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

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Conflict of interest

Maarten A.H. van Leeuwen, Adel Aminian and 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

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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

- 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

TF = transfemoral
TFA = transfemoral access
Fr = French

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 Hospilatier 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

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

Objectives

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

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

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

Inclusion (figure 1)

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

Randomization

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

Endpoints

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

Secondary safety and efficacy endpoints are:

- Procedural success (defined as angiographic success without in-hospital MACE), procedural time, fluoroscopy time, contrast use and crossover rate (crossover is defined as conversion from TF to TR or vice versa; conversion to contralateral TR or TF access site is not considered crossover).
- Clinically relevant BARC bleedings or vascular complications (requiring intervention) that are not related to the randomized access (CEC adjudicated)

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

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

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

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

Sample size calculation and statistics
Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the proportion of access site related bleeding or vascular complication to be 3.5% with radial access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1) will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients will be needed. Data will be analyzed according to the intention-to-treat analysis. All statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago, Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-Square test will also be used for our secondary objectives with binary outcomes. For our

secondary objectives with continuous variables we will use the Student's t-test (normally distributed) or the Mann-Whitney U test (non-normally distributed). Statistical analysis will be performed by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

Patient and Public Involvement
No patients were involved in the development of the research question or design of this study.

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.

Discussion
TRA is nowadays the standard for PCI, mainly driven by the lower risk of bleeding and vascular complications compared to TFA, with even a mortality benefit in ACS patients (2,3,25,26). Randomized data in patients with stable coronary artery disease are limited and more heterogeneous, and show less beneficial effect of radial over femoral access (1,27,28). Moreover, complex coronary lesions are absent or at least not specifically described in most trials supporting current guidelines on myocardial revascularization. Currently, the femoral artery is still considered the preferred access site for complex PCI by many operators (11,16,29–31), despite the increased risk of bleeding and vascular complications, especially when large bore guiding catheters (≥7 Fr) are required (11,32–34). During CTO-PCI, the use of large-bore guiding catheters has been reported in 60-70% of cases and is associated with a higher procedural success rate (9,16). Large-bore guiding catheters have better materials' compatibility, especially when using guide extensions and microcatheters. The use of CrossBoss/Stingray (Boston Scientific, Marlborough, MA, USA) for antegrade dissection/re-entry technique is only possible with large-bore guiding catheters (35). When performing PCI of heavily calcified lesions with rotational atherectomy using large burr sizes, large-bore guiding catheters will be needed as well (36). Application of large-bore guiding catheters for complex PCI of left main and true bifurcations is advocated by experts, though efficacy and safety data are lacking. Limited data show comparable feasibility of TRA versus TFA for left main as well as bifurcation PCI with a tendency towards less bleeding complications(11,37).

The most important argument to refrain from TR PCI for complex coronary lesions is the limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer diameter of 2.97-3.19 mm (38). As such, the percentage of patients with a radial artery smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and between 60% up to 85% in women (39). This suggests that using a standard 7 Fr sheath for TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent complication after radial access, with increasing RAO rates with increasing sheath size (40). In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO may require intervention because of extremity dysfunction or ischemia (41,42). Moreover, RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as conduit for CABG or creating a hemodialysis shunt (43). Other arguments to use the femoral artery for complex PCI have been suggested, such as improved back-up with potential higher procedural success rates and shorter procedural time and lower radiation dose. However, this

is not supported by observational data showing similar effectiveness, procedural success rates, cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).

Several technologies have been developed to facilitate large bore access through the radial artery (44). A sheathless approach for example was shown to be a feasible alternative for large bore radial access (45). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc, Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr) compared with a standard 7 Fr sheath (46). However, PCI with sheathless guiding catheters requires specific experience due to the highly hydrophilic coating, and limited evidence exists regarding the true impact on RAO (47,48). Miniaturization of TR equipment can also be achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness ("slender technology"), thin-walled sheaths have reduced their outer diameter while maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm, compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent prospective multicenter study has shown the feasibility and safety of using the 7 Fr Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural success and low rate of vascular complications (14).

