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Rationale and design for the treatment effects of systematic two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions (DEFINITION Ⅱ Trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020019
Article Type:	Protocol
Date Submitted by the Author:	10-Oct-2017

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Keywords:	coronary bifurcation lesions, systematic two-stent techniques, provisional stenting technique

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Rationale and design for the treatment effects of systematic two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions

(DEFINITION II Trial)

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Abstract

Introduction: Provisional stenting (PS) for simple coronary bifurcation lesions is the mainstay of treatment. Systematic two-stent approach is widely used for complex bifurcation lesions (CBLs). However, randomized comparison of PS and two-stent techniques for CBLs has never been studied. Accordingly, the present study is designed to elucidate the benefits of two-stent treatment over PS in patients with CBLs.

Methods and analysis: The DEFINITION Ⅱ study is a prospective, multinational, randomized, endpoint-driven trial to compare the benefits of two-stent technique with PS for CBLs. A total of 660 patients with CBLs will be randomized in a 1:1 fashion to receive either PS or two-stent technique. The primary endpoint is the rate of 12-month target lesion failure (TLF) defined as the composite of cardiac death, target vessel myocardial infarction (MI), and target lesion revascularization (TLR). The major secondary endpoints include all cause death, MI, target vessel revascularization (TVR), in-stent restenosis, stroke, and each individual component of the primary endpoint. The safety endpoint is the occurrence of definite or probable stent thrombosis (ST).

Ethics and dissemination: The study protocol and informed consent have been reviewed and approved by the Institutional Review Board at each participating center. The written informed consent was obtained from all enrolled patients. Findings of the study will be published in a peer-reviewed journal, and disseminated at conferences.

Trial registration number: NCT02284750; Pre-results.

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Strengths and limitations of this study

- This is the first prospective, multinational, randomized, endpoint-driven trial to compare the systematic two-stent and provisional stenting (PS) techniques in patients with complex coronary bifurcation lesions (CBLs).

- This study is built on DEFINITION registry, which for the first time introduced the anatomical differentiation of coronary bifurcation lesion's complexity, and reported that PS for CBLs was associated with an increment of major adverse cardiac events as compared with simple bifurcation lesions.

- Selection of primary and secondary endpoints is in accordance with the current practice in other cardiovascular clinical trials.

- All participating sites are experienced in two-stent techniques (including DK crush and culotte), which may not be reflective of clinical practice in smaller hospitals.

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Background

Percutaneous coronary intervention (PCI) of bifurcation lesions is technically demanding and poor outcome at follow-up, as reflected by more frequent in-stent restenosis (most localize at the ostium of daughter branch) and more requirements of revascularization. For a great majority of coronary bifurcation lesions, particularly when a small (diameter<2.0mm) side branch (SB) with focal (usually <5 mm in length) lesions is involved, provisional stenting (PS) is considered as the default approach[1-6]. However, the efficacy of PS for larger (≥2.5 mm in diameter) SB with longer lesion (>5mm in length) is under reported[7,8]. Furthermore, there is a lack of angiographical criteria for differentiating simple from complex bifurcation lesions (CBLs). In this regard, DEFINITION registry study [9] for the first time introduced the anatomical differentiation of bifurcation lesion's complexity, which consisted of 2 major and 6 minor criteria. Based on DEFINITION criteria, CBLs was defined as one major plus any two minor criteria. Investigators further reported that PS for CBLs was associated with an increment of mortality, ST, and major adverse cardiac events (MACE) and stent thrombosis as compared with simple bifurcation lesions. Unfortunately, PS has not been compared with systematic two-stent techniques in a randomized fashion for patients with CBLs. Therefore, we designed this prospective, multi-center, randomized (DEFINITION Ⅱ) study to investigate the superiority of systematic two-stent approaches to PS treatment for patients with CBLs classified by DEFINITION registry.

Study design and methods

Study hypothesis

This study is designed to test the hypothesis that the application of systematic two-stent techniques will lead to fewer rate of target lesion failure (TLF), including cardiac death, target-vessel myocardial infarction (MI), or target lesion revascularization (TLR), compared to PS technique in patients with CBLs at 12 months after the indexed PCI procedure. CBLs are defined according to DEFINITION study [9], and the criteria are shown in Table 1.

