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ULTrasound-guided TRAnsfemoral puncture in COmplex Large bORe PCI: study protocol of the UltraCOLOR trial

Thomas A Meijers ,[1] Alexander Nap,[2] Adel Aminian,[3] Joseph Dens,[4] Koen Teeuwen,[5] Jan-Peter van Kuijk,[6] Marleen van Wely,[7] Thomas Schmitz,[8] Yoann Bataille,[9] Adriaan O Kraaijeveld,[10] Vincent Roolvink,[1] Renicus S Hermanides,[1] Thijs L Braber,[1] Niels van Royen,[7] Maarten A H van Leeuwen [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Maarten A H van Leeuwen; m.a.h.van.leeuwen@isala.nl

ABSTRACT

Introduction Although recently published evidence favours transradial access (TRA) when using large-bore guiding catheters for percutaneous coronary intervention (PCI) of complex coronary lesions, the femoral artery will still be used in a considerate proportion of patients undergoing complex PCI, especially in PCI of chronic total occlusions (CTO). Ultrasound-guided puncture of the femoral artery may reduce clinically relevant access site complications, but robust evidence is lacking up to date.

Methods and analysis A total of 542 patients undergoing complex PCI, defined as PCI of CTO, complex bifurcation, heavy calcified lesion or left main, in which the 7-F or 8-F transfemoral access is required, will be randomised to ultrasound-guided puncture or fluoroscopy-guided puncture. The primary outcome is the incidence of the composite end-point of clinically relevant access site related bleeding and/or vascular complications requiring intervention. Access site complications 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 ('Medisch Ethische Toetsing Commissie Isala Zwolle') for all Dutch sites, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi—ISPPC' for Centre Hospitalier Universitaire de Charleroi and 'Ethik Kommission de Ärztekammer Nordrhein' for Elisabeth-Krankenhaus). The trial outcomes will be published in peer-reviewed journals of the concerned literature. The *ul*trasound guided *tra*nsfemoral access in *co*mplex *l*arge b*o*r*e* PCI trial has been administered in the ClinicalTrials.gov database, reference number: NCT03846752.

Registration details ClinicalTrials.gov identifier: NCT03846752.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The design as a randomised 1:1 open-label study and the vast experience with large bore transfemoral access in complex percutaneous coronary intervention of the participating centres
⇒ Clinical Event Committee adjudicated and clinically relevant primary endpoint.
⇒ As a limitation, bias could be derived from the unblinded nature of the study for the treating interventional cardiologist.
⇒ As a limitation, experience and proficiency using ultrasound may vary among operators and centres, although mitigated by thorough on-site or online instruction in addition to use of a step-by-step instruction manual.

BACKGROUND

For complex percutaneous coronary intervention (PCI), transfemoral access (TFA) remains frequently used when large bore guiding catheters are considered necessary.[1 2] However, femoral access is strongly associated with increased bleeding and vascular complications, especially when large-bore guiding catheters are used.[3–5] The recently published Complex Large Bore Radial access (COLOR) and Femoral or Radial Approach in the Treatment of Chronic Total Occlusion (FORT CTO) trials support the use of large bore transradial access (TRA) for complex PCI, leading to significantly less access site complications and similar procedural success rates as compared with TFA.[6 7] A considerate proportion of patients will not be suitable for large bore TRA, though, for example, in case of anticipated small radial artery size, previous radial artery harvesting for coronary artery bypass grafting, arteriovenous shunts for haemodialysis, radial artery occlusion or spasm. In addition, when dual arterial access is applied in case of CTO PCI, large bore radial combined with large bore femoral artery access is predominantly used, as demonstrated in both the COLOR and FORT CTO trials. Improvement and refinement of femoral access site management are therefore of the utmost importance.