In the literature, several outcome measures have been used to evaluate access site related bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(49), the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO)(50) or BARC (20). Access site hematoma size has also been used as an outcome measure in studies comparing radial with femoral access. BARC bleeding ≥2 has shown to independently predict 1-year mortality and capture more clinically significant bleeding than TIMI minor/major and GUSTO moderate/severe criteria (20,21). Importantly, hematoma size alone, not meeting criteria for other bleeding outcome measures, has not shown any association with clinically relevant endpoints (51). The current trial will use the BARC bleeding score for the primary outcome measure to detect a clinically relevant difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC. Besides bleeding and vascular complications, vascular access may also have a potential effect on extremity function (52,53). Although upper extremity dysfunction is present in a small proportion of patients after TRA, it can lead to important morbidity for the affected patients (52–55). Extremity dysfunction may be more pronounced in patients with large-bore access. In addition, current literature does not provide an insight around prevalence and significance of lower extremity function after TFA (53). Therefore, we will assess the occurrence of extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be valuable information for both patients and doctors.

In conclusion, The COLOR trial is the first prospective multicenter randomized trial comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290 patients are randomized. The results of this trial will provide important insights about the safety and efficacy of large-bore TRA and TFA for complex PCI, with a potential impact on daily practice.

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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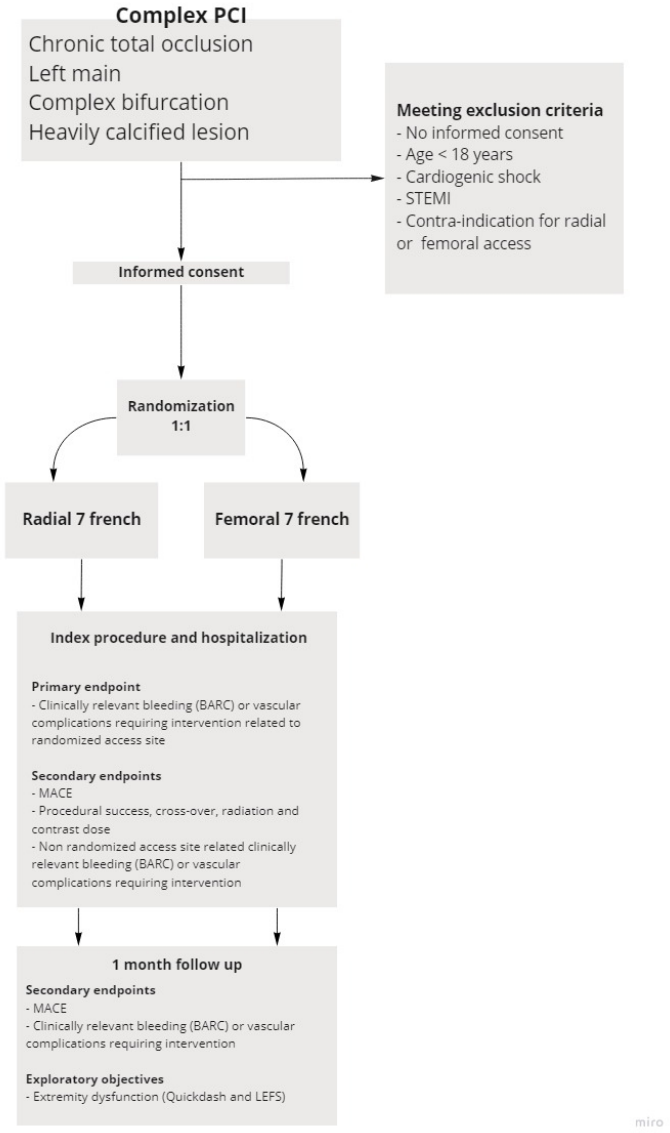

Figure 1: enrollment flowchart of the COLOR trial

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
Administrative information			
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
Introduction			
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			
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
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P 6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P 6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P 6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	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
Ethics and dissemination			
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" license.

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

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

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Conflict of interest

Maarten A.H. van Leeuwen, Adel Aminian and 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.