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Study design

This is a prospective, multi-center, randomized-controlled, superiority trial at up to 45 sites worldwide to enroll 660 subjects with CBLs in native coronary artery. The overall study flowchart is presented in Figure 1. This study has been registered at clinicaltrials.gov (NCT02284750), according to the statement of the International Committee of Medical Journal Editors. The study is performed in accordance with the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practices. The study protocol and informed consent have been reviewed and approved by the Institutional Review Board at each participating center. The written informed consent for participation in the trial was obtained from all enrolled patients.

Study population and randomization

A number of 660 patients scheduled for elective PCI with CBLs suitable for DES implantation are openly randomized 1:1 to either systematic two-stent or PS technique. The detailed inclusion and exclusion criteria for the present study are listed in Table 2. The planned enrollment duration is between December 2015 and December 2018, and the enrollment period may be extended if necessary. There were 446 patients enrolled until September 2017.

The randomization serial number for patients will be performed by Interactive Web Randomization System (IWRS). The randomization serial number for each participating center will be undergone by the same system.

Study intervention and medication

Patients allocated to the two-stent group will receive double kissing (DK) crush, or culotte technique.

DK crush technique. DK crush stenting technique has been described in details elsewhere [7,10-12]. Briefly, a stent with stent/artery ratio of 1.1:1 is advanced into side branch (SB). Another balloon with balloon/artery ratio of 1:1 is positioned in main vessel (MV). Inflating

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SB stent with 2-3mm protrusion into MV, and then the stent balloon and SB wire are removed after confirming that there was no dissection in distal SB by angiogram. Inflating previous balloon in MV performs first crush. First kissing balloon inflation is performed after rewiring SB from the proximal stent cell. MV stent with stent/artery ratio of 1.1:1 is inflated and crushed SB stent again, which then followed by rewiring SB and final kissing balloon inflation (FKBI). Proximal optimization technique (POT) is recommended to perform before and after FKBI. Post dilatation with non-complaint balloon is recommended for all stent, with suggested inflation pressure > 18 atm.

Culotte technique. Culotte stenting has been described in details elsewhere[13].

Provisional stenting technique. PS was defined as a stent implantation in the main vessel with the jailed wire or jailed balloon protecting SB [14,15], followed by kissing balloon dilatation if there was at least one of following: >type B dissection and TIMI flow < 3 at the ostial side branch [5]. An additional stent was required for the side branch if any of the following issues was observed after kissing balloon inflation: > type B dissection or thrombolysis in myocardial infarction (TIMI) flow < 3. POT is also recommended after MV stenting.

Intracoronary imaging. Intracoronary imaging tools such as intravascular ultrasound (IVUS), or optical coherence tomography (OCT) are at the discretion of the operators.

Study stents. Stents for all implanted lesions are drug-eluting stents (DESs), including Firebird-2, or Firehawk (Microport Co., Shanghai, China); EXCEL (Jiwei Co., Shandong, China); BuMA stent (Sino Medical, Tianjin, China); Partner or Nano (Lepu Med, Beijing, China); Xience or Xience Prime (Abbott Vascular, Santa Clara, California); and Endeavor Resolute or Endeavor Integrity (Medtronic, Minneapolis, Minnesota).

Medication. All patients in the trial are treated with dual antiplatelet therapy for at least one year according to contemporary guidelines and local practice. A loading dose of aspirin (300mg) and clopidogrel (300mg, or ticagrelor 180mg) are recommended at least 6 hours before PCI procedure. Heparin or an alternative antithrombotic agent (such as bivalirudin) must be used during the procedure to maintain the activated clotting time (ACT) >280

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seconds. After PCI, lifelong aspirin in a dose of 100mg/d will be prescribed. Duration of clopidogrel treatment with 75mg/d (or ticagrelor with 90mg twice a day) is at least 12-month.

Biomarker assessment. Total creatine kinase (CK), CK-Myocardial-Band isoenzyme (MB), and troponin T/I are dynamically measured before the procedure and until 72 h post-procedure.

Study endpoints

The primary endpoint in the present trial is TLF at 12 months after indexed procedure, defined by the composite of cardiac death, target vessel MI, and TLR. The major secondary endpoints include all cause death, MI, target-vessel revascularization (TVR), in-stent restenosis, stroke, and each individual component of the primary endpoint. The safety endpoint is the risk of Academic Research Consortium (ARC) defined stent thrombosis. Other endpoints are listed in Table 3. The detailed definitions of study endpoints are described in the Appendix.

All endpoints are site-reported in an electronic web-based capture system with additional submission of supporting medical documents. All clinical events are assessed by an independent committee that was blinded to the study.