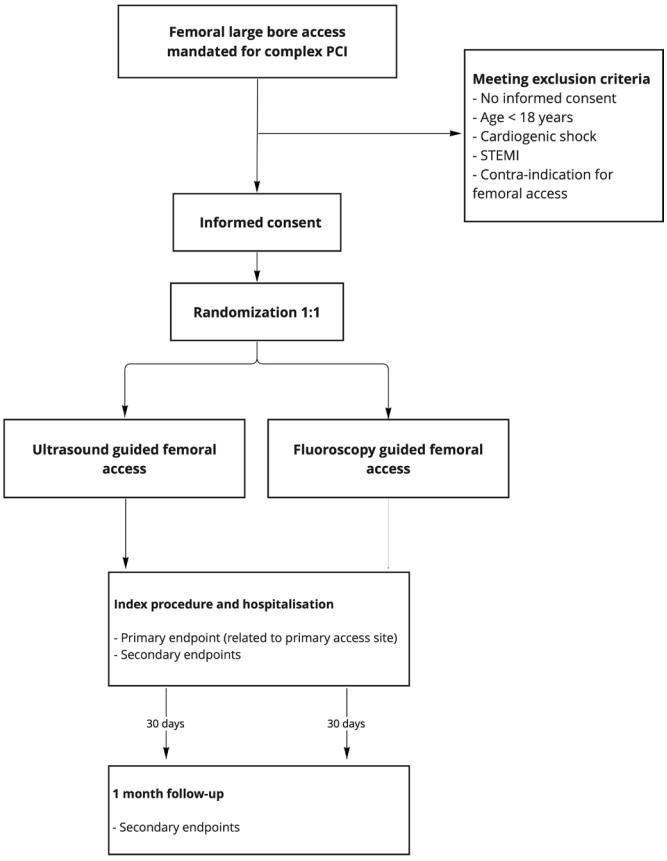

Figure 1 Study flow chart. Graphic representation of inclusion for the *ul*trasound guided *tra*nsfemoral access in *co*mplex *l*arge b*or*e PCI trial. PCI, percutaneous coronary intervention; STEMI-ST, segment elevation myocardial infarction.

Ultrasound-guided puncture of the femoral artery might reduce bleeding or vascular complications. By direct visualisation of the puncture site, the use of ultrasound may prevent a too high or too low puncture, both associated with clinically significant bleeding and vascular complications.[8–10] Additionally, it can prevent puncture into calcified lesions and may decrease the risk of vascular closure device (VCD) failure, which occurs in about 3% of cases.[11 12] Accidental puncture or even damage of adjacent structures, such as the femoral nerve or femoral vein, can also be avoided by using ultrasound-guided puncture.

Data regarding the benefit of ultrasound-guided femoral artery puncture is scarce. For transfemoral transcatheter aortic valve replacement, limited non-randomised evidence shows substantial reductions in access-related vascular and bleeding complications when using ultrasound-guided femoral puncture for large-bore cannulation.[13] Ultrasound-guided access of the femoral artery for coronary procedures, however, is not common practice and is not recommended in current international guidelines. In experienced complex PCI centres ultrasound was used for large-bore TFA in the minority of patients (40% in the COLOR trial).[6] It was previously shown that ultrasound-guided puncture of the femoral artery in patients undergoing coronary catheterisation or intervention with standard 5-F or 6-F sheaths might reduce vascular complications. However, this was mainly driven by large haematomas which proved not to be associated with increased morbidity or mortality.[14–16] A recently published meta-analysis of randomised trials addressing ultrasound-guided cannulation of the femoral artery showed no significant difference in major bleeding, possibly because of the small sample size of most studies and variable endpoint definitions.[17] In 2022, a retrospective trial including 418 patients requiring femoral access showed clear reduction of access site complications using ultrasound-guided access combined with VCD.[18]

The primary aim of this trial will be to assess if application of ultrasound guidance for complex PCI with large-bore access (≥ 7F) reduces the occurrence of clinically relevant bleeding and vascular complications.

METHODS

Study design

The *ul*trasound guided *tra*nsfemoral access in *co*mplex *l*arge b*or*e PCI (UltraCOLOR) trial is an investigator-initiated international multicentre study with a prospective, randomised controlled design. Participating centres are the Isala Heart Center (Zwolle, the Netherlands), Catharina Hospital (Eindhoven, the Netherlands), Radboud University Medical Center (Nijmegen, The Netherlands), Elisabeth-Krankenhaus (Essen, Germany), Centre Hospilatier Universitaire de Charleroi (Charleroi, Belgium), St. Antonius Hospital (Nieuwegein, the Netherlands), Utrecht University Medical Center (Utrecht, the Netherlands) Hospital Oost-Limburg (Genk, Belgium), Amsterdam University Medical Center (Amsterdam, The Netherlands) and Jessa hospital (Hasselt, Belgium). All centres have been selected based on their experience with complex PCI and ultrasound-guided access.

Trial organisation

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 (patient information file/informed consent form can be found under online supplemental material I). 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 (AEs) is being performed by an independent Data Safety Monitoring Board (DSMB). A Clinical Events Committee (CEC) will review and adjudicate all end-point related AEs. The UltraCOLOR trial has been administered in the ClinicalTrials.gov database, reference number: NCT04837404

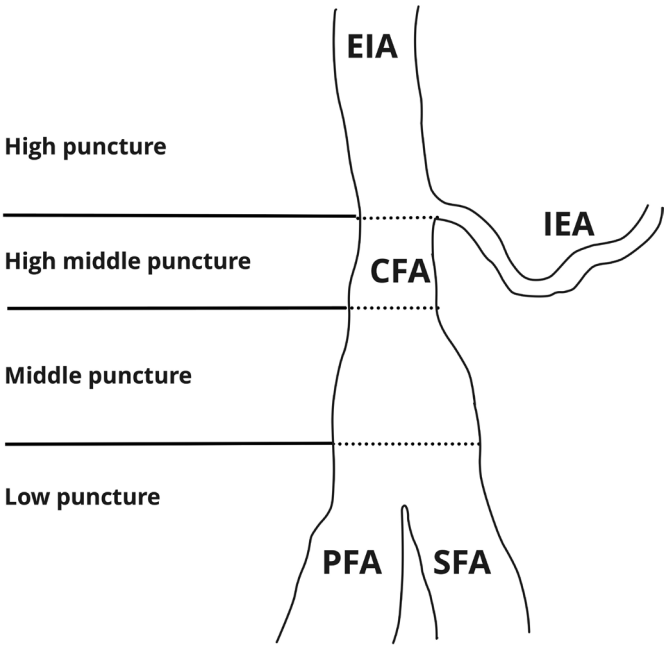

Figure 2 Puncture height classification for femoral artery access. CFA, common femoral artery; EIA, external iliac artery; IEA, inferior epigastric artery; PFA, profunda femoral artery; SFA, superficial femoral artery.