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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

TRA= transradial access
TF = transfemoral
TFA = transfemoral access
Fr = French

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 transradial (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 Hospilatier Universitaire de Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-Limburg (Genk, Belgium), Geneva University Hospital (Geneva, Switzerland), VU University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United Kingdom). All centers have been selected based on their high volumes and experience with complex PCI and large bore access. For CTO, each center has a dedicated program for an average of 6 years, with 1-3 dedicated CTO operators and an average of 110 procedures per year (spreading from 55 to 200 procedures per year). 83% of CTO procedures are done with dual arterial access, with biradial access in 20%, bifemoral access in 24% and radial/femoral (hybrid) access in the remaining 49% of cases. Large bore access is used in 89% of cases. For non-CTO complex PCI, the participating centers have a dedicated program for an average of 11 years, performing an average of 245 procedures per year with 3-5 complex PCI operators.

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

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

Objectives

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

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

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

Inclusion

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

Randomization

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

Endpoints

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

will be classified according to the Bleeding Academic Research Consortium (BARC) criteria (20), and considered clinically relevant when the score is ≥ 2 (CEC adjudicated)(21). Severity and type of intervention of vascular complications is specified in the CEC manual (Supplementary file I).

Secondary safety and efficacy endpoints are:

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

Index percutaneous coronary intervention and hospitalization

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

Extremity dysfunction

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

Follow-up

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

Sample size calculation and statistics

Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the proportion of access site related bleeding or vascular complication to be 3.5% with radial access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1) will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients will be needed. Data will be analyzed according to the intention-to-treat analysis. All statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago, Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-Square test will also be used for our secondary objectives with binary outcomes. For our secondary objectives with continuous variables we will use the Student's t-test (normally distributed) or the Mann-Whitney U test (non-normally distributed). A pre-specified battery of sub-group analyses will be performed as well, including several independent risk factors for clinically significant bleeding and vascular complications. For demographics and baseline characteristics, these sub-groups consist of age ≥ 75 years, female sex, low body weight (Body Mass Index < 18.5), hypertension, peripheral arterial disease, left ventricular ejection fraction < 30%, severe renal dysfunction (Modification of Diet in Renal Disease (MDRD) < 30ml/1.73m2) and pre-existent anemia (hemoglobin <6.8 mmol/l) (13,25–30). For procedural characteristics, sub-group analyses will be performed for use of secondary access site, ultrasound guided puncture, ACT > 150 seconds right before sheath removal and use of closure device (31–34). In addition, primary and secondary endpoints will be specified for the entire population as well as for each group of complex lesions separately (CTO, left main disease, complex bifurcation and heavy calcification). Statistical analysis will be performed by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

Ethics and dissemination

Ethical approval for the study was granted by the local Ethics Committee ('Medisch Ethische Toetsing Commissie Isala Zwolle' for all Dutch sites, 'Commissie voor medische ethiek ZNA' for ZNA Middelheim, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi – ISPPC' for Centre Hospilatier Universitaire de Charleroi, 'Commission cantonale d'éthique de la recherche CCER – Republique et Canton de Geneve' for Geneva University Hospital, 'Ethik Kommission de Ärztekammer Nordrhein' for Elisabeth-Krankenhaus and 'Riverside Research Ethics Committee' for Frimley NHS) after reviewing the protocol, site-specific informed consentforms (local language and English versions, see also supplementary file II), participant education and recruitment materials, other requested documents and any subsequent modifications. Trained research nurses or physicians directly involved in the trial will introduce the trial to eligible patients. Patients will also a receive patient information form (PIF). The research nurse or physician will discuss the trial with patients in light of the information provided in the PIF and will obtain written consent from patients willing to participate in the trial. No reimbursement is provided to study participants. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All reports, data collection, process, and administrative forms will be identified by a coded identification-number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Safety and progress reports to the EC's will be made at least annually and within three months of study termination or completion. These reports will include the total number of participants enrolled and summaries of the DSMB. Any modifications to the

protocol which may have impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will have to be approved by the Ethics Committee prior to implementation. The study findings will be disseminated via publication of peer-reviewed manuscripts and presentations at international conferences, as well as through media publications. Results will be published irrespective of whether the findings are positive or negative.