Follow-up

After hospital discharge, clinical follow-up is performed with visits (preferred) or telephone contact at 1-, 6-, and 12-month. Follow-up will be continued to 5 year after index procedure annually. Angiographic follow-up will be encouraged for all patients, will be undergone at 13-month after index procedure unless clinically indicated earlier.

Angiographic analysis

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Quantitative coronary angiographic (QCA) analysis at baseline, post-procedure and follow-up is performed by the QCA-laboratories at Nanjing Heart Center. The images are analyzed by two experienced technicians who are blinded to the study design, with the inter- and intra-observer variability under 5% (Kappa test).

Basic angiograms for all lesions should consist of at least injections after intracoronary injection of 100-200 μg nitroglycerin. Bifurcation-view must be gained for all patients; there should be an angulation difference between the two baseline angiograms of at least 30°. The diagnostic/guiding catheter should be well visible, near the center of the angiogram and filled with dye. The index lesions should be well visible, near the center of the angiogram and shown without foreshortening. Between the pre- and post-angiograms all balloon inflations and stent implantations should be documented by short cine-runs.

Statistical analysis

All analysis will be performed in the intent-to-treat (ITT) population, defined as all patients randomized, regardless of the treatment actually received. The primary variable is time from randomization to first occurrence of any event from TLF. From previous studies, we hypothesized that the rate of a 1-year TLF would be 15% in the systematic two-stent technique group and 25% in the provisional stenting group. Accordingly, a total sample size of 600 is needed to detect a power of 0.8 (Type Ⅱ error = 0.2, α = 0.05, 2-tailed). Because of the considerable uncertainty, the enrollment is extended to 660 patients (10% increment).

The distribution of continuous variables will be assessed by the Kolmogrov-Smirnov test. Categorical variables are expressed as frequencies or percentages and compared by Chi-square statistics or Fisher's exact test. Continuous variables are summarized as means ± standard deviation (SD) or median and compared using Students' t-test (for normal data) and Mann-Whitney U-test (for non-normally distributed variables). Survival curves with time-to-event data are generated by the Kaplan-Meier method and compared using the log-rank test. Comparison between the two groups will be performed using the Cox

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proportional hazard model. A p value <0.05 is considered statistically significance. All analyses are performed with the use of the statistical program SPSS 24.0 (SPSS Institute Inc, Chicago, Illinois).

The extensive subgroup analysis will be performed to evaluate variation of treatment effects, as well as a test of interaction with treatment for each subgroup variable. The substudies of clinical factors include age (age > 75 years old), sex, diabetes mellitus, hyperlipidemia, hypertension, current smoking, acute coronary syndrome, cardiac dysfunction (left ventricular ejection fraction < 40%), and renal insufficiency (estimated glomerular filtration rate < 60ml/min/1.73 m^2). In addition, the substudies of angiographic and procedural factors include unprotected distal left main bifurcation lesion, the use of IVUS, and complete revascularization. Therefore, there are in total of 12 prespecified subgroup analyses to explore the consistency of effects on two-stent techniques for complex bifurcation lesions.

Trial organization

The trial has been designed by the principal investigator (PI) and the executive committee. The executive committee members are also responsible for reporting the results, and drafting the manuscripts. The executive committee, together with the steering committee, the data and safety monitoring committee, and the independent endpoints adjudication committee are involved in the present trial.

All centers with experience in two-stent techniques (including DK crush and culotte) can participate in the study. The details about trial organization are listed in the Appendix.

Discussion

Several randomized studies have demonstrated that PS technique using a jailed wire in the SB is the gold standard treatment for the majority of bifurcation lesions[1-6], however, the bifurcation lesions enrolled in these studies were not all true bifurcation lesions, either moderate narrow, or focus lesion at the SB ostium. DKCRUSH Ⅱ trial[7] has demonstrated

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that two-stent technique using DK-crush was associated with lower rate of TVR in true coronary bifurcation lesions with SB lesion length of 15mm compared with PS. Meta-analysis also showed that two-stent technique remained an optional treatment for true bifurcation lesions with large side branches[16]. In addition, consensus from European Bifurcation Club[17] suggested that true bifurcations with large side branches and ostial disease extending more than 5 mm from the carina are likely to require two-stent techniques. Therefore, a novel bifurcation classification is needed to identify which bifurcation lesions should be treated with two-stent techniques instead of provisional stenting.