Objectives

The primary objective of this study is to confirm the hypothesis that ultrasound-guided puncture for complex PCI with large-bore access (≥ 7F) is superior to fluoroscopy-guided puncture with regard to clinically relevant bleeding (Bleeding Academic Research Consortium (BARC) 2, 3 or 5) and/or vascular access-site complications.

As secondary objectives, ultrasound-guided and fluoroscopy-guided TFA will be compared with regard to procedural duration, first pass puncture, accidental venous puncture and VCD failure. MACE at discharge and 1-month follow-up will be compared between both randomised groups. Clinically relevant complications of the additional access site (if applicable) will also be studied.

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, heavily calcified lesions which may require calcium modification techniques (rotational atherectomy or intravascular lithotripsy) and complex bifurcations in whom the operator anticipates the use of at least one 7-F or 8-F femoral access site, are screened for inclusion. See figure 1 for study flow chart. 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 characterised 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 large bore femoral access, such as occlusive peripheral artery disease, will be excluded as well.

Randomisation

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 according to a computer-generated random schedule in random permuted blocks with stratification by site.[22] There will be no blinding of the randomisation assignment.

Endpoints

Primary endpoint is defined as

- Clinically relevant access site related bleeding or vascular complication requiring intervention of the primary femoral access site during hospitalisation. Bleeding will be classified according to the 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.

Secondary endpoints are defined as

- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the primary femoral access site at 1 month.
- MACE (hospitalisation and 1 month).
- Procedural duration.
- First pass puncture.
- Number of access attempts.
- Accidental venepuncture.
- Cross-over (fluoroscopy guided to ultrasound guided or vice versa).
- Suboptimal femoral artery puncture, based on the ileofemoral angiogram (scored by operator according to figure 2).
- Vascular complication not requiring intervention of the primary femoral access site (hospitalisation and 1 month).
- Vascular complication not requiring intervention of the secondary femoral or radial access site (hospitalisation and 1 month).
- BARC 2, 3 or 5 access-site related bleeding or vascular complication requiring intervention of the secondary femoral or radial access site (hospitalisation and 1 month).

Index PCI and hospitalisation

Femoral access will be performed according to the randomised strategy. After sheath placement, a bolus of unfractionated heparin will be given, adapted to the patient's body weight. The need for additional arterial

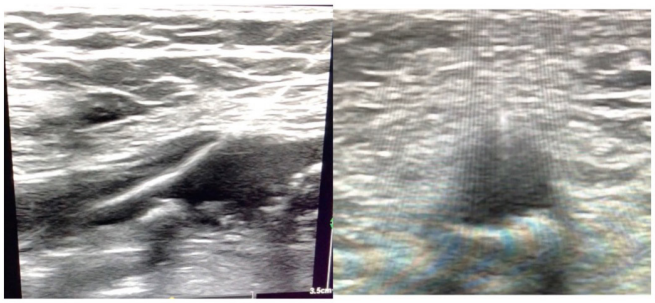

Figure 3 Long axis (left) and short axis (right) view of guidewire entering the common femoral artery at the correct position.

access is left to the discretion of the operator. In case of dual large-bore femoral access, the operator decides which access site (right or left femoral artery) will be used for the primary endpoint (this is defined as primary access) and which access site for the secondary endpoint (this is defined as secondary access) before application of local anaesthetics. In case of secondary radial access site, the application of ultrasound for radial access will be left to the discretion of the operator. In case of bifemoral access, the application of the randomised strategy (ultrasound or angio based) for the secondary femoral access is highly recommended. PCI strategy and choice of materials will be left to the discretion of the operator as well. The activated clotting time during and at the end of the procedure will be obtained before removal of the arterial sheath(s). Active anticoagulants during procedure will be reported. An ileofemoral angiogram is mandated before closure device placement to check for complications and access location, in which adequate projection of the C-arc to clearly identify the bifurcation is important. It is recommended to perform this angiogram right after sheath placement, and before administration of intra-arterial heparin. Haemostasis will be achieved according to the local protocol using a closure device unless contraindicated, in the latter case manual compression with bandage will be applied for hemostasis. Failure of VCD will be documented. Pain score related to the primary femoral access site directly after haemostasis will be collected according to the numerical rating scale (NRS). Before discharge, all access sites should be checked for potential complications including haematoma (haematoma size is documented). Additional ultrasound should be performed within 1 month in case of suspected femoral artery occlusion or other vascular complications of the (additional) femoral or radial artery.