Patient and Public Involvement
No patient involved

Discussion

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

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

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

In the literature, several outcome measures have been used to evaluate access site related bleeding complications, such as the Thrombolysis in Myocardial Infarction (TIMI)(67), the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO)(68) or BARC (20). Access site hematoma size has also been used as an outcome measure in studies comparing radial with femoral access. BARC bleeding ≥2 has shown to independently predict 1-year mortality and capture more clinically significant bleeding than TIMI minor/major and GUSTO moderate/severe criteria (20,21). Importantly, hematoma size alone, not meeting criteria for other bleeding outcome measures, has not shown any association with clinically relevant endpoints (69). The current trial will use the BARC bleeding score for the primary outcome measure to detect a clinically relevant difference in bleedings between TRA and TFA for complex PCI, adjudicated by a CEC. Besides bleeding and vascular complications, vascular access may also have a potential effect on extremity function (70,71). Although upper extremity dysfunction is present in a small proportion of patients after TRA, it can lead to important morbidity for the affected patients (70–73). Extremity dysfunction may be more pronounced in patients with large-bore access. In addition, current literature does not provide an insight around prevalence and significance of lower extremity function after TFA (71). Therefore, we will assess the occurrence of extremity dysfunction utilizing the QuickDASH and LEFS questionnaires, which will be valuable information for both patients and doctors.

In conclusion, The COLOR trial is the first prospective multicenter randomized trial comparing TRA with TFA using large-bore guiding catheters for complex PCI. Currently 290 patients are randomized. The results of this trial will provide important insights about the safety and efficacy of large-bore TRA and TFA for complex PCI, with a potential impact on daily practice.

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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Figure legend

Figure 1: Inclusion flowchart for the COLOR trial.
Caption: *Graphic representation of inclusion for the COLOR trial. STEMI = ST elevation myocardial infarction, BARC = Bleeding Academic Research Group, MACE = Major Adverse Cardiovascular Events.*

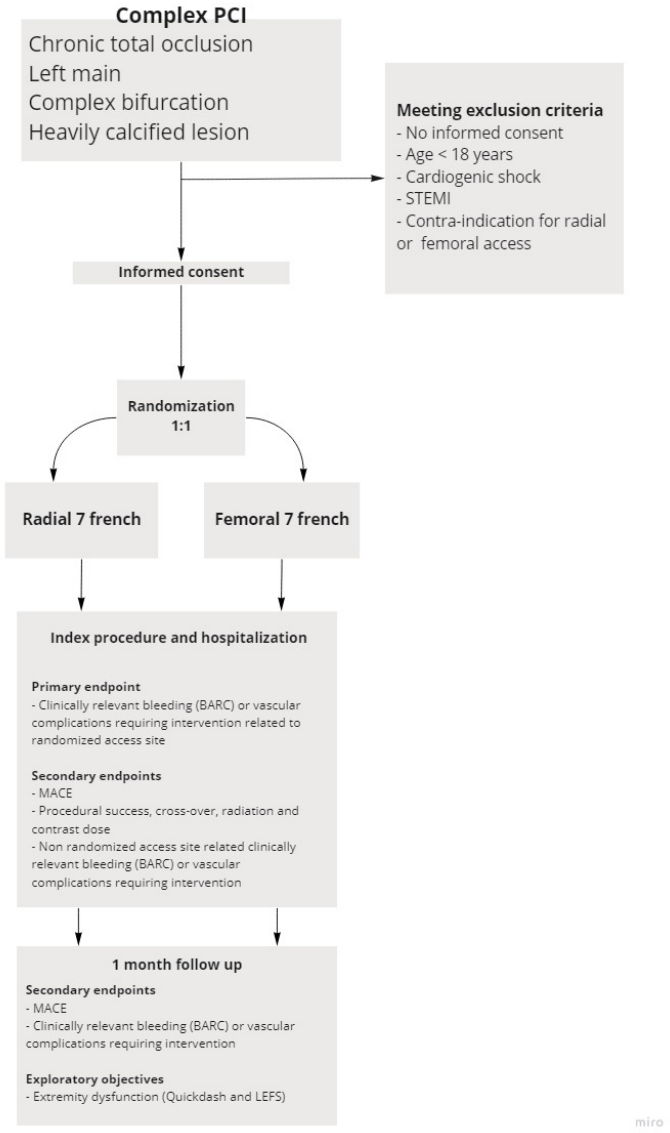

Figure 1: enrollment flowchart of the COLOR trial

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

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)

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

Zwolle, and is being conducted by multiple cardiologists in the Netherlands, Belgium, Germany, Switzerland and England. The study requires 388 subjects from different countries.