The practical and easy-to-use classification was proposed in DEFINITION registry by Shao-Liang Chen[9], which including 2 major criteria and 6 minor criteria. According to the newly established criteria, 70% exhibited simple bifurcation lesions, and the remaining 30% were classified as CBLs in 3660 patients with true coronary bifurcation lesions (Medina 1,1,1 and 0,1,1) and an SB diameter ≥2.5 mm by visual estimation. As was expected, two-stent techniques did not show any benefits over provisional stenting for the simple bifurcation lesions. However, for CBLs two-stent techniques were associated with less in-hospital mortality and one-year MACE than PS. The important finding will be further verified in the randomized DEFINITION-Ⅱ trial.

Left main (LM) bifurcation lesions are unique bifurcation lesions. Not only the diameter of SB is bigger, but also bifurcation angle is huger compared with non-LM bifurcation. The culotte stenting with bare metal stents has been largely abandoned because of high restenosis rates. Since the introduction of DESs, culotte stenting has regained its popularity. Murasato reported the restriction of the stent expansion like a “napkin ring” in culotte stenting using close-cell design stents[18]. In our bench study, even using open-cell design stents in T type bifurcation, significant stent underexpansion was revealed in culotte stenting contrast to DK crush[19]. DKCRUSH-Ⅲ trial had confirmed that DK crush was associated with lower TLR and stent thrombosis for LM bifurcation compared with culotte stenting at 3-year follow-up [10,20]. Considering the shortages of culotte stenting, we strongly

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recommend use of culotte stenting in non-LM bifurcation instead of LM bifurcations. PS with jailed balloon is a safer alternative than jailed wire to protect SB, especially for high risk of SB occlusion after MV stenting [14,15]. Giving CBLs will be enrolled in the study, if a patient is randomized into PS group, either jailed balloon or jailed wire will be allowed to use at the discretion of the operators.

Conclusions

Strategies for coronary bifurcation lesions should be individualized. PS is the default approach for simple bifurcation lesions. The DEFINITION Ⅱ study is investigating whether systematic two-stent technique will be superior to PS in CBLs regarding the incidence of TLF at 12 months.

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Table 1. Criteria of complex bifurcation lesions

Criteria	Lesion characteristics
Major 1	Distal LM bifurcation: SB-DS ≥70% and SB lesion length ≥10 mm
Major 2	Non-LM bifurcation: SB-DS ≥90% and SB lesion length ≥10 mm
Minor 1	Moderate to severe calcification
Minor 2	Multiple lesions
Minor 3	Bifurcation angle <45° or >70°
Minor 4:	Main vessel RVD <2.5 mm
Minor 5	Thrombus-containing lesions
Minor 6	MV lesion length ≥25 mm
Major 1 + any 2 minor 1–6 = complex bifurcation lesion	
Major 2 + any 2 minor 1–6 = complex bifurcation lesion	

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Table 2 Inclusion and exclusion criteria

Inclusion Criteria:
1. Provision of informed consent prior to any study specific procedures; 2. Men and women 18 years and older; 3. Established indication to PCI according to the guidelines of American Heart Association and American College of Cardiology; 4. Native coronary lesion suitable for drug-eluting stent placement; 5. True bifurcation lesions (Medina 0,1,1/1,1,1 /1,0,1); 6. Reference vessel diameter in side branch ≥2.5mm by visual estimation.
Exclusion Criteria:
1. Pregnancy and breast feeding mother; 2. Co-morbidity with an estimated life expectancy of < 50 % at 12 months; 3. Scheduled major surgery in the next 12 months; 4. Inability to follow the protocol and comply with follow-up requirements or any other reason that the investigator feels would place the patient at increased risk; 5. Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 30 days; 6. Known allergy against ticagrelor, or against clopidogrel, or aspirin History of major hemorrhage (intracranial, gastrointestinal, etc.); 7. Chronic total occlusion lesion in either LAD, or LCX or RCA not re-canalized; 8. Severe calcification needing rotational atherectomy； 9. Patient with STEMI (within 24-hour from the onset of chest pain to admission).

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Table 3. Study endpoints.

Primary endpoint ● Target lesion failure: composite of cardiac death, target vessel myocardial infarction (MI), and target lesion revascularization (TLR) at 12 months
Secondary endpoints ● All-cause death: cardiac death, non-cardiac death ● MI: periprocedural MI, spontaneous MI ● Revascularization: TLR, target vessel revascularization (TVR) ● Stroke: ischemic stroke, hemorrhagic stroke ● Combined endpoint of all-cause death, MI, TVR ● In-stent restenosis ● Other outcome parameters: NYHA functional class, Braunwald class, net gain of lumen diameter, contrast volume, procedural time, devices consumed during indexed procedure, X-ray exposure time, X-ray dose, DAP-total, DAP-record, DAP-fluoro
Safety endpoints ● Stent thrombosis ● Bleeding complications

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Acknowledgements The authors appreciate the contributions of Ling Lin, Hai-Mei Xu, and Ying-Ying Zhao to data collection. They also acknowledge Bao-Xiang Duan, Lin Lin, Ji Yong, and Linda Lison for their contribution in the data and safety monitoring.