Fluoroscopy-guided femoral access

A detailed step-by-step approach of fluoroscopy-guided femoral puncture is provided to all participating centres. Step 1 comprises disinfection of the groin and identification of the course of the femoral artery by palpation. The X-ray tube is placed in anterior–posterior position at the level of the groin. In step 2, fluoroscopy is used to identify the ideal site of femoral artery puncture, which is a point~1 cm lateral to the most medial aspect of the femoral head, midway between its superior and inferior borders (Rupp's rule[9]). The lower border of the femoral head is marked with a metal clamp or haemostat. In step 3, a local anaesthetic is administered subcutaneously, followed by skin puncture at the lower border of the femoral head (marked at step 2) with the needle entering the skin at a 30°–45° angle while palpating the femoral artery (with a steeper angle in more obese patients). Use of micropuncture and/or skin nick is optional and according to operators' experience and preference.[25] Finally in step 4, once the femoral artery is cannulated, good pulsatile blood flow should be ensured before advancing the guidewire through the needle into the femoral artery, iliac artery and descending aorta under fluoroscopic guidance followed by sheath placement. It is recommended to perform the obligated femoral artery angiogram right after sheath placement (in order to detect possible complications before administration of intra-arterial heparin). Height of femoral artery access is checked and scored according to figure 2 (groups 1–4). Use of ultrasound in the fluoroscopy-guided group (in case of failure to cannulate the femoral artery) is considered cross-over.

Ultrasound-guided femoral access

For the ultrasound-guided group, 2-dimensional real-time ultrasound will be used to identify the optimal location for puncture of the femoral artery.[14] A full description of a step-by-step approach of ultrasound-guided femoral puncture is provided to all participating centres. Step 1 comprises disinfection of the groin and identification of the course of the femoral artery by palpation. Use of fluoroscopy to identify the femoral head is optional in the ultrasound-guided group. Next, a 5–12 MHz lineair (vascular) ultrasound probe is inserted into a sterile cover after application of non-sterile ultrasound gel inside the cover. The operator should ensure that there is no air between probe and cover. Sterile ultrasound gel is used on the skin. In step 2, settings for the ultrasound device visualisation (depth and gain) should be optimised. In step 3, the common femoral artery (CFA) trajectory and bifurcation should be both visualised in short and long axes (figure 3). A reasonable calcium-free spot should be identified for the puncturing the CFA. Local anaesthetic is administered subcutaneously under direct visualisation with ultrasound. In step 4, an 18-gauge needle is used for arterial puncture at a 30°–45° angle under continuous ultrasound visualisation. Use of micropuncture with an 21-gauge needle and/or skin nick is optional and according to operators' experience and preference.[25] The needle entry in the designated CFA location is monitored first by 'tenting' of the CFA in the middle of the 'dome' of the artery (figure 3). The correct height and freedom of calcification may be additionally confirmed in the longitudinal view. Puncture can then be performed with subsequent appearance of pulsatile arterial blood from the needle. In step 5, good pulsatile blood flow should

be ensured before advancing the guidewire through the needle into the femoral artery, iliac artery and descending aorta. Verification of correct entrance location and guidewire position may be confirmed with ultrasound in both short and long axis views before sheath placement. It is recommended to perform the obligated femoral artery angiogram right after sheath placement (in order to detect possible complications before administration of intra-arterial heparin). Height of femoral artery access should also be checked and scored according to figure 2 (groups 1–4).

Follow-up

Follow-up will be performed 1 month after index PCI by either phone call or outpatient clinic visit. MACE and access site bleeding or vascular complications will be documented. Residual pain of the primary femoral access site will be scored according to the NRS. AEs will be monitored from inclusion to 1-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

The appropriate sample size was estimated at n=271 subjects, based on a type 1 error rate of 5% and a power of 80%, assuming a 16% complication rate in the comparator group and 49% reduction (7.84% complication rate) in the ultrasound-guided group.[6 15] A total of 542 subjects (271 subjects in each group) will need to be randomised in this trial.

The primary analysis will take place after last subject follow-up. An intention-to-treat analysis will be performed. Demographics and baseline characteristics, primary and secondary outcomes per group will be analysed using descriptive statistics. Categorical variables will be summarised by frequency and percentages. Continuous variables will be summarised by mean, SD as well as median and IQR. A subject reaches the primary endpoint when at least one complication according to the definition has occurred. The primary outcome is the incidence of access-site related BARC 2, 3 or 5 or vascular complication requiring intervention during index hospitalisation. In case of double arterial access (eg, in CTO procedures), the primary endpoint will only be scored for the primary access site. For our primary objective we will use the Pearson Chi-Square test. To account for confounding variables, the main analysis will be performed using logistic regression with treatment allocation and use of additional antiplatelets as fixed effects. The effect of the intervention will be presented as the OR of access-site related BARC 2, 3 or 5 or vascular complication requiring intervention during index hospitalisation and its 95% CI. Crude proportions by treatment arm will also be reported with an unadjusted OR and 95% CI, and a χ^2 (or Fisher exact) test p value. For secondary endpoints, differences in incidences will be statistically tested between groups by using Fisher's exact test or Pearson's χ^2 test. Differences in means of continuous data will be statistically tested by performing Student's t-test or, in case the data are not normally distributed, the Mann-Whitney-Wilcoxon test. The time to event for MACE will be plotted by means of Kaplan-Meier survival curves. In case a patient is lost to follow-up or the outcome variable is missing, we will use the latest time available if the event of interest did not occur during the observation period (censoring). We will test for differences between the survival distributions in the two treatment groups by means of the logrank test. All statistical tests will be two tailed. A p-value<0.05 is considered to be statistically significant.