All research is looked at by an independent group of people called Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favorable opinion by the local Ethics Committee.

3. Background of the study

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

4. What your participation will entail

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

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

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

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

Aside from the potential difference in sheath, the treatment you will receive will be exactly the same as if you did not participate in the study. The procedure may sometimes require the use of a 2nd catheter. In that case, the cardiologist will determine where the access site for the second catheter will be.

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

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

5. What is expected of you?

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

6. Possible complications and other/adverse effects/complaints

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

-Bleeding

-Vascular problems

-Blood vessel closure

7. Possible advantages and disadvantages

Before you decide to participate in the study, it is important to consider the possible advantages and disadvantages.

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

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

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

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

If you do participate, you can change your mind and withdraw at any time, even during 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

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

9. End of the study

Your participation in the study ends when:

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

The researcher feels it is better for you to stop;

The Isala cardiology partnership, the government or the supervising medical.
The entire study is complete when all participants are finished.

10. Use and storage of your records

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

Some people will be allowed to access your medical and personal information. Access to your medical and personal Information will be by the study Doctor/Investigator and the research team at site. The Sponsor, representatives of the Sponsor (including the Contract Research Organisation, study monitors, auditors and project manager. Ethics committee and government agencies where permitted or required by law. This is necessary to confirm that the study has been conducted properly and reliably. - They will keep your information confidential. By signing the consent form, you agree to the collection, storage and viewing of your medical and personal records.

11. More information on your rights with regard to data processing

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

identified.

A description of this study will be available on http://www.ClinicalTrials.gov, and this web site will not include information that can identify you.
ISALA Heart Centre, Zwolle, is the Sponsor for this study based in the Netherlands. We will be using information from your medical records in order to undertake this study and will act as the data controller for this study. This means that we are for looking after your information and using it properly. ISALA Heart Centre will keep identifiable information about you for 15 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

The local site will keep your name, ID number and contact details confidential and will not pass this information to ISALA Heart Centre. The local site will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for you care, and to oversee the quality of the study. Certain individuals from ISALA Heart Centre and regulatory organisations may look at your medical and research records to check the accuracy or the research study. ISALA Heart Centre will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

12. Insurance for subjects

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

13. Informing your GP

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

15. Questions

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

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

16. Signing the consent form

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

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

Thank you for your reading this information sheet.

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
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
Administrative information			
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
Introduction			
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			
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
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P 6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P 6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P 6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P 6
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 7
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
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
	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	P 7
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	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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Complex Large-Bore Radial Percutaneous Coronary Intervention: Rationale of the COLOR trial study protocol

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

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

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Conflict of interest

Maarten A.H. van Leeuwen, Adel Aminian and 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.

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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 – Republique et Canton de Geneve', '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

MACE = major adverse cardiovascular events
AE = adverse event
SAE = serious adverse event
TR= transradial
TRA= transradial access
TF = transfemoral
TFA = transfemoral access
Fr = French

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 transradial (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 Hospilatier Universitaire de Charleroi (Charleroi, Belgium), ZNA Middelheim (Antwerpen, Belgium), Hospital Oost-Limburg (Genk, Belgium), Geneva University Hospital (Geneva, Switzerland), VU University Medical Center (Amsterdam, The Netherlands) and Frimley NHS (Surrey, United Kingdom). All centers have been selected based on their high volumes and experience with complex PCI and large bore access. For CTO, each center has a dedicated program for an average of 6 years, with 1-3 dedicated CTO operators and an average of 110 procedures per year (spreading from 55 to 200 procedures per year). 83% of CTO procedures are done with dual arterial access, with biradial access in 20%, bifemoral access in 24% and radial/femoral (hybrid) access in the remaining 49% of cases. Large bore access is used in 89% of cases. For non-CTO complex PCI, the participating centers have a dedicated program for an average of 11 years, performing an average of 245 procedures per year with 3-5 complex PCI operators.