Contributiors
SLC made substantial contributions to study conception and design, and to the drafting and critical revision of the manuscript. JJZ and XFG wrote the first draft. YLH, JK, LT, and ZG provided data management and statistical expertise. DT, SL, LKM, FL, SY, JZ, MM, LL, RYZ, HSZ, TS, PX, ZNJ, LH, WHY, XSQ, QHL, LH, CP, YW, LJL, LZ, XMW, SYW, QHL, JQY, LLC, FL, AER, LMZ, SQD, KV, YSZ, MYY, CC, IS, YX, YLT, ZLS, QJ, YHZ, XW, FY, NLT, SL, and ZZL provided comments and suggestions in critical revision of the article. All authors approved the final version of the article.

Funding The present trial was support by National Science Foundation of China (NSFC 81270191, NSFC 91439118) and Health and Family Planning Commission Foundation of Nanjing (YKK16124)

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board at each participating center.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure legend

Figure. 1 Flowchart of study design.

SB: side branch; RVD: reference vessel diameter; DS: diameter stenosis; LMd: left main distal bifurcation; MV: main vessel; PS: provisional stenting; TLF: target lesion failure; TV-MI: target-vessel myocardial infarction; TLR: target lesion revascularization.

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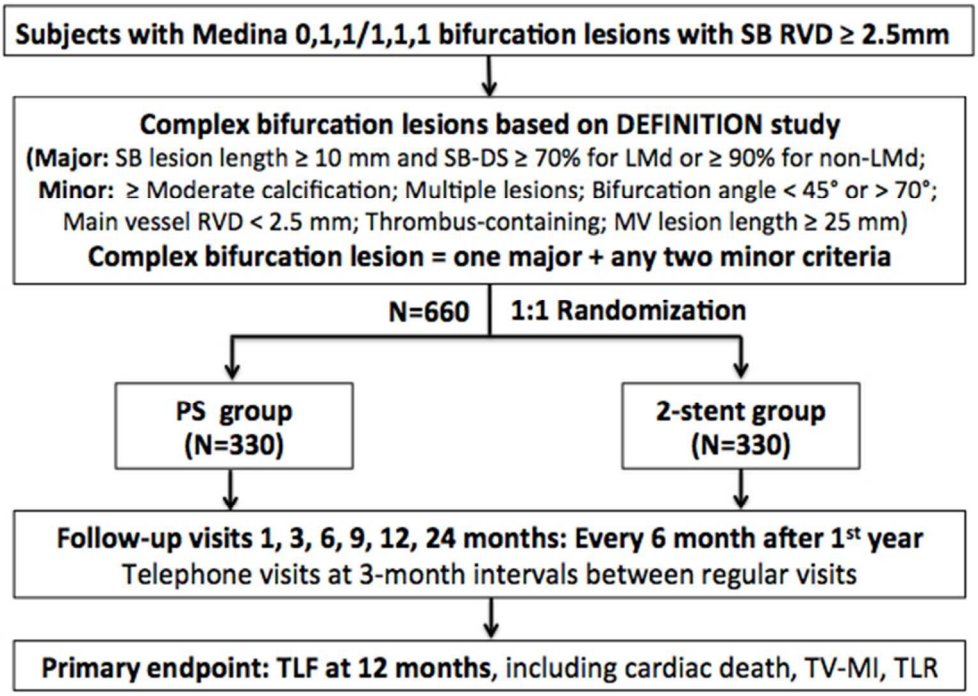

Flowchart of study design.