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, 'Comité Medische Ethiek Ziekenhuis Oost-Limburg' for Hospital Oost-Limburg, 'Comité d'éthique CHU-Charleroi—ISPPC' for Centre Hospilatier Universitaire de Charleroi, 'Ethik Kommission de Ärztekammer Nordrhein' for Elisabeth-Krankenhaus and (insert METC Hasselt) after reviewing the protocol, site-specific informed consent forms (local language and English versions), 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 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 ECs will be made at least annually and within 3 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. The Standard Protocol Items: Recommendations for Interventional Trials checklist of this trial can be found under online supplemental material II).

Patient and public involvement

No patients or public involved in the design of the study.

DISCUSSION

Although several observational trials and, more recently, two randomised controlled trials have shown that complex PCI performed through large bore TRA reduces access site complications without compromising on procedural efficacy, large bore TFA will still be applied in a considerate amount of patients. This will especially be true when dual arterial access is used in CTO PCI. Dual arterial access as part of the hybrid algorithm is used for distal target visualisation and retrograde access.[26 27] In both the COLOR trial and the FORT trial, biradial access was used only in a minority of patients regardless of randomised access site (21% and 30%, respectively).[6 7] In a substudy of the RECHARGE registry, full transradial access (single TRA or dual TRA) was compared with TFA (either single TFA, dual TFA or TFA combined with TRA) using propensity matching.[28] Although procedural success was comparable between both groups, only a minority (48%) of the full TRA group had dual arterial access. Comparable procedural success rates were also noted in an observational study by Meah *et al*, comparing biradial with femoral (either radial/femoral or bifemoral) access.[29] Next to patients requiring dual arterial access, patients with contraindications for large bore radial access or failed attempt to TRA also need to be treated by large bore TFA. In the COLOR trial, almost 10% of screened patients were not eligible for large bore TRA. The need for additional measures to reduce large bore femoral access bleeding and vascular complications is therefore still of paramount importance.

Ultrasound-guided puncture is widely accepted and used in central venous access. It is endorsed by American Institute of Ultrasound in Medicine guidelines mainly because of less access site related complications, shorter procedural time and time to cannulation.[30–32] For large bore TFA, guidelines regarding ultrasound-guided puncture are lacking up to now due to gaps in scientific evidence. Possible advantages are numerous though. Ultrasound-guided puncture prevents puncture above the inguinal ligament, which is associated with retroperitoneal haemorrhage[33–35] and also prevents puncture below the CFA bifurcation, which is associated with pseudoaneurysm and arteriovenous fistula.[8 10] The ideal puncture site is therefore defined above (proximal to) the CFA bifurcation and below the inferior margin of the inferior epigastric artery (‘middle puncture’ as depicted in figure 2). Up to 30% of patients have a high or very high CFA bifurcation.[36] In these patients, fluoroscopy-guided femoral artery puncture using the margins of the femoral head as markers does not prevent puncture in or below the bifurcation. Ultrasound-guided puncture circumvents these limitations and may therefore be superior to fluoroscopy-guided puncture. In addition, the diameter of the superficial and profunda femoral arteries are usually smaller than the CFA, limiting the use of a VCD. For example, the use of an Angioseal (Terumo, Japan) closure device in vessels with a diameter of less than 5 mm is not recommended.[37 38] Ultrasound-guided puncture may prevent cannulation in the profunda or superficial femoral arteries and therefore prevent VCD failure.

Several studies have been performed regarding ultrasound-guided puncture in regular coronary angiography or PCI using regular 5-F or 6-F sheaths. The Femoral Arterial Access with Ultrasound Trial by Seto *et al* compared fluoroscopy-guided puncture with ultrasound-guided puncture using standard sized sheaths (average 5.6 F) and showed a reduction in vascular complications, mainly driven by reduction in large haematomas (>5 cm).[14] More recently, Katirsibasi *et al* reported lower rates of haematomas, pain and arteriovenous fistulae in patients randomised to ultrasound-guided puncture compared with manual technique.[39] Both trials were included in a meta-analysis by Sorrentino *et al* in 2020, showing significant reduction in any access site complications with ultrasound-guided access, but no clinically significant reduction in major access-site related bleeding events.[17] In 2022, Iannopolli *et al* retrospectively analysed access site related bleeding in 418 patients receiving femoral access (median sheath size 6 F) for multiple combinations of puncture and closure techniques. Access site complications were classified using the BARC criteria. Incidence of bleeding was significantly lower in patients treated with ultrasound-guided access combined with a suture-based VCD.[18] Heterogeneity in safety endpoint definitions and study designs hampers comparability of previous trials, though. The UltraCOLOR trial uses the standardised BARC criteria to classify bleeding complications of the access site.[23] 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, haematoma size alone, not meeting criteria for other bleeding outcome measures, has not been shown to have an association with clinically relevant endpoints.[16] Randomised controlled trials adequately powered to detect a significant difference in clinically relevant bleeding or vascular complications are lacking, especially for large bore TFA. Since the risk for access site complications is the greatest in patients requiring large bore access for complex PCI, the UltraCOLOR trial was designed to test the advantage of ultrasound-guided puncture in this group of patients.

