate in the study. Those examinations include an  
60 electrocardiography (ECG), a blood test and an inspection of the access site (groin or  
wrist).

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4 The study will require the collection of your medical records for up to one month after  
5 the procedure.  
6  
7

### 8 **5. What is expected of you?**

9 For a good outcome of the study, it is important that you answer the questions during  
10 the study visit and the 1-month check-up to the best of your knowledge.  
11  
12

### 13 **6. Possible complications and other/adverse effects/complaints**

14  
15 In general, the procedure is performed using standard methods and participation in  
16 this study will not result in additional adverse effects. The materials used (including the  
17 sheaths) have been approved and are already in use for complex PCI procedures for  
18 patients who are not participating in a study. The only inconvenience you may  
19 experience is that we will contact you after one month to ask you some questions.  
20 Trans-Femoral and Trans-radial access will be performed according to the local protocol  
21 with the direct needle technique or venous cannula technique. The complications are  
22 the same as standard of care procedure and will be fully covered by the  
23 Doctor/Investigator during the discussion before consenting to the procedure.  
24 Complications that may arise from inserting and removing a sheath are:  
25  
26

- 27 -Bleeding
- 28 -Vascular problems
- 29 -Blood vessel closure
- 30
- 31
- 32
- 33
- 34
- 35

### 36 **7. Possible advantages and disadvantages**

37  
38 Before you decide to participate in the study, it is important to consider the possible  
39 advantages and disadvantages.  
40  
41

42 If you participate in the study, there is a chance that you will receive exactly the same  
43 treatment as if you were not participating. If you are selected for the treatment group  
44 with the modern sheath through the wrist, you may have a reduced chance of  
45 accesssite complications, but this has not yet been proven. PCI performed through the  
46 femoral artery can also result in a longer hospital stay.  
47  
48  
49  
50

### 51 **8. If you do not wish to participate or wish to end participation in the study**

52 You decide whether or not to participate in the study. Participation is voluntary.  
53  
54

55 If you do not wish to participate, the PCI procedure with the thicker catheter will be  
56 performed in the usual manner. This can be done through the groin or the wrist.  
57  
58

59 If you do participate, you can change your mind and withdraw at any time, even during  
60 the study. You will then receive the standard treatment again. You do not have to  
provide a reason for stopping. If the procedure has already begun, it cannot be

1  
2  
3 reversed and you will also require a follow-up check-up. The data collected up to the  
4 moment of withdrawal will be used for the study.  
5

## 6 7 **9. End of the study**

8  
9 Your participation in the study ends when:

- 11 You have had the check-up one month after the procedure;
- 12 You choose to stop;

13  
14 The researcher feels it is better for you to stop;

15  
16 The Isala cardiology partnership, the government or the supervising medical.

17  
18 The entire study is complete when all participants are finished.  
19

## 20 21 22 **10. Use and storage of your records**

23  
24 All of your records will remain confidential. To protect your privacy, your records will be  
25 given a code. Your name and other information which directly identifies you will be  
26 omitted. The records can only be traced back to you with the key to the code. Only the  
27 study doctor and research staff know which code you have. The study will only ever  
28 use your data with that code, never with your name. The key to the code will remain in  
29 possession of the study team. Reports on the study will also only use that code.  
30  
31

32  
33  
34 Some people will be allowed to access your medical and personal information. Access to  
35 your medical and personal Information will be by the study Doctor/Investigator and the  
36 research team at site. The Sponsor, representatives of the Sponsor (including the  
37 Contract Research Organisation, study monitors, auditors and project manager. Ethics  
38 committee and government agencies where permitted or required by law. This is  
39 necessary to confirm that the study has been conducted properly and reliably. - They will  
40 keep your information confidential. By signing the consent form, you agree to the  
41 collection, storage and viewing of your medical and personal records.  
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## 51 52 **11. More information on your rights with regard to data processing**

53  
54 All the information that is collected during the study is kept confidential and there are  
55 strict laws in place which safeguard the privacy of the patient at every stage. We will  
56 be using your information (samples and medical records) in order to undertake this  
57 study and we will act as the data controller for this study. This means that we are  
58 responsible for looking after your information and using it properly. Your identity and  
59 contact details will be confidential and all the data collected will be anonymized so you  
60 cannot be



1  
2  
3 identified.

4 A description of this study will be available on <http://www.ClinicalTrials.gov>, and this  
5 web site will not include information that can identify you.

6 ISALA Heart Centre, Zwolle, is the Sponsor for this study based in the Netherlands.  
7 We will be using information from your medical records in order to undertake this  
8 study and will act as the data controller for this study. This means that we are for  
9 looking after your information and using it properly. ISALA Heart Centre will keep  
10 identifiable information about you for 15 years after the study has finished. Your  
11 rights to access, change or move your information are limited, as we need to  
12 manage your information in specific ways in order for the research to be reliable and  
13 accurate. If you withdraw from the study, we will keep the information about you  
14 that we have already obtained. To safeguard your rights, we will use the minimum  
15 personally identifiable information possible.  
16  
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23 The local site will keep your name, ID number and contact details confidential and  
24 will not pass this information to ISALA Heart Centre. The local site will use this  
25 information as needed, to contact you about the research study, and make sure that  
26 relevant information about the study is recorded for you care, and to oversee the  
27 quality of the study. Certain individuals from ISALA Heart Centre and regulatory  
28 organisations may look at your medical and research records to check the accuracy  
29 or the research study. ISALA Heart Centre will only receive information without any  
30 identifying information. The people who analyse the information will not be able to  
31 identify you and will not be able to find out your name, NHS number or contact  
32 details.  
33  
34  
35  
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37

## 38 **12. Insurance for subjects**

39  
40 If you participate in the study you will face the same risks as for the standard  
41 treatment of your condition. The study is insured with HDI Global SE – UK Policy  
42 Number 390-08414363 and has a liability insurance for £5 million.  
43  
44  
45  
46

## 47 **13. Informing your GP**

48  
49 We will always notify your GP and/or treating specialist that you are participating in the  
50 study. This is for your own safety. If you do not agree to this, you cannot participate in  
51 the study. In the event of complications, we may contact your doctor or GP for  
52 information such as your medical history or use of medicines.  
53  
54  
55

## 56 **15. Questions**

57  
58 If you have any questions or concerns, please contact the study doctor or the  
59 research team.  
60

1  
2  
3 If you have any complaints or require general advice you can contact the hospital's  
4 Patient Advice and Liaison Service (PALS).  
5

## 6 **16. Signing the consent form**

7  
8  
9 Once you have had sufficient time to think about it, you will be asked to decide  
10 whether or not to participate in this study. If you consent, we will ask you to confirm  
11 your consent in writing on the appropriate consent form. By giving your written  
12 consent, you acknowledge that you have understood the information and agree to  
13 participation in  
14 the study.  
15  
16

17  
18 The signature sheet will be kept by the researcher. You will receive a duplicate or a  
19 second copy of the consent form.  
20

21  
22 Thank you for your reading this information sheet.  
23  
24  
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**Consent form**

## COLOR trial

- I have read the information letter. I was given the opportunity to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether or not to participate. I am aware that participation is voluntary.
- I am also aware that I can decide not to participate or to withdraw from the study at any time. I need not give a reason for this.
- I consent to informing my GP that I am participating in this study.
- I am aware that some people have access to my records. Those people are listed in this information letter.
- I consent to the collection and use of my information in the manner and for the purposes listed in the information letter.
- I consent to the storage of my information at the research site for 15 years after this study.
- I wish to participate in this study.