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

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

Objectives

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

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

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

Inclusion

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

Randomization

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

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

Endpoints

Clinically relevant access site related bleeding or vascular complication requiring intervention of the randomized access site during hospitalization is defined as primary endpoint. Bleeding will be classified according to the Bleeding Academic Research Consortium (BARC) criteria (23), and considered clinically relevant when the score is ≥ 2 (CEC adjudicated)(24). Severity and type of intervention of vascular complications is specified in the CEC manual (Supplementary file I).

Secondary safety and efficacy endpoints are:

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

Index percutaneous coronary intervention and hospitalization

Radial access will be performed according to the local protocol, using direct needle technique or venous cannula technique, followed by introduction of a 7 Fr Glidesheath Slender. A standard cocktail of nitroglycerine and verapamil will be given intra-arterially after radial sheath placement. Femoral access will be performed using direct needle technique, followed by introduction of a standard 7 Fr femoral sheath. Use of ultrasound for vascular access will be left to the operator's discretion. A bolus of unfractionated heparin will be given after sheath placement, adapted to the patient's body weight. Activated clotting time (ACT) measurements will be performed during the procedure according to local protocol. Additional arterial access will be left to the discretion of the operator, i.e. in case of double arterial access for hybrid CTO treatment. In case of randomization to TRA, a 7 Fr Glidesheath Slender must be inserted in the right or left radial artery. Then, the operator can decide which secondary access site he/she will use and which sheath size is needed for this secondary access. This can be the contralateral radial artery (bi-radial approach) or the femoral artery. If the patient is randomized to femoral access and needs dual access, a 7 Fr femoral sheath must be placed in the femoral artery (randomized access site) and the operator can decide which second access he/she will use (radial or femoral). Only clinically significant bleeding or vascular complications attributable to the randomized access site will be analyzed for the primary endpoint, complications attributable to the secondary access site will be analyzed as secondary endpoint. PCI will be performed according to standard procedures with modern drug eluting stents. The applied technique for complex PCI will be left to the discretion of the operator. Patent hemostasis after radial access with the reverse Barbeau test is highly recommended (25). The type of femoral artery hemostasis will be left to the discretion of the treating interventional cardiologist; however the application of a closure device is advocated. The visual analogue scale (VAS) will be used to assess post-procedural pain of the access site(s). Before discharge the access site(s) will be checked for bleeding and vascular complications. Radial artery patency will be checked with the reverse Barbeau test (25). Additional ultrasound or doppler will be performed in those patients with suspected radial or femoral occlusion or the presence of other vascular complications.

Extremity dysfunction

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

Follow-up

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

Sample size calculation and statistics

Based on a superiority design with a type 1 error of 5% and a power of 80%, assuming the proportion of access site related bleeding or vascular complication to be 3.5% with radial access and 11.3% with femoral access, a total of 352 patients (using a sampling ratio of 1) will be needed (18). Taking into account a 10% rate loss to follow-up, a total of 388 patients will be needed. Data will be analyzed according to the intention-to-treat analysis. All statistical tests will be two-tailed, and a p-value of <0.05 will be considered statistically significant. All statistical analyses will be performed with SPSS (SPSS, Inc., Chicago, Illinois). For our primary objective we will use the Pearson Chi-Square test. The Pearson Chi-Square test will also be used for our secondary objectives with binary outcomes. For our secondary objectives with continuous variables we will use the Student's t-test (normally distributed) or the Mann-Whitney U test (non-normally distributed). A pre-specified battery of sub-group analyses will be performed as well, including several independent risk factors for clinically significant bleeding and vascular complications. For demographics and baseline characteristics, these sub-groups consist of age ≥ 75 years, female sex, low body weight (Body Mass Index < 18.5), hypertension, peripheral arterial disease, left ventricular ejection fraction < 30%, severe renal dysfunction (Modification of Diet in Renal Disease (MDRD) < 30ml/1.73m2) and pre-existent anemia (hemoglobin <6.8 mmol/l) (13,28–33). For procedural characteristics, sub-group analyses will be performed for use of secondary access site, ultrasound guided puncture, ACT > 150 seconds right before sheath removal and use of closure device (34–37). In addition, primary and secondary endpoints will be specified for the entire population as well as for each group of complex lesions separately (CTO, left main disease, complex bifurcation and heavy calcification). Statistical analysis will be performed by an independent contract research organization (Diagram BV, Zwolle, the Netherlands).