One of the potential limitations in performing a trial assessing ultrasound-guided puncture is the heterogenic proficiency of operators in using ultrasound for femoral access and variable puncture techniques.

Therefore, participation was limited to high volume complex PCI centres and operators with ample experience in ultrasound-guided access and large bore femoral access site management. In addition, all participating centres received on-site or online training through a prerecorded demonstration video. As for the control group, extensive instructions regarding fluoroscopy-guided puncture were provided as well. These measures should limit the intra-operator variability. Another possible limitation is that the operator is inevitably unblinded to the randomised strategy. This has been countered by establishing an independent and blinded Clinical Event Committee which will adjudicate all safety endpoints of this trial.

In conclusion, the UltraCOLOR trial is the first prospective multicentre randomised trial comparing ultrasound guided with fluoroscopy-guided TFA using large-bore guiding catheters for complex PCI. Currently, 300 patients have been randomised. The results of this trial will provide important insights in the role of ultrasound guidance for large bore TFA. If this trial can show that the use of ultrasound has clear benefits regarding access site complications, it will have a significant impact on daily practice.

Author affiliations
[1]Department of Cardiology, Isala Heart Centre, Zwolle, The Netherlands
[2]Department of Cardiology, Amsterdam UMC Locatie VUmc, Amsterdam, The Netherlands
[3]Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium
[4]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium
[5]Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands
[6]Department of Cardiology, Sint Antonius Hospital, Nieuwegein, The Netherlands
[7]Department of Cardiology, Radboudumc, Nijmegen, The Netherlands
[8]Department of Cardiology, Elisabeth-Krankenhaus-Essen GmbH, Essen, Germany
[9]Department of Cardiology, Jessa Ziekenhuis vwz, Hasselt, Belgium
[10]Department of Cardiology, University Medical Centre Utrecht, Utrecht, The Netherlands

Twitter Joseph Dens @Jo Dens

Contributors MvL, AN and TAM substantially contributed to conception and design of the study protocol. TAM, AA, KT, MvW, TS, JD, YB, AOK, J-PvK, TLB, RH, VR and MvL contributed to acquisition of data. TAM and MvL contributed to analysis of data. TAM, AN, MvL and NvR contributed to interpretation of data. TAM, AN, NvR and MvL reviewed the literature, contributed to the design and wrote the draft of the manuscript. TAM, AA, KT, MvW, TS, JD, YB, AOK, J-PvK, TLB, RH, VR, NvR and MvL contributed to refinement of the study protocol and approved the final manuscript.

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ORCID iDs
Thomas A Meijers http://orcid.org/0000-0002-4298-1607
Maarten A H van Leeuwen http://orcid.org/0000-0002-4264-4280

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Supplemental material I: English language version of the patient information/informed consent form

Patient information for participation in medical-scientific research

ULTRACOLOR study

Comparative research into whether or not to use ultrasound when puncturing the femoral artery in the case of complex coronary artery angioplasty procedures with large catheters.

Introduction

Dear Sir/Madam,

With this information letter we want to ask you if you want to participate in medical-scientific research. Participation is voluntary. You will receive this letter because you will undergo an coronary angioplasty treatment in which your cardiologist expects to need a thicker catheter than with a typical coronary angioplasty treatment, and for that reason will use the femoral artery as an access route.
You can read here what kind of research it is, what it means for you, and what the advantages and disadvantages are. It is a lot of information. Would you like to read the information and decide whether you want to participate? If you wish to participate, you can fill in the form found in Annex B.

Ask your questions

You can make your decision with the information you will find in this information letter. In addition, we recommend that you do the following as well:
- Ask questions to the researcher who gives you this information.
- Talk to your partner, family or friends about this research.
- Ask questions to the independent expert.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

1. General information

The cardiology department of the Isala hospital in Zwolle has initiated this research.

Below we will refer to the cardiology department as the 'client'. Researchers, these can be doctors, conduct the research in different hospitals.
This study requires 542 subjects from different countries.
The medical-ethical review committee of Isala Zwolle has approved this research.

2. What is the purpose of the research?

Soon you will receive a complex coronary angioplasty treatment with a large catheter. The aim of this study is to investigate whether the use of ultrasound when puncturing the femoral artery leads to less complications (such as bleeding).

3. What is the background to the research?

Nowadays, cardiac catheterisation and coronary angioplasty is often carried out via the wrist artery. However, if a thicker catheter (tube) has to be used for this coronary angioplasty procedure, the groin is often still used as an access route. This is because of the larger size of this artery. Ultrasound is used to determine the optimal puncture site at the groin. This could lead to minor complications, but that has never been properly researched and is therefore not done by default.