49x35mm (300 x 300 DPI)

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Appendix 1. Definitions of major study endpoints

Endpoint	Definition
Death	● **Cardiovascular death** includes sudden cardiac death, death due to acute myocardial infarction (MI), arrhythmia, heart failure, stroke, other cardiovascular causes, or bleeding ● **Non-cardiovascular death** is defined as any death with known cause not of cardiac or vascular cause ● All deaths are considered cardiac in origin unless a non-cardiac cause is confirmed clinically or at autopsy.
Myocardial infarction	**Post-procedure MI**: occurrence within 48 hours after PCI ● Patients with normal baseline CK-MB: the peak CK-MB measured within 48 hours of the procedure rises to ≥ 10 × upper reference limit (URL), or to ≥ 5 × URL with new pathologic Q-waves in at least 2 contiguous leads or new persistent left bundle branch block (LBBB) ● Patients with elevated baseline CK-MB in whom the biomarker levels are stable or falling: the CK-MB rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level **Spontaneous MI**: occurrence more than 48 hours after PCI ● The rise of cardiac biomarkers (CK-MB or troponin) > 1x URL, with one of the follows: ➢ Evidence of prolonged ischemia as demonstrated by prolonged chest pain ➢ Ischemic ST-segment changes or new pathological Q waves ➢ Angiographic evidence of a flow limiting complication ➢ Imaging evidence of new loos of viable myocardium or new regional wall motion abnormality **Target vessel MI:** spontaneous MI associated with target vessel, which was identified by electrocardiographic changes or coronary angiography. Each MI will also be classified as ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI)
Revascularization	**Target lesion revascularization (TLR)** ● Repeat revascularization (including PCI and coronary artery bypass grafting) for target lesions, in the presence of symptoms or objective signs of ischemia **Target vessel revascularization (TVR)** ● Repeat revascularization (including PCI and coronary artery bypass grafting) for target vessels, in the presence of symptoms or objective signs of ischemia

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	Target vessel non-target lesion revascularization ● Target vessel non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography
Stent thrombosis	Academic Research Consortium (ARC) classification **Definite stent thrombosis** ● Symptoms suggestive of an acute coronary syndrome and angiographic or pathological confirmation of stent thrombosis **Probable stent thrombosis** ● Unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis **Possible stent thrombosis** ● Any unexplained death after 30 days Stent thrombosis will also be classified as acute stent thrombosis (0–24 hours after PCI), subacute stent thrombosis (24 hours-30 days), late stent thrombosis (31 days–1 year), or very late stent thrombosis (>1 year)
Bleeding	Bleeding Academic Research Consortium (BARC) classification **Type 0**: no bleeding **Type 1**: bleeding that is not actionable and doses not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment **Type 2**: any overt, actionable sign of hemorrhage that doses not fit the criteria for 3, 4, or 5 **Type 3**: ● **Type 3a**: overt bleeding with hemoglobin drop of 3 to 5 g/dl; any transfusion with overt bleeding ● **Type 3b**: overt bleeding with hemoglobin drop ≥ 5g/dl; cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring intravenous vasoactive agents ● **Type 3c**: intracranial hemorrhage; intraocular bleeding compromising vision **Type 4**: CABG-related bleeding **Type 5**: fatal bleeding
Stroke	Global or focal cerebral, spinal cord, or retinal injury resulting in acute neurological dysfunction and was further classified into ischemic and hemorrhagic stroke

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Appendix 2. Trial organization

Principal investigator:

Shao-Liang Chen, Nanjing First Hospital, Nanjing Medical University

Steering committee:

Shao-Liang Chen, Gregg W Stone, Bo Xu , Imad Sheiban, Ya-ling Han

Core laboratory:

Nanjing Heart Center

Study statistician:

School of Public Health, Nanjing Medical University

Data and safety monitoring committee:

Bao-Xiang Duan, Lin Lin, Ji Yong, Linda Lison

Participating hospitals and collaborators of DEFINITION II trial:

1. Nanjing First Hospital, Nanjing Medical University, Nanjing, China;
2. The General Hospital of Shenyang Military, Shenyang, China;
3. Xijing Hospital, 4th Military Medical University, Xi'an, China;
4. Medicine Siriraj Hospital, Bangkok, Thailand;
5. Taicang People's Hospital, Taicang, China;
6. Anhui Provincial Hospital, Hefei, China;
7. Huainan Eastern Hospital, Huainan, China;
8. Yixin People's Hospital, Yixin, China;
9. Cangzhou Central Hospital, Cangzhou, China;
10. Binawaluya Cardiac Center, Jakarta, Indonesia;
11. Guangzhou Red Cross Hospital, Guangzhou, China;
12. Shanghai Ruijin Hospital, Shanghai, China;
13. Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;
14. Medistra Hospital, University of Indonesia, Jakarta, Indonesia;
15. Gansu Provincial Hospital, Lanzhou, China;
16. Beijing Anzhen Hospital, Capital Medical University, Beijing, China;
17. Changshu First People's Hospital, Changshu, China;
18. Cheng-Hsin General Hospital, Taipei, China;
19. Zhangjiagang First People's Hospital, ZhangjiaGang, China;
20. Changzhou Hospital of Traditional Chinese Medicine, Changzhou, China;
21. Jiangxi Provincial People's Hospital, Nanchang, China;
22. Bangkok General Hospital, Bangkok, Thailand;
23. Xia'Men Zhongshan Hospital, Xia'Men, China;
24. Huainan First People's Hospital, Huainan, China;
25. Jintan People's Hospital, Jintan, China;

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26. Wuxi Third People 's Hospital, Wuxi, China;
27. Daqing Oil General Hospital, Daqing, China;
28. The Second Hospital of Shandong University, Ji'nan, China;
29. Xinyang Central Hospital, Xinyang, China;
30. Fujian Union Hospital, Fuzhou, China;
31. Jilin Heart Hospital, Changchun, China;
32. Otamendi Hospital, Buenos Aires, Argentina;
33. Chuzhou First People 's Hospital, Chuzhou, China;
34. Huainan Xinhua Hospital, Huainan, China;
35. Bangle Hospital, Bangkok, Thailand;
36. Huai'an Second People's Hospital, Huai'an, China;
37. Qingdao Fuwai Hospital, Qingdao, China;
38. The Affiliated Hospital of Guangdong Medical University, Guangdong, China;
39. University of Turin, Turin, Italy;
40. The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China;
41. Xuyi People's Hospital, Xuyi, China;
42. Wuxi Huishan District People's Hospital, Wuxi, China;
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The treatment effects of systematic two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: Rationale and design of a prospective, randomized, and multicenter DEFINITION Ⅱ Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020019.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Nov-2017

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical management
Keywords:	coronary bifurcation lesions, systematic two-stent techniques, provisional stenting technique

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The treatment effects of systematic two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: Rationale and design of a prospective, randomized, and multicenter DEFINITION II Trial

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Abstract

Introduction: Provisional stenting (PS) for simple coronary bifurcation lesions is the mainstay of treatment. A systematic two-stent approach is widely used for complex bifurcation lesions (CBLs). However, a randomized comparison of PS and two-stent techniques for CBLs has never been studied. Accordingly, the present study is designed to elucidate the benefits of two-stent treatment over PS in patients with CBLs.

Methods and analysis: This DEFINITION II study is a prospective, multinational, randomized, endpoint-driven trial to compare the benefits of the two-stent technique with PS for CBLs. A total of 660 patients with CBLs will be randomized in a 1:1 fashion to receive either PS or the two-stent technique. The primary endpoint is the rate of 12-month target lesion failure (TLF) defined as the composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven target lesion revascularization (TLR). The major secondary endpoints include all causes of death, MI, target vessel revascularization (TVR), in-stent restenosis, stroke, and each individual component of the primary endpoints. The safety endpoint is the occurrence of definite or probable stent thrombosis (ST).

Ethics and dissemination: The study protocol and informed consent have been approved by the Institutional Review Board of Nanjing First Hospital, and accepted by each participating center. Written informed consent was obtained from all enrolled patients. Findings of the study will be published in a peer-reviewed journal and disseminated at conferences.

Trial registration number: NCT02284750; Pre-results.

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Strengths and limitations of this study

- This is the first prospective, multinational, randomized, endpoint-driven trial to compare the systematic two-stent and provisional stenting (PS) techniques in patients with complex coronary bifurcation lesions (CBLs).

- This study is built on the DEFINITION registry, which for the first time introduced an anatomical differentiation of coronary bifurcation lesion complexity and reported that PS for CBLs was associated with an increment of cardiac death compared with simple bifurcation lesions.

- Selection of primary and secondary endpoints is in accordance with current practice in other cardiovascular clinical trials.

- All participating sites are well-versed in two-stent techniques (including double kissing crush and culotte), which may not be reflective of clinical practice in smaller hospitals.

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Background

Percutaneous coronary intervention (PCI) for bifurcation lesions is technically demanding and has a poor outcome at follow-up, as reflected by more frequent occurrences of in-stent restenosis (most localize at the ostium of the daughter branch) and more requirements for revascularization. For a great majority of coronary bifurcation lesions, particularly when a small (diameter<2.0 mm) side branch (SB) with a focal (usually <5 mm in length) lesion is involved, provisional stenting (PS) is considered as the default approach[1-6]. However, the efficacy of PS for a larger (≥2.5 mm in diameter) SB with a longer lesion (>5 mm in length) is underreported[7,8]. Furthermore, there is a lack of angiographical criteria for differentiating simple from complex bifurcation lesions (CBLs). In this regard, the DEFINITION registry study [9] introduced for the first time an anatomical differentiation of bifurcation lesion complexity, which consisted of 2 major and 6 minor criteria. Based on the DEFINITION criteria, a CBLs is defined as one major plus any two minor criteria. Investigators further reported that PS for CBLs was associated with an increment in cardiac death and major adverse cardiac events (MACE) compared with simple bifurcation lesions. Unfortunately, PS has not been compared with systematic two-stent techniques in a randomized fashion for patients with CBLs. Therefore, we design this prospective, multi-center, randomized (DEFINITION Ⅱ) study to investigate the superiority of systematic two-stent approaches for PS treatment for patients with CBLs, as classified by the DEFINITION registry.

Methods and analysis

Study hypothesis

This study is designed to test the hypothesis that the application of systematic two-stent techniques will lead to a lower rate of target lesion failure (TLF), including cardiac death, target-vessel myocardial infarction (MI), or clinically driven target lesion revascularization (TLR), compared to the PS technique, in patients with CBLs at 12 months after the indexed PCI procedure. CBLs are defined according to the DEFINITION study [9], and the criteria are shown in Table 1.

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Study design

This is a prospective, multi-center, randomized, controlled, superiority trial at up to 45 sites worldwide (Appendix) to enroll 660 subjects with CBLs in a native coronary artery. The overall study flowchart is presented in Figure 1. This study has been registered at clinicaltrials.gov (NCT02284750), according to the statement of the International Committee of Medical Journal Editors.

Study population and randomization

The 660 patients scheduled for elective PCI with CBLs suitable for drug-eluting stent (DES) implantation are openly randomized 1:1 to either the systematic two-stent or the PS technique. Detailed inclusion and exclusion criteria for the present study are listed in Table 2. The planned enrollment duration is between December 2015 and December 2018, and the enrollment period may be extended if necessary. There are 446 patients enrolled up to September 2017.

A randomization serial number for patients will be created by the Interactive Web Randomization System (IWRS). The randomization serial number for each participating center will be generated by the same system.

Study intervention and medication

Patients allocated to the two-stent group will receive the double kissing (DK) crush, or the culotte technique.

DK crush technique. The DK crush stenting technique has been described in detail elsewhere [7,10-12]. Briefly, a stent with a stent/artery ratio of 1.1:1 is advanced into a side branch (SB). Another balloon with balloon/artery ratio of 1:1 is positioned in the main vessel (MV). Inflating the SB stent with a 2-3 mm protrusion into the MV, and then the stent balloon and SB wire are removed after confirming that there is no dissection in the distal SB by angiogram. Inflating the previous balloon in the MV performs the first crush. First, the

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kissing balloon inflation is performed after rewiring the SB from the proximal stent cell. An MV stent with a stent/artery ratio of 1.1:1 is inflated and crushes the SB stent again, which is then followed by rewiring the SB and the final kissing balloon inflation (FKBI). A proximal optimization technique (POT) should be performed before and after FKBI. Post dilatation with a non-complaint balloon is recommended for all stents, with a suggested inflation pressure > 18 atm.

Culotte technique. Culotte stenting has been described in detail elsewhere[13]. In brief, the MV and SB are both wired. The SB is then stented first with a wire jailed in the MV. The MV is rewired through the stent struts (through a distal stent strut where possible), following balloon dilation and MV stenting. Then, second, rewiring the SB from a distal access is undertaken. A mandatory attempted FKBI is performed. Post-dilations with non-complaint balloon are undertaken to optimize stent expansion. POT in the stented segment proximal to the bifurcation is recommended.

Provisional stenting technique. PS is defined as a stent implantation in the MV with the jailed wire or jailed balloon protecting the SB [14,15], followed by kissing balloon dilatation if there is at least one of the following: > type B dissection and thrombolysis in myocardial infarction (TIMI) flow < 3 at the ostial SB[5]. An additional stent is required for the SB if any of the following issues are observed after kissing balloon inflation: > type B dissection or TIMI flow < 3. POT is also recommended after MV stenting.

Intracoronary imaging. Intracoronary imaging tools, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), are at the discretion of the operators.

Study stents. Stents for all implanted lesions are drug-eluting stents (DESs), including Firebird-2, or Firehawk (Microport Co., Shanghai, China); EXCEL (Jiwei Co., Shandong, China); BuMA stent (Sino Medical, Tianjin, China); Partner or Nano (Lepu Med, Beijing, China); Xience or Xience Prime (