Ethics and dissemination

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

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

Patient and Public Involvement

No patient involved

Discussion

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

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

The most important argument to refrain from TR PCI for complex coronary lesions is the limited diameter of the radial artery. Current standard 7 Fr radial sheaths have an outer diameter of 2.97-3.19 mm (59). As such, the percentage of patients with a radial artery smaller than the outer diameter of a 7 Fr sheath ranges between 29% and 67% in men and between 60% up to 85% in women (60). This suggests that using a standard 7 Fr sheath for TRA will result in sheath to artery mismatch in a significant proportion of patients, increasing the risk of vascular complications. Radial artery occlusion (RAO) is the most frequent complication after radial access, with increasing RAO rates with increasing sheath size (61). In most instances, RAO will not lead to any clinical sequelae, however in rare cases RAO may require intervention because of extremity dysfunction or ischemia (62,63). Moreover, RAO prohibits future re-cannulation of the radial artery, harvesting the radial artery as conduit for CABG or creating a hemodialysis shunt (64). Other arguments to use the femoral artery for complex PCI have been suggested, such as improved back-up with potential higher procedural success rates and shorter procedural time and lower radiation dose. However, this is not supported by observational data showing similar effectiveness, procedural success rates, cross-over rates, radiation dose and contrast use for TRA and TFA (11,16,17,39).
Several technologies have been developed to facilitate large bore access through the radial artery (65). A sheathless approach for example was shown to be a feasible alternative for large bore radial access (66). The 7.5 Fr Eaucath sheathless guiding catheter (ASAHI Intecc, Aichi, Japan) has the same inner diameter as a regular 7 Fr guiding catheter, but an outer diameter of 2.49 mm, resulting in a large reduction in outer diameter (approximately 2 Fr) compared with a standard 7 Fr sheath (67). However, PCI with sheathless guiding catheters requires specific experience due to the highly hydrophilic coating, and limited evidence exists regarding the true impact on RAO (68,69). Miniaturization of TR equipment can also be achieved through a sheath-based approach. Thanks to a reduction in sheath wall thickness ("slender technology"), thin-walled sheaths have reduced their outer diameter while maintaining the same inner diameter. The 7 Fr Glidesheath Slender (Terumo, Japan) is the first commercially available 7 Fr thin-walled sheath, combining an inner diameter of 2.46mm, compatible with any 7 Fr guiding catheter, with a reduced outer diameter of 2.79mm. A recent prospective multicenter study has shown the feasibility and safety of using the 7 Fr Glidesheath Slender for complex TR-PCI in daily practice with a high rate of procedural success and low rate of vascular complications (14).

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

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

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

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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Figure legend

Figure 1: Inclusion flowchart for the COLOR trial.
Caption: *Graphic representation of inclusion for the COLOR trial. STEMI = ST elevation myocardial infarction, BARC = Bleeding Academic Research Group, MACE = Major Adverse Cardiovascular Events.*