4. How does the investigation proceed?

Step 1: Are you suitable to participate?

We first want to know if you are suitable to participate. That is why the researcher does a number of tests:

- Physical. The researcher will see if your femoral artery can be used properly for the coronary angioplasty procedure. Sometimes there are reasons that this artery is not suitable, in which case you cannot participate in this study. There may also be other reasons why you cannot participate, for example in the case of cardiogenic shock or myocardial infarction (STEMI).

- Research into your medical history.

Step 2: the treatment

During the coronary angioplasty treatment, your femoral artery is punctured using X-ray fluoroscopy or ultrasound. With fluoroscopy, the artery cannot be seen directly, but the hip joint where the artery runs nearby is visible, so that we can puncture the vessel at the right height. In ultrasound, we use an ultrasound device to determine exactly where the vessel is running, and in this way we can find a suitable place to puncture the vessel. The treatment you receive is also the same as the treatment you would have received if you did not participate in the study.

For this research we make 2 groups:

- Group 1. The people in this group get the femoral artery punctured with the help of X-ray fluoroscopy.
- Group 2. The people in this group get the femoral artery punctured with the help of ultrasound.

Randomization with a computer-based program determines which puncture method of the femoral artery you get.

Step 3: research and measurements

For the examination, you only need to be in the hospital during your admission of the coronary angioplasty treatment. It is not necessary for you to additionally visit the hospital . For the examination, your medical data will be collected from your hospitalization to one month after the treatment.

Step 4: follow-up check

After one month, the researcher will call you. You will then receive questions about your health. This phone call will take about 10 minutes.

What is different from standard care?

There is not much different in this study than in standard care. Only the telephone check-up after one month by the researcher is extra.

How long does the study take?

Are you participating in the research? Then it takes about 1 month in total.

5. What agreements do we make with you?

We would like the research to go well. That is why we make the following agreements with you:

- You answer the questions during the admission and (telephone) check-up to the best of your knowledge and belief.
- You contact the researcher in these situations:

- ○ You will be admitted to a hospital or treated.
- ○ You suddenly have problems with your health.
- ○ You no longer wish to participate in the study.
- ○ Your phone number, address or e-mail address changes.

6. What side effects, adverse effects or discomforts can occur?

In principle, the treatment is carried out according to standard methods and there are no additional adverse effects if you participate in this study. The materials used (including the sheaths and the ultrasound device) are approved and are already used for complex coronary angioplasty treatments in patients who are not participating in a study. The only inconvenience you may experience is that after 1 month you will be approached to answer a number of questions.

Complications that can occur due to the insertion and removal of a sheath are:

- Bleeding
- Blood vessel damage

7. What are the advantages and disadvantages of participating in the study?

Participating in the research can have advantages and disadvantages. They are listed below. Think about this carefully, and talk about it with others.

If you are drawn to the treated group where ultrasound is used, you may have less chance of major complications at the site of puncture, but that is not certain.

Participating in the study can have the following disadvantage:
- You must adhere to the agreements that belong to the investigation.

Don't want to participate?

You decide whether you want to participate in the study. Don't want to participate? Then the treatment is carried out in the usual way. The performing cardiologist then determines whether he uses ultrasound to puncture the vessel.

8. When does the study stop?

The researcher will let you know if there is new information about the study that is important to you. The researcher will then ask you if you will continue to participate.

In these situations, the research stops:

- The telephone check-up after one month after the treatment is over.
- You want to stop the research yourself. This is allowed at any time. Then report this immediately to the researcher. You don't have to tell them why you're quitting. You will then be treated in the usual way. Once the treatment has started, it can of course no longer be reversed. The researcher will still invite you for a follow-up check.
- The researcher thinks it is better for you to stop.
- One of the following authorities decides that the investigation must stop:
  - ○ department of cardiology Isala, ○ the government, or ○ the medical ethics committee that assesses the research.

What happens if you stop the research?

The researchers use the data collected up to the moment of stopping.

The entire study is over when all participants are included and have received their follow-up.

9. What happens after the investigation?

Will you receive the results of the study?

About a year after the end of the study, the researcher will let you know what the most important results of the study are. Don't want to know? Then tell the researcher. He won't tell you.

10. What do we do with your data?

Are you participating in the research? Then you also give permission to collect, use and store your data.

What data do we store?

We store this data:
- Your name
- your gender
- your address
- your date of birth
- data about your health
- (medical) data that we collect during the research

Why do we collect, use and store your data?

We collect, use and store your data in order to be able to answer the questions of this research. And to be able to publish the results.

How do we protect your privacy?

To protect your privacy, we give your data a code. We only put this code on all of your data. We store the key to the code in a secure place in the local research institution. If we process your data and body material, we always use only that code, hence all data are anonymized. Also in reports and publications about the research, no one can recall that it was about you.

Who can see your data?

Some people can view your name and other personal data without a code. These are people who check whether the researchers are conducting the research properly and reliably. These people can access your data:

- Members of the committee that monitors the safety of the investigation.
- An inspector hired by the client.
- National and international supervisory authorities. For example, the Health and Youth Care Inspectorate.