Name of participant:

Signature:

Date : \_\_ / \_\_ / \_\_

-----

Name of investigator:

Signature:

Date : \_\_ / \_\_ / \_\_

-----



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P
	2b	All items from the World Health Organization Trial Registration Data Set	P 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	P 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1
	5b	Name and contact information for the trial sponsor	P 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P 4
	6b	Explanation for choice of comparators	P 4
Objectives	7	Specific objectives or hypotheses	P 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P 4

## Methods: Participants, interventions, and outcomes

1				
2				
3				
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P 4
5				
6				
7				
8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P 5
9				
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13	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
14				
15				
16		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
17				
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20				
21		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
22				
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25		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
26				
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28	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P 5
29				
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36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 1
37				
38				
39				
40				
41	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P 6
42				
43				
44				
45	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
46				
47				

## Methods: Assignment of interventions (for controlled trials)

### Allocation:

51				
52				
53	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P 6
54				
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	N/A
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	N/A
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
14			procedure for revealing a participant's allocated intervention during	
15			the trial	
16				
17				
18				
19				
20	<b>Methods: Data collection, management, and analysis</b>			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P11-12
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27		18b	Plans to promote participant retention and complete follow-up,	P 6
28			including list of any outcome data to be collected for participants who	
29			discontinue or deviate from intervention protocols	
30	Data	19	Plans for data entry, coding, security, and storage, including any	P 6
31	management		related processes to promote data quality (eg, double data entry;	
32			range checks for data values). Reference to where details of data	
33			management procedures can be found, if not in the protocol	
34	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P 6
35	methods		Reference to where other details of the statistical analysis plan can be	
36			found, if not in the protocol	
37		20b	Methods for any additional analyses (eg, subgroup and adjusted	P 6
38			analyses)	
39		20c	Definition of analysis population relating to protocol non-adherence	N/A
40			(eg, as randomised analysis), and any statistical methods to handle	
41			missing data (eg, multiple imputation)	
42				
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52	<b>Methods: Monitoring</b>			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	N/A
54			and reporting structure; statement of whether it is independent from	
55			the sponsor and competing interests; and reference to where further	
56			details about its charter can be found, if not in the protocol.	
57			Alternatively, an explanation of why a DMC is not needed	
58				
59				
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1				
2		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
3				
4				
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 4
7				
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10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
12				
13				
14				
15	<b>Ethics and dissemination</b>			
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 7
18				
19				
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P 7-8
21				
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P 7
27				
28				
29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
30				
31				
32	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P 7
33				
34				
35				
36				
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 1
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
41				
42				
43				
44				
45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 7
49				
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53				
54		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
55				
56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
58				
59				
60				

## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp II
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

For peer review only



# BMJ Open

## Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR trial study protocol

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4 1  
5 2 Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR  
6 3 trial study protocol  
7 4  
8 5

9 6 Thomas A. Meijers MD<sup>a\*</sup>, Adel Aminian MD<sup>b\*</sup>, Koen Teeuwen MD, PhD<sup>c</sup>, Marleen van  
10 7 Wely MD<sup>d</sup>, Thomas Schmitz MD, PhD<sup>e</sup>, Maurits T. Dirksen MD, PhD<sup>f</sup>, René J. van der  
11 8 Schaaf MD, PhD<sup>g</sup>, Juan F. Iglesias MD, PhD<sup>h</sup>, Pierfrancesco Agostoni MD, PhD<sup>i</sup>, Joseph  
12 9 Dens MD, PhD<sup>j</sup>, Paul Knaapen MD, PhD<sup>k</sup>, Sudhir Rathore MD, FRCP<sup>l</sup>, Jan Paul Ottervanger  
13 10 MD, PhD<sup>a</sup>, Jan Henk E. Dambrink MD, PhD<sup>a</sup> Vincent Roolvink MD, PhD<sup>a</sup>, A.T. Marcel  
14 11 Gosselink MD, PhD<sup>a</sup>, Renicus S. Hermanides MD, PhD<sup>a</sup>, Niels van Royen MD, PhD<sup>d</sup>,  
15 12 Maarten A.H. van Leeuwen MD, PhD<sup>a</sup>

16 13  
17 14  
18 14 \* Both authors contributed equally.  
19 15

20 16 Word count: 3758  
21 17

22 18 Departments and institutions

23 19 <sup>a</sup> Department of Cardiology, Isala Heart Center, Zwolle, the Netherlands

24 20 <sup>b</sup> Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi,  
25 21 Belgium

26 22 <sup>c</sup> Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

27 23 <sup>d</sup> Department of Cardiology, Radboud University Medical Center, Nijmegen, the  
28 24 Netherlands

29 25 <sup>e</sup> Department of Cardiology, Elisabeth Krankenhaus, Essen, Germany

30 26 <sup>f</sup> Department of Cardiology, Northwest Clinics, Alkmaar, the Netherlands

31 27 <sup>g</sup> Department of Cardiology, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the  
32 28 Netherlands

33 29 <sup>h</sup> Department of Cardiology, Geneva University Hospital, Geneva, Switzerland

34 30 <sup>i</sup> Department of Cardiology, ZNA Middelheim, Antwerp, the Netherlands

35 31 <sup>j</sup> Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium

36 32 <sup>k</sup> Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands

37 33 <sup>l</sup> Department of Cardiology, Frimley Health NHS Foundation Trust, Surrey, United  
38 34 Kingdom  
39 35

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42 38 unrestricted grant.  
43 39

44 40 Conflict of interest

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46 42 Terumo corp., Juan F. Iglesias and Thomas Schmitz have received honoraria/speakers fee for  
47 43 Terumo corp., the other authors have no conflicts of interest to declare.  
48 44

49 45 Clinical trial registration

50 46 ClinicalTrials.gov identifier: NCT03846752.  
51 47

52 48 Address for correspondence

53 49 dr. M.A.H. van Leeuwen, Isala Heart Center, Dr. van Heesweg 2, 8025 AB Zwolle, The  
54 50 Netherlands. Email: m.a.h.van.leeuwen@isala.nl  
55 51  
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**Abstract****Introduction**

The radial artery has become the standard access site for percutaneous coronary intervention (PCI) in stable coronary artery disease and acute coronary syndrome, because of less access site related bleeding complications. Patients with complex coronary lesions are underrepresented in randomized trials comparing radial with femoral access with regard to safety and efficacy. The femoral artery is currently the most applied access site in patients with complex coronary lesions, especially when large bore guiding catheters are required. With slender technology, transradial PCI may be increasingly applied in patients with complex coronary lesions when large bore guiding catheters are mandatory and might be a safer alternative as compared to the transfemoral approach.

**Methods and analysis**

A total of 388 patients undergoing complex PCI will be randomized to radial 7 French access with Terumo Glidesheath Slender (Terumo Corp., Japan) or femoral 7 French access as comparator. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Procedural success and major adverse cardiovascular events up to 1 month will also be compared between both groups.

**Ethics and dissemination**

Ethical approval for the study was granted by the local Ethics Committee at each recruiting center ('Medisch Ethische Toetsing Commissie Isala Zwolle', 'Commissie voor medische ethiek ZNA', 'Comité Medische Ethiek Ziekenhuis Oost-Limburg', 'Comité d'éthique CHU-Charleroi – ISPPC', 'Commission cantonale d'éthique de la recherche CCER – République et Canton de Genève', 'Ethik Kommission de Ärztekammer Nordrhein' and 'Riverside Research Ethics Committee'). The trial outcomes will be published in peer-reviewed journals of the concerned literature. The COLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

**Strengths and limitations of this study**

- The design as a randomized 1:1 open label study (radial 7 Fr versus femoral 7) and the vast experience with complex PCI of the participating centers
- Clinical Event Committee adjudicated and clinically relevant primary endpoint
- First study assessing extremity dysfunction after complex large bore PCI
- As a limitation, bias could be derived from the unblinded nature of the study for the treating interventional cardiologist
- As a limitation, use of secondary access sites for hybrid approach of CTO lesions will influence efficacy outcomes, although it will not influence the primary endpoint.

**Keywords**

Complex percutaneous coronary intervention - Chronic total occlusion - Radial access - Femoral access - Slender

**Abbreviations**

PCI = percutaneous coronary intervention

CTO = chronic total occlusion

CABG = coronary artery bypass grafting

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

1  
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3 101 MACE = major adverse cardiovascular events  
4 102 AE = adverse event  
5 103 SAE = serious adverse event  
6 104 TR= transradial  
7 105 TRA= transradial access  
8 106 TF = transfemoral  
9 107 TFA = transfemoral access  
10 108 Fr = French  
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For peer review only

## 151 **Background**

152 The radial artery has become the standard access site for percutaneous coronary interventions  
153 (PCI), driven not only by lower rates of major bleeding and vascular complications, but also  
154 by reduced mortality in patients presenting with acute coronary syndrome (ACS) (1–3). This  
155 has led the 2018 ESC/EACTS Guidelines on myocardial revascularization to recommend  
156 transradial access (TRA) over transfemoral access (TFA) as a class Ia indication in ACS  
157 patients undergoing invasive management (4). In patients with stable coronary artery disease,  
158 several small randomized trials comparing radial and femoral access have shown significantly  
159 less bleeding in favor of radial access but no mortality benefit (5–7). Of note, patients with  
160 complex coronary lesions were not included in these trials or not specifically described. PCI  
161 of chronic total occlusions (CTO), left main disease, heavily calcified or complex bifurcation  
162 lesions often require the use of large-bore guiding catheters (7 Fr or larger inner diameter).  
163 Indeed, large-bore guiding catheters provide more back-up and stability in addition to better  
164 materials' compatibility, leading to higher procedural success rates in more complex lesions  
165 (8,9). Because of potential radial artery-sheath mismatch, spasms or back-up problems, the  
166 femoral artery is still the most applied access site for complex PCI (10,11). In return, TFA  
167 with increased sheath size is associated with bleeding and vascular complications and adverse  
168 clinical outcome, including myocardial infarction (MI), stroke and death (12,13). The recent  
169 availability of modern slender technology, such as the thin-walled radial introducer sheath  
170 (Glidesheath Slender®, Terumo Corp., Japan), has the potential to expand the use of TRA for  
171 complex PCI. As compared to the average outer diameter of a standard sheath, the outer  
172 diameter of these slender sheaths has been reduced by approximately 1 Fr while maintaining  
173 the inner-diameter equivalent. In a prospective single-arm study it was recently shown that  
174 complex transradial (TR) PCI with a 7 Fr Glidesheath Slender is safe and effective (14).  
175 Several observational studies have been published describing feasibility of large bore TRA for  
176 PCI of CTO's, left main disease, heavily calcified lesions and complex bifurcations without  
177 affecting procedural success rates (9,11,15–18). However, randomized data comparing TRA  
178 and TFA for percutaneous treatment of complex coronary lesions are lacking. Therefore, we  
179 have designed a randomized study, comparing the safety and efficacy of TRA and TFA for  
180 complex PCI using large-bore guiding catheters.

## 181 **Methods**

### 182 *Study design*

183 The Complex Large-Bore Radial PCI (COLOR) trial is an investigator-initiated international  
184 multi-center study with a prospective, randomized controlled design. Participating centers are  
185 the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the  
186 Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-  
187 Krankenhaus (Essen, Germany), NorthWest Clinics (Alkmaar, the Netherlands), Onze Lieve  
188 Vrouwe Gasthuis Hospital (Amsterdam, the Netherlands), Centre Hospitalier Universitaire de  
189 Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-  
190 Limburg (Genk, Belgium), Geneva University Hospital (Geneva, Switzerland), VU  
191 University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United  
192 Kingdom). All centers have been selected based on their high volumes and experience with  
193 complex PCI and large bore access. For CTO, each center has a dedicated program for an  
194 average of 6 years, with 1-3 dedicated CTO operators and an average of 110 procedures per  
195 year (spreading from 55 to 200 procedures per year). 83% of CTO procedures are done with  
196 dual arterial access, with biradial access in 20%, bifemoral access in 24% and radial/femoral  
197 (hybrid) access in the remaining 49% of cases. Large bore access is used in 89% of cases. For  
198 non-CTO complex PCI, the participating centers have a dedicated program for an average of  
199 11 years, performing an average of 245 procedures per year with 3-5 complex PCI operators.

201 76% of these cases are done with TRA and 24% with TFA. Large bore access is used in 62%  
202 of all complex non CTO PCI.

203

#### 204 *Trial organization*

205 The trial is approved by the appropriate ethics review board at each clinical site. Written  
206 informed consent will be obtained from all patients before enrollment. The trial was designed  
207 in accordance with the declaration of Helsinki. All data will be collected in an electronic data  
208 capturing system, the eDREAM (electronic case record form Diagnostic REsearch And  
209 Management). Diagram BV, Zwolle, the Netherlands will be responsible for overall trial and  
210 data management, as well as monitoring of the study. Evaluation of serious adverse events is  
211 being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical  
212 Events Committee (CEC) will review and adjudicate all end-point related adverse events. The  
213 COLOR trial has been administered in the ClinicalTrials.gov database, reference number:  
214 NCT03846752.

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#### 216 *Objectives*

217 The primary objective of this study is to investigate whether TR PCI is superior to  
218 transfemoral (TF) PCI in complex coronary lesions with large-bore guiding catheters with  
219 respect to clinically relevant access site related bleeding and/or vascular complications.

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221 As secondary objectives, TR and TF large-bore access will be compared with regard to  
222 procedural success, procedural time, fluoroscopy time, contrast use, crossover rates, major  
223 adverse cardiovascular events (MACE) and non-access site related bleeding or vascular  
224 complications for complex PCI.

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226 For exploratory purposes extremity dysfunction and discomfort will be compared between TR  
227 and TF treated patients for complex PCI with large-bore guiding catheters.

228

#### 229 *Inclusion*

230 All patients of 18 years or older, presenting with stable coronary artery disease, unstable  
231 angina or non-ST elevation myocardial infarction and planned for PCI of the following  
232 complex coronary lesions: CTO, left main stem, heavily calcified lesions which may require  
233 calcium modification techniques (rotational atherectomy or intravascular lithotripsy) and  
234 complex bifurcations in whom the operator anticipates that a 7 Fr guiding catheter is  
235 indicated, are screened for inclusion. CTO is defined as a lesion exhibiting TIMI 0-1 flow in a  
236 native coronary artery with an occlusion duration of  $\geq 3$  months (19). Heavily calcified lesions  
237 are characterized by multiple persisting opacifications of the coronary wall visible in more  
238 than one projection surrounding the complete lumen of the coronary artery at the site of the  
239 lesion (20). Complex bifurcation includes lesions with Medina classification 0.1.1, 1.1.1 or  
240 1.0.1 (21). Patients with ST elevation myocardial infarction or cardiogenic shock will be  
241 excluded. Patients with contraindications for femoral or radial access, such as occlusive  
242 peripheral artery disease, known severe spasm or known anatomical variants prohibiting  
243 radial or femoral access on both sides will be excluded as well. See also Figure 1 for graphic  
244 representation of study inclusion.

245

#### 246 *Randomization*

247 After providing written informed consent, eligible subjects are randomly assigned to receive  
248 one of the two study treatments in a 1:1 ratio. Treatment assignments are performed centrally  
249 through a dedicated website as part of the electronic Case Report Form (eCRF) according to a  
250 computer-generated random schedule in random permuted blocks with stratification by site

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3 251 (22). There will be no blinding of the randomization assignment.

4 252

5 253 *Endpoints*

6 254 Clinically relevant access site related bleeding or vascular complication requiring intervention  
7 255 of the randomized access site during hospitalization is defined as primary endpoint. Bleeding  
8 256 will be classified according to the Bleeding Academic Research Consortium (BARC) criteria  
9 257 (23), and considered clinically relevant when the score is  $\geq 2$  (CEC adjudicated)(24). Severity  
10 258 and type of intervention of vascular complications is specified in the CEC manual  
11 259 (Supplementary file I).

12 260 Secondary safety and efficacy endpoints are:

13 261 - Procedural success (defined as successful PCI of the target lesion with a residual stenosis of  
14 262 less than 20%, without in-hospital MACE), procedural time, fluoroscopy time, contrast use  
15 263 and crossover rate (crossover is defined as conversion from TF to TR or vice versa;  
16 264 conversion to contralateral TR or TF access site is not considered crossover).

17 265 - Clinically relevant BARC bleedings or vascular complications (requiring intervention) that  
18 266 are not related to the randomized access (CEC adjudicated)

19 267 - MACE, defined as composite of death, MI and repeat revascularization, during  
20 268 hospitalization and at 1 month (CEC adjudicated)

21 269

22 270 *Index percutaneous coronary intervention and hospitalization*

23 271 Radial access will be performed according to the local protocol, using direct needle technique  
24 272 or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A  
25 273 standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial  
26 274 sheath placement. Femoral access will be performed using direct needle technique, followed  
27 275 by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will  
28 276 be left to the operator's discretion. A bolus of unfractionated heparin will be given after  
29 277 sheath placement, adapted to the patient's body weight. Activated clotting time (ACT)  
30 278 measurements will be performed during the procedure according to local protocol. Additional  
31 279 arterial access will be left to the discretion of the operator, i.e. in case of double arterial access  
32 280 for hybrid CTO treatment. In case of randomization to TRA, a 7 Fr Glidesheath Slender must  
33 281 be inserted in the right or left radial artery. Then, the operator can decide which secondary  
34 282 access site he/she will use and which sheath size is needed for this secondary access. This can  
35 283 be the contralateral radial artery (bi-radial approach) or the femoral artery. If the patient is  
36 284 randomized to femoral access and needs dual access, a 7 Fr femoral sheath must be placed in  
37 285 the femoral artery (randomized access site) and the operator can decide which second access  
38 286 he/she will use (radial or femoral). Only clinically significant bleeding or vascular  
39 287 complications attributable to the randomized access site will be analyzed for the primary  
40 288 endpoint, complications attributable to the secondary access site will be analyzed as  
41 289 secondary endpoint. PCI will be performed according to standard procedures with modern  
42 290 drug eluting stents. The applied technique for complex PCI will be left to the discretion of the  
43 291 operator. Patent hemostasis after radial access with the reverse Barbeau test is highly  
44 292 recommended (25). The type of femoral artery hemostasis will be left to the discretion of the  
45 293 treating interventional cardiologist; however the application of a closure device is advocated.  
46 294 The visual analogue scale (VAS) will be used to assess post-procedural pain of the access  
47 295 site(s). Before discharge the access site(s) will be checked for bleeding and vascular  
48 296 complications. Radial artery patency will be checked with the reverse Barbeau test (25).

49 297 Additional ultrasound or doppler will be performed in those patients with suspected radial or  
50 298 femoral occlusion or the presence of other vascular complications.

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### 301 *Extremity dysfunction*

302 Two validated questionnaires will be used to assess the occurrence of upper and lower  
303 extremity dysfunction. Upper extremity function will be measured with the QuickDASH  
304 (Quick Disabilities of Arm, Shoulder and Hand) score (26) measured at baseline (before PCI)  
305 and at 1 month follow-up. Lower extremity function will be measured with the LEFS (Lower  
306 Extremity Functional Scale) (27). Both questionnaires are valid, reliable and responsive to  
307 monitor and assess pain and function of the extremities.

### 308 309 *Follow-up*

310 Follow-up will be performed 1 month after index procedure discharge by either phone call or  
311 outpatient clinic visit. MACE and access site bleeding or vascular complications will be  
312 documented. Extremity function and discomfort will be assessed, using the aforementioned  
313 scores. Adverse Events (AE's) will be monitored from inclusion to one-month follow-up and  
314 will be assessed by an independent DSMB, composed of two experienced cardiologists and  
315 one statistician, reviewing patient safety and study integrity.

### 316 317 *Sample size calculation and statistics*

318 Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the  
319 proportion of access site related bleeding or vascular complication to be 3.5% with radial  
320 access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1)  
321 will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients  
322 will be needed. Data will be analyzed according to the intention-to-treat analysis. All  
323 statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically  
324 significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago,  
325 Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-  
326 Square test will also be used for our secondary objectives with binary outcomes. For our  
327 secondary objectives with continuous variables we will use the Student's t-test (normally  
328 distributed) or the Mann-Whitney U test (non-normally distributed). A pre-specified battery  
329 of sub-group analyses will be performed as well, including several independent risk factors  
330 for clinically significant bleeding and vascular complications. For demographics and baseline  
331 characteristics, these sub-groups consist of age  $\geq 75$  years, female sex, low body weight  
332 (Body Mass Index < 18.5), hypertension, peripheral arterial disease, left ventricular ejection  
333 fraction < 30%, severe renal dysfunction (Modification of Diet in Renal Disease (MDRD) <  
334 30ml/1.73m<sup>2</sup>) and pre-existent anemia (hemoglobin <6.8 mmol/l) (13,28–33). For procedural  
335 characteristics, sub-group analyses will be performed for use of secondary access site,  
336 ultrasound guided puncture, ACT > 150 seconds right before sheath removal and use of  
337 closure device (34–37). In addition, primary and secondary endpoints will be specified for the  
338 entire population as well as for each group of complex lesions separately (CTO, left main  
339 disease, complex bifurcation and heavy calcification). Statistical analysis will be performed  
340 by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

### 341 342 *Ethics and dissemination*

343 Ethical approval for the study was granted by the local Ethics Committee ('Medisch Ethische  
344 Toetsing Commissie Isala Zwolle' for all Dutch sites, 'Commissie voor medische ethiek  
345 ZNA' for ZNA Middelheim, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for  
346 Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi – ISPPC' for Centre Hospitalier  
347 Universitaire de Charleroi, 'Commission cantonale d'éthique de la recherche CCER –  
348 Republique et Canton de Geneve' for Geneva University Hospital, 'Ethik Kommission de  
349 Ärztekammer Nordrhein' for Elisabeth-Krankenhaus and 'Riverside Research Ethics  
350 Committee' for Frimley NHS) after reviewing the protocol, site-

351 specific informed consent forms (local language and English versions, see also supplementary  
352 file II), participant education and recruitment materials, other requested documents and any  
353 subsequent modifications. Trained research nurses or physicians directly involved in the trial  
354 will introduce the trial to eligible patients. Patients will also receive patient information  
355 form (PIF). The research nurse or physician will discuss the trial with patients in light of the  
356 information provided in the PIF and will obtain written consent from patients willing to  
357 participate in the trial. No reimbursement is provided to study participants. All study-related  
358 information will be stored securely at the study site. All participant information will be stored  
359 in locked file cabinets in areas with limited access. All reports, data collection, process, and  
360 administrative forms will be identified by a coded identification-number only to maintain  
361 participant confidentiality. All records that contain names or other personal identifiers, such  
362 as locator forms and informed consent forms, will be stored separately from study records  
363 identified by code number. All local databases will be secured with password-protected  
364 access systems. Safety and progress reports to the EC's will be made at least annually and  
365 within three months of study termination or completion. These reports will include the total  
366 number of participants enrolled and summaries of the DSMB. Any modifications to the  
367 protocol which may have impact on the conduct of the study, potential benefit of the patient  
368 or may affect patient safety, including changes of study objectives, study design, patient  
369 population, sample sizes, study procedures, or significant administrative aspects will require a  
370 formal amendment to the protocol. Such amendment will have to be approved by the Ethics  
371 Committee prior to implementation. The study findings will be disseminated via publication  
372 of peer-reviewed manuscripts and presentations at international conferences, as well as  
373 through media publications. Results will be published irrespective of whether the findings are  
374 positive or negative.

#### 376 *Patient and Public Involvement*

377 No patient involved

#### 379 **Discussion**

380 TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and  
381 vascular complications compared to TFA, with even a mortality benefit in ACS patients  
382 (2,3,38,39). Randomized data in patients with stable coronary artery disease are limited and  
383 more heterogeneous, and show less beneficial effect of radial over femoral access (1,40,41).  
384 Moreover, complex coronary lesions are absent or at least not specifically described in most  
385 trials supporting current guidelines on myocardial revascularization. Currently, the femoral  
386 artery is still considered the preferred access site for complex PCI by many operators  
387 (11,16,42–44), despite the increased risk of bleeding and vascular complications, especially  
388 when large bore guiding catheters ( $\geq 7$  Fr) are required (11,45–48). During CTO-PCI, the use  
389 of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a  
390 higher procedural success rate (9,16). Large-bore guiding catheters have better materials'  
391 compatibility, especially when using guide extensions and microcatheters. The use of  
392 CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-  
393 entry technique is only possible with large-bore guiding catheters (49). Although registries  
394 show increased temporal adoption of TRA for PCI of heavily calcified lesions with use of  
395 rotational atherectomy with similar procedural success rates and less bleeding, TFA is still  
396 used in a large proportion of these procedures, which often mandate large bore guiding  
397 catheters especially for accommodating larger burr sizes (50,51). Application of large-bore  
398 guiding catheters for complex PCI of left main and true bifurcations is advocated by experts,  
399 though efficacy and safety data are lacking. Limited data show comparable feasibility of TRA

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3 400 versus TFA for left main as well as bifurcation PCI with a tendency towards less bleeding  
4 401 complications (11,52–58).  
5 402

6 403 The most important argument to refrain from TR PCI for complex coronary lesions is the  
7 404 limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer  
8 405 diameter of 2.97-3.19 mm (59). As such, the percentage of patients with a radial artery  
9 406 smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and  
10 407 between 60% up to 85% in women (60). This suggests that using a standard 7 Fr sheath for  
11 408 TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing  
12 409 the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent  
13 410 complication after radial access, with increasing RAO rates with increasing sheath size (61).  
14 411 In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO  
15 412 may require intervention because of extremity dysfunction or ischemia (62,63). Moreover,  
16 413 RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as  
17 414 conduit for CABG or creating a hemodialysis shunt (64). Other arguments to use the femoral  
18 415 artery for complex PCI have been suggested, such as improved back-up with potential higher  
19 416 procedural success rates and shorter procedural time and lower radiation dose. However, this  
20 417 is not supported by observational data showing similar effectiveness, procedural success rates,  
21 418 cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).  
22 419 Several technologies have been developed to facilitate large bore access through the radial  
23 420 artery (65). A sheathless approach for example was shown to be a feasible alternative for  
24 421 large bore radial access (66). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc,  
25 422 Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer  
26 423 diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr)  
27 424 compared with a standard 7 Fr sheath (67). However, PCI with sheathless guiding catheters  
28 425 requires specific experience due to the highly hydrophilic coating, and limited evidence exists  
29 426 regarding the true impact on RAO (68,69). Miniaturization of TR equipment can also be  
30 427 achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness  
31 428 (“slender technology”), thin-walled sheaths have reduced their outer diameter while  
32 429 maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the  
33 430 first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm,  
34 431 compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent  
35 432 prospective multicenter study has shown the feasibility and safety of using the 7 Fr  
36 433 Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural  
37 434 success and low rate of vascular complications (14).  
38 435

39 436 In the literature, several outcome measures have been used to evaluate access site related  
40 437 bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(70), the  
41 438 Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary  
42 439 arteries (GUSTO)(71) or BARC (23). Access site hematoma size has also been used as an  
43 440 outcome measure in studies comparing radial with femoral access. BARC bleeding  $\geq 2$  has  
44 441 shown to independently predict 1-year mortality and capture more clinically significant  
45 442 bleeding than TIMI minor/major and GUSTO moderate/severe criteria (23,24). Importantly,  
46 443 hematoma size alone, not meeting criteria for other bleeding outcome measures, has not  
47 444 shown any association with clinically relevant endpoints (72). The current trial will use the  
48 445 BARC bleeding score for the primary outcome measure to detect a clinically relevant  
49 446 difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC.  
50 447 Besides bleeding and vascular complications, vascular access may also have a potential effect  
51 448 on extremity function (73,74). Although upper extremity dysfunction is present in a small  
52 449 proportion of patients after TRA, it can lead to important morbidity for the affected patients

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3 450 (73–76). Extremity dysfunction may be more pronounced in patients with large-bore access.  
4 451 In addition, current literature does not provide an insight around prevalence and significance  
5 452 of lower extremity function after TFA (74). Therefore, we will assess the occurrence of  
6 453 extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be  
7 454 valuable information for both patients and doctors.  
8 455

9 456 In conclusion, The COLOR trial is the first prospective multicenter randomized trial  
10 457 comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290  
11 458 patients are randomized. The results of this trial will provide important insights about the  
12 459 safety and efficacy of large-bore TRA and TFA for complex PCI. If this trial can show that  
13 460 TRA is not only as effective but also safer (less clinically relevant bleeding and vascular  
14 461 complications) in complex large bore PCI, it has a potential impact on daily practice.  
15 462

### 16 463 **Contributorship statement**

17 464 Maarten van Leeuwen and Adel Aminian substantially contributed to conception and design  
18 465 of the study protocol. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely,  
19 466 Thomas Schmitz, Rene van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco  
20 467 Agostoni, Joseph Dens, Paul Knaapen, Sudhir Rathore and Maarten van Leeuwen contributed  
21 468 to acquisition of data. Thomas Meijers, Adel Aminian and Maarten van Leeuwen contributed  
22 469 to analysis of data. Thomas Meijers, Adel Aminian, Maarten van Leeuwen and Niels van  
23 470 Royen contributed to interpretation of data. Thomas Meijers, Adel Aminian and Maarten van  
24 471 Leeuwen reviewed the literature, contributed to the design and wrote the draft of the  
25 472 manuscript. Thomas Meijers, Adel Aminian, Koen Teeuwen, Marleen van Wely, Thomas  
26 473 Schmitz, René van der Schaaf, Maurits Dirksen, Juan Iglesias, Pierfrancesco Agostoni, Joseph  
27 474 Dens, Paul Knaapen, Sudhir Rathore, Jan Paul Ottervanger, Jan Henk Dambrink, Vincent  
28 475 Roolvink, Marcel Gosselink, Renicus Hermanides, Niels van Royen and Maarten van  
29 476 Leeuwen contributed to refinement of the study protocol and approved the final manuscript.  
30 477  
31 478

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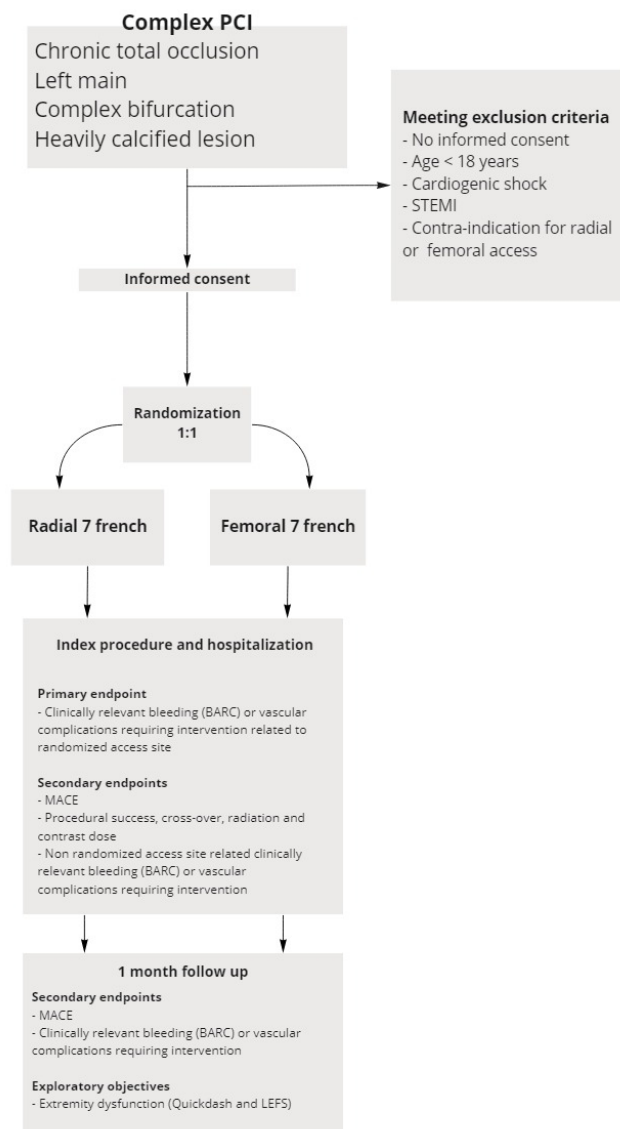


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### Figure legend

33 730 Figure 1: Inclusion flowchart for the COLOR trial.

34 731 **Caption:** *Graphic representation of inclusion for the COLOR trial. STEMI = ST elevation*  
35 732 *myocardial infarction, BARC = Bleeding Academic Research Group, MACE = Major*  
36 733 *Adverse Cardiovascular Events.*  
37 734



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Figure 1: enrollment flowchart of the COLOR trial

300x413mm (72 x 72 DPI)

**Supplementary file I: CEC manual for adjudicating bleeding and vascular complications**

Classification and Definition

**Bleeding**

BARC 0

No bleeding or hematoma.

BARC 1

Every bleeding or hematoma not meeting the criteria for BARC 2 or higher.

BARC 2

Any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, (prolonged) hospitalization, or treatment by a health care professional.

Specified for radial access and femoral access in this appendix

BARC 3a

Overt bleeding + Hb drop of 3-5 g/dl (1.9 – 3.1 mmol/L), or any transfusion with overt bleeding (independent of Hb)

BARC 3b

Overt bleeding + Hb drop >5g/dl (>3.1 mmol/L), or cardiac tamponade, or bleeding requiring surgical intervention and/or IV vasoactive agents

BARC 3c

Intracranial hemorrhage or intraocular bleedings

BARC 4

CABG related bleeding

BARC 5

Fatal bleeding

**Vascular complications**

Retroperitoneal hematoma, (pseudo) aneurysm, infection and arteriovenous-fistula or vascular occlusion requiring intervention. Specified for radial access and femoral access in this appendix

Radial access

*Specification of BARC 2 bleedings*

1. Prolonged hospitalization

Any bleeding that leads to one or more extra hospitalization day(s)

- Based on standard discharge policy of hospital

- For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

2. Additional compression therapy

Any additional compression therapy after successful primary hemostasis

- Bleeding after removal of first TR band and additional compression bandage or TR band is needed

- Ongoing bleeding with first TR band and additional compression therapy is needed

- Adding 1 or 2cc of air in the first TR band due to slight oozing should not be scored as BARC 2

3. Additional investigations

Any additional investigation for (potential) bleeding/hematoma should be scored as

BARC 2. This includes imaging (i.e. ultrasound, CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

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#### 4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation of medical therapy (i.e. vitamin K, hematological products)
  - Percutaneous intervention (i.e. coiling)

#### *Specification of vascular complications*

- Vascular complications requiring intervention: percutaneous, surgical, medical
- (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
  - Infection (i.e. antibiotics)
  - Arteriovenous-fistula (i.e. percutaneous or surgical intervention)
  - Radial artery occlusion (percutaneous intervention, heparin therapy)
  - Dissection (i.e. percutaneous or surgical intervention)
  - Compartment syndrome (i.e. percutaneous or surgical intervention)

#### Femoral access

#### *Specification BARC 2 bleeding*

##### 1. Prolonged hospitalization

- Any bleeding that leads to one or more extra hospitalization day(s)
- Based on standard discharge policy of hospital
  - For the primary endpoint check if prolonged hospitalization is caused by bleeding complication of the randomized access site

##### 2. Additional compression therapy

- Any additional compression therapy after successful primary hemostasis:
- New compression therapy after removal of the first bandage, or additional compression after closure device
  - Prolonging compression bandage due to slight oozing should not be scored BARC 2, when this will not lead to prolonged hospitalization (one or more days).

##### 3. Additional investigations

- Any additional investigation for (potential) bleeding/hematoma should be scored as BARC 2. This includes imaging (i.e. ultrasound, angiography or CT) or blood testing (i.e. Hb, hematocrite) that is not part of standard care or the study protocol

##### 4. Additional therapy

- Any additional or change of therapy related to bleeding/hematoma
- This includes cessation of medication (i.e. antiplatelet and anticoagulants) or initiation medical therapy (i.e. vitamin K, hematological products)
  - Percutaneous intervention (i.e. coiling or stenting of peripheral arteries)

#### *Specification of vascular complications*

- Vascular complications requiring intervention: percutaneous, surgical, medical:
- Retroperitoneal hematoma (i.e. coiling, surgery)
  - (pseudo) aneurysm (i.e. compression therapy, thrombin injection)
  - Infection (i.e. antibiotics)
  - Arteriovenous-fistula (i.e. percutaneous or surgical intervention)

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- Femoral artery occlusion or severe stenosis (percutaneous or surgical intervention)
  - Dissection (i.e. percutaneous or surgical intervention)
  - Compartment syndrome (i.e. percutaneous or surgical intervention)

For peer review only

## Supplementary file II

# Participation Information Sheet and Consent Form

Centre Number: \_\_\_\_\_ Patient Number: \_\_\_\_\_

**Study Title: COLOR study** - Comparative study of complex Percutaneous Coronary Intervention (PCI) procedures with large catheters through the radial artery or femoral artery.

**Principle Investigator:** Site specific

**Name and Address:** Site specific

**Telephone:** Site specific

**Sponsor:** ISALA Heart Centre, Zwolle, Netherlands.

## 1. Introduction

We would like to invite you to take part in this study. Participation is voluntary. If you would like to participate, we need your written consent. Before you decide whether to participate in the study or not, you should know what the study entails. Read this information carefully and ask the researcher for an explanation if you have any questions. If you would like more information, you can also consult the independent expert listed at the end of this letter. You can also discuss it with your partner, friends or family.

## 2. General information

This study was initiated by the cardiology partnership of the Isala hospital in

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3 Zwolle, and is being conducted by multiple cardiologists in the Netherlands,  
4 Belgium, Germany, Switzerland and England. The study requires 388 subjects  
5 from different countries.  
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8 All research is looked at by an independent group of people called Research Ethics  
9 Committee to protect your safety, rights, wellbeing and dignity. This study has been  
10 reviewed and given favorable opinion by the local Ethics Committee.  
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### 13 14 **3. Background of the study**

15  
16 The radial artery (artery in the arm) is smaller than the femoral artery (artery in the leg).  
17 Cardiac catheterization and PCI are already often performed through the radial artery. If  
18 the PCI procedure required a thicker catheter because the cardiologist needed more  
19 sturdiness to complete it, the groin was often used as the access site due to the larger  
20 artery. With the development of a thin-walled radial artery sheath, complex PCI  
21 procedures with thicker catheters can now also be performed through the radial artery. A  
22 complex PCI procedure through the radial artery may lead to fewer access-site  
23 complications than through the femoral artery, while providing a similar PCI result, but  
24 this has not yet been properly researched.  
25  
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### 32 **4. What your participation will entail**

33  
34 If you wish to participate, we will first check whether both the groin and the wrist can  
35 be used for the PCI procedure.  
36

37  
38 Before the procedure, we will ask you questions regarding whether or not you can use  
39 your arms and legs properly. We will ask you the same questions again one month  
40 after the procedure. You will also be asked to complete 2 questionnaires.  
41

42  
43 If both the radial and femoral arteries can be used, we will randomly assign you,  
44 - to determine whether you will be treated through the wrist or the groin.  
45

46  
47 If you are selected for the wrist procedure, we will use the modern sheath. If you are  
48 selected for the groin procedure, we will use the standard sheath.  
49

50  
51 Aside from the potential difference in sheath, the treatment you will receive will be  
52 exactly the same as if you did not participate in the study. The procedure may  
53 sometimes require the use of a 2<sup>nd</sup> catheter. In that case, the cardiologist will  
54 determine where the access site for the second catheter will be.  
55  
56

57  
58 The examinations you receive before and after the treatment are also exactly the same  
59 as if you did not participate in the study. Those examinations include an  
60 electrocardiography (ECG), a blood test and an inspection of the access site (groin or  
wrist).

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3  
4 The study will require the collection of your medical records for up to one month after  
5 the procedure.  
6  
7

### 8 **5. What is expected of you?**

9 For a good outcome of the study, it is important that you answer the questions during  
10 the study visit and the 1-month check-up to the best of your knowledge.  
11  
12

### 13 **6. Possible complications and other/adverse effects/complaints**

14  
15 In general, the procedure is performed using standard methods and participation in  
16 this study will not result in additional adverse effects. The materials used (including the  
17 sheaths) have been approved and are already in use for complex PCI procedures for  
18 patients who are not participating in a study. The only inconvenience you may  
19 experience is that we will contact you after one month to ask you some questions.  
20 Trans-Femoral and Trans-radial access will be performed according to the local protocol  
21 with the direct needle technique or venous cannula technique. The complications are  
22 the same as standard of care procedure and will be fully covered by the  
23 Doctor/Investigator during the discussion before consenting to the procedure.  
24 Complications that may arise from inserting and removing a sheath are:  
25  
26

- 27 -Bleeding
  - 28 -Vascular problems
  - 29 -Blood vessel closure
- 30  
31  
32  
33  
34  
35

### 36 **7. Possible advantages and disadvantages**

37  
38 Before you decide to participate in the study, it is important to consider the possible  
39 advantages and disadvantages.  
40  
41

42 If you participate in the study, there is a chance that you will receive exactly the same  
43 treatment as if you were not participating. If you are selected for the treatment group  
44 with the modern sheath through the wrist, you may have a reduced chance of  
45 accesssite complications, but this has not yet been proven. PCI performed through the  
46 femoral artery can also result in a longer hospital stay.  
47  
48  
49  
50

### 51 **8. If you do not wish to participate or wish to end participation in the study**

52 You decide whether or not to participate in the study. Participation is voluntary.  
53  
54

55 If you do not wish to participate, the PCI procedure with the thicker catheter will be  
56 performed in the usual manner. This can be done through the groin or the wrist.  
57  
58

59 If you do participate, you can change your mind and withdraw at any time, even during  
60 the study. You will then receive the standard treatment again. You do not have to  
provide a reason for stopping. If the procedure has already begun, it cannot be



1  
2  
3 reversed and you will also require a follow-up check-up. The data collected up to the  
4 moment of withdrawal will be used for the study.  
5

## 6 7 **9. End of the study**

8  
9 Your participation in the study ends when:

- 11 You have had the check-up one month after the procedure;
- 12 You choose to stop;

13  
14 The researcher feels it is better for you to stop;

15  
16 The Isala cardiology partnership, the government or the supervising medical.

17  
18 The entire study is complete when all participants are finished.  
19

## 20 21 22 **10. Use and storage of your records**

23  
24 All of your records will remain confidential. To protect your privacy, your records will be  
25 given a code. Your name and other information which directly identifies you will be  
26 omitted. The records can only be traced back to you with the key to the code. Only the  
27 study doctor and research staff know which code you have. The study will only ever  
28 use your data with that code, never with your name. The key to the code will remain in  
29 possession of the study team. Reports on the study will also only use that code.  
30  
31

32  
33  
34 Some people will be allowed to access your medical and personal information. Access to  
35 your medical and personal Information will be by the study Doctor/Investigator and the  
36 research team at site. The Sponsor, representatives of the Sponsor (including the  
37 Contract Research Organisation, study monitors, auditors and project manager. Ethics  
38 committee and government agencies where permitted or required by law. This is  
39 necessary to confirm that the study has been conducted properly and reliably. - They will  
40 keep your information confidential. By signing the consent form, you agree to the  
41 collection, storage and viewing of your medical and personal records.  
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## 51 52 **11. More information on your rights with regard to data processing**

53  
54 All the information that is collected during the study is kept confidential and there are  
55 strict laws in place which safeguard the privacy of the patient at every stage. We will  
56 be using your information (samples and medical records) in order to undertake this  
57 study and we will act as the data controller for this study. This means that we are  
58 responsible for looking after your information and using it properly. Your identity and  
59 contact details will be confidential and all the data collected will be anonymized so you  
60 cannot be

1  
2  
3 identified.

4 A description of this study will be available on <http://www.ClinicalTrials.gov>, and this  
5 web site will not include information that can identify you.

6 ISALA Heart Centre, Zwolle, is the Sponsor for this study based in the Netherlands.  
7 We will be using information from your medical records in order to undertake this  
8 study and will act as the data controller for this study. This means that we are for  
9 looking after your information and using it properly. ISALA Heart Centre will keep  
10 identifiable information about you for 15 years after the study has finished. Your  
11 rights to access, change or move your information are limited, as we need to  
12 manage your information in specific ways in order for the research to be reliable and  
13 accurate. If you withdraw from the study, we will keep the information about you  
14 that we have already obtained. To safeguard your rights, we will use the minimum  
15 personally identifiable information possible.  
16  
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23 The local site will keep your name, ID number and contact details confidential and  
24 will not pass this information to ISALA Heart Centre. The local site will use this  
25 information as needed, to contact you about the research study, and make sure that  
26 relevant information about the study is recorded for you care, and to oversee the  
27 quality of the study. Certain individuals from ISALA Heart Centre and regulatory  
28 organisations may look at your medical and research records to check the accuracy  
29 or the research study. ISALA Heart Centre will only receive information without any  
30 identifying information. The people who analyse the information will not be able to  
31 identify you and will not be able to find out your name, NHS number or contact  
32 details.  
33  
34  
35  
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37

## 38 **12. Insurance for subjects**

39  
40 If you participate in the study you will face the same risks as for the standard  
41 treatment of your condition. The study is insured with HDI Global SE – UK Policy  
42 Number 390-08414363 and has a liability insurance for £5 million.  
43  
44  
45  
46

## 47 **13. Informing your GP**

48  
49 We will always notify your GP and/or treating specialist that you are participating in the  
50 study. This is for your own safety. If you do not agree to this, you cannot participate in  
51 the study. In the event of complications, we may contact your doctor or GP for  
52 information such as your medical history or use of medicines.  
53  
54  
55

## 56 **15. Questions**

57  
58 If you have any questions or concerns, please contact the study doctor or the  
59 research team.  
60

1  
2  
3 If you have any complaints or require general advice you can contact the hospital's  
4 Patient Advice and Liaison Service (PALS).  
5

## 6 **16. Signing the consent form**

7  
8  
9 Once you have had sufficient time to think about it, you will be asked to decide  
10 whether or not to participate in this study. If you consent, we will ask you to confirm  
11 your consent in writing on the appropriate consent form. By giving your written  
12 consent, you acknowledge that you have understood the information and agree to  
13 participation in  
14 the study.  
15  
16

17  
18 The signature sheet will be kept by the researcher. You will receive a duplicate or a  
19 second copy of the consent form.  
20

21  
22 Thank you for your reading this information sheet.  
23  
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**Consent form**

## COLOR trial

- I have read the information letter. I was given the opportunity to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether or not to participate. I am aware that participation is voluntary.
- I am also aware that I can decide not to participate or to withdraw from the study at any time. I need not give a reason for this.
- I consent to informing my GP that I am participating in this study.
- I am aware that some people have access to my records. Those people are listed in this information letter.
- I consent to the collection and use of my information in the manner and for the purposes listed in the information letter.
- I consent to the storage of my information at the research site for 15 years after this study.
- I wish to participate in this study.

Name of participant:

Signature:

Date : \_\_ / \_\_ / \_\_

-----

Name of investigator:

Signature:

Date : \_\_ / \_\_ / \_\_

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P
	2b	All items from the World Health Organization Trial Registration Data Set	P 3
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	P 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P 1
	5b	Name and contact information for the trial sponsor	P 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P 4
	6b	Explanation for choice of comparators	P 4
Objectives	7	Specific objectives or hypotheses	P 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P 4

## Methods: Participants, interventions, and outcomes

1				
2				
3				
4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P 4
5				
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7				
8	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P 5
9				
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13	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
14				
15				
16		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
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20				
21		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
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25		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
26				
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28	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P 5
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36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 1
37				
38				
39				
40				
41	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P 6
42				
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44				
45	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
46				
47				

## Methods: Assignment of interventions (for controlled trials)

### Allocation:

51				
52				
53	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P 6
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1				
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	N/A
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
4	mechanism		describing any steps to conceal the sequence until interventions are	
5			assigned	
6				
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,	N/A
8			and who will assign participants to interventions	
9				
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	N/A
11	(masking)		participants, care providers, outcome assessors, data analysts), and	
12			how	
13		17b	If blinded, circumstances under which unblinding is permissible, and	N/A
14			procedure for revealing a participant's allocated intervention during	
15			the trial	
16				
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20	<b>Methods: Data collection, management, and analysis</b>			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other	P11-12
22	methods		trial data, including any related processes to promote data quality (eg,	
23			duplicate measurements, training of assessors) and a description of	
24			study instruments (eg, questionnaires, laboratory tests) along with	
25			their reliability and validity, if known. Reference to where data	
26			collection forms can be found, if not in the protocol	
27		18b	Plans to promote participant retention and complete follow-up,	P 6
28			including list of any outcome data to be collected for participants who	
29			discontinue or deviate from intervention protocols	
30	Data	19	Plans for data entry, coding, security, and storage, including any	P 6
31	management		related processes to promote data quality (eg, double data entry;	
32			range checks for data values). Reference to where details of data	
33			management procedures can be found, if not in the protocol	
34	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.	P 6
35	methods		Reference to where other details of the statistical analysis plan can be	
36			found, if not in the protocol	
37		20b	Methods for any additional analyses (eg, subgroup and adjusted	P 6
38			analyses)	
39		20c	Definition of analysis population relating to protocol non-adherence	N/A
40			(eg, as randomised analysis), and any statistical methods to handle	
41			missing data (eg, multiple imputation)	
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52	<b>Methods: Monitoring</b>			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role	N/A
54			and reporting structure; statement of whether it is independent from	
55			the sponsor and competing interests; and reference to where further	
56			details about its charter can be found, if not in the protocol.	
57			Alternatively, an explanation of why a DMC is not needed	
58				
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2		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
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6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P 4
7				
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11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
12				
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14				
15	<b>Ethics and dissemination</b>			
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 7
18				
19				
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P 7-8
21				
22				
23				
24				
25				
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P 7
27				
28				
29				
30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
31				
32	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P 7
33				
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37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P 1
38				
39				
40	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
41				
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45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
46				
47				
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P 7
49				
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54		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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56				
57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
58				
59				
60				



**Appendices**

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp II
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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