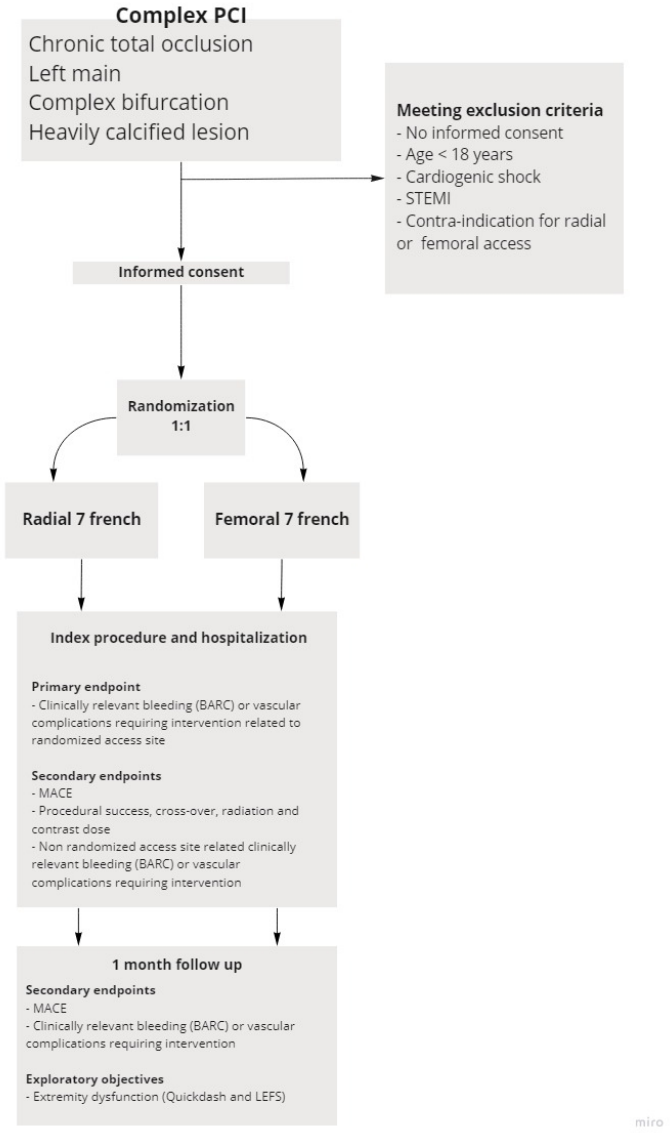

Figure 1: enrollment flowchart of the COLOR trial

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

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)

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

Zwolle, and is being conducted by multiple cardiologists in the Netherlands, Belgium, Germany, Switzerland and England. The study requires 388 subjects from different countries.

All research is looked at by an independent group of people called Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favorable opinion by the local Ethics Committee.

3. Background of the study

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

4. What your participation will entail

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

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

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

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

Aside from the potential difference in sheath, the treatment you will receive will be exactly the same as if you did not participate in the study. The procedure may sometimes require the use of a 2nd catheter. In that case, the cardiologist will determine where the access site for the second catheter will be.

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

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

5. What is expected of you?

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

6. Possible complications and other/adverse effects/complaints

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

-Bleeding

-Vascular problems

-Blood vessel closure

7. Possible advantages and disadvantages

Before you decide to participate in the study, it is important to consider the possible advantages and disadvantages.

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

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

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

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

If you do participate, you can change your mind and withdraw at any time, even during 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

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

9. End of the study

Your participation in the study ends when:

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

The researcher feels it is better for you to stop;

The Isala cardiology partnership, the government or the supervising medical.
The entire study is complete when all participants are finished.

10. Use and storage of your records

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

Some people will be allowed to access your medical and personal information. Access to your medical and personal Information will be by the study Doctor/Investigator and the research team at site. The Sponsor, representatives of the Sponsor (including the Contract Research Organisation, study monitors, auditors and project manager. Ethics committee and government agencies where permitted or required by law. This is necessary to confirm that the study has been conducted properly and reliably. - They will keep your information confidential. By signing the consent form, you agree to the collection, storage and viewing of your medical and personal records.

11. More information on your rights with regard to data processing

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

identified.

A description of this study will be available on http://www.ClinicalTrials.gov, and this web site will not include information that can identify you.
ISALA Heart Centre, Zwolle, is the Sponsor for this study based in the Netherlands. We will be using information from your medical records in order to undertake this study and will act as the data controller for this study. This means that we are for looking after your information and using it properly. ISALA Heart Centre will keep identifiable information about you for 15 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

The local site will keep your name, ID number and contact details confidential and will not pass this information to ISALA Heart Centre. The local site will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for you care, and to oversee the quality of the study. Certain individuals from ISALA Heart Centre and regulatory organisations may look at your medical and research records to check the accuracy or the research study. ISALA Heart Centre will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

12. Insurance for subjects

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

13. Informing your GP

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

15. Questions

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

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

16. Signing the consent form

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

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

Thank you for your reading this information sheet.

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
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
Administrative information			
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
Introduction			
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			
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
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P 6
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P 6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P 6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P 6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P 6
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P 7
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
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
	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	P 7
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	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.