These people keep your data secret. We ask you to give permission for this inspection.

How long do we keep your data?

We store your data for 15 years at the research location and at the client.

What happens in the event of unexpected discoveries?

During the examination, we may happen to find something that is important for your health or for the health of your family members. The researcher will then contact your general practitioner or specialist. You then discuss with your general practitioner or specialist what needs to be done. With the form you give permission to inform your general practitioner or specialist.

Can you withdraw your consent to the use of your data?

You can withdraw your consent to the use of your data at any time. But beware: do you withdraw your consent, and have researchers already collected data for a study? Then they may still use this data.

Would you like to know more about your privacy?

- Would you like to know more about your rights when processing personal data? Take a look

at www.autoriteitpersoonsgegevens.nl.

- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person responsible for the processing of your personal data. For your research, this is:
    - Isala (see Appendix A for contact details, and website)
- If you have any complaints about the processing of your personal data, we recommend that you first discuss them with the investigation team. You can also go to Isala's Data Protection Officer. Or you submit a complaint to the Dutch Data Protection Authority.

Where can you find more information about the study?

You can find more information about the study on the following website(s).
www.ClinicalTrials.gov. You can find the survey by searching by number: NCT04837404.

11. Do you receive compensation if you participate in the study?

The treatment for the examination will not cost you anything. You will also not receive any compensation if you participate in this study.

12. Are you insured during the examination?

You are not additionally insured for this examination. Because participating in the study has no additional risks. That is why the client of the medical-ethical review committee does not have to take out additional insurance.

13. We inform your general practitioner and/or treating specialist

The researcher will send your general practitioner and/or treating specialist a message to let you know that you are participating in the study. This is for your own safety. In case of complications, we can contact your (family) doctor, for example about your medical history or about medication use.

14. Do you have any questions?

Questions about the research can be asked to the research team. Do you want advice from someone who has no interest in it? Then go to independent doctor. He knows a lot about the research, but does not cooperate with this research.
Do you have a complaint? Then discuss this with the researcher or doctor who is treating you. Would you rather not do this? Then go to the complaints officer of your hospital. Appendix A shows where you can find it.

15. How do you consent to the research?

You can first think about this research. Then you tell the researcher whether you understand the information and whether or not you want to participate. Would you like to participate? Then fill in the consent form that you will find with this information letter. You and the researcher will both receive a signed version of this declaration of consent.

Thank you for your time.

16. Appendices to this information

A. Contact Us
B. Consent form

Appendix A: Contact details for Isala

- **Research team department Cardiology:**

  Principal Investigator: dr. M.A.H. van Leeuwen T.038-4242374

  Research physician: T.A. Meijers T.038-4242374

- **Independent doctor:**

  Prof. M.R. Meijerink, interventional radiologist T.020-4442874

- **Complaints**:

Complaints can be reported to the complaints officer as follows:

  - By phone: T.038-4244727
  - Online: Complaint form on website -https://www.isala.nl/praktische-information/-rights-obligations-and-complaints-/complaint handling/
  - Mail: Isala

    Complaints reception, attn. complaints officer

    P.O. Box 10400

    NL-8000 GK Zwolle

- **Data Protection Officer of the institution**

  Mrs L. Boekel, Email: e.w.boekel@isala.nl, T.038-4247955

Appendix B: subject consent form

Belonging to ULTRACOLOR study

- I have read the information letter. I was also able to ask questions. My questions have been answered well enough. I had enough time to decide if I would participate.
- I know that participation is voluntary. I also know that I can decide at any time not to participate in the research. Or to stop. I don't have to say why I want to stop.
- I give the researcher permission to let my general practitioner/specialist(s) who treats me know that I am participating in this study.
- I give the researcher permission to request information from my general practitioner about my medical history or about the medicines I use.
- I give the researcher permission to give my general practitioner or specialist information about unexpected findings from the study that are important for my health.
- I give the researchers permission to collect and use my data. The researchers do this only to answer the research question of this research.
- I know that for the purpose of checking the research, some people can see all my data. Those people are in this information letter. I give these people permission to view my data for this check.

- Would you like to tick yes or no in the table below?

I give permission to ask myself after this research if I want to participate in a follow-up study.	Yes ☐	No☐
I give permission, in the event that I die during the duration of the investigation, to request my official cause of death data from the Central Bureau of Statistics.	Yes ☐	No☐

- I want to participate in this research.

My name is (test subject): .....

Signature:..... Date : __ / __ / __

I declare that I have fully informed this subject about the aforementioned research.

Will information be available during the study that could influence the subject's consent? Then I will let this test subject know in time.

Name of researcher (or his representative):.....

Signature:..... Date: __ / __ / __

The subject receives a complete information letter, together with a signed version of the consent form.

Supplemental material II: Spirit Checklist

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 1
	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 4
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 5
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 7
	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 6
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 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P 8

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 8

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	P9
	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 7
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 8
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 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P 9
	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 9
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 9
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 9
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 9
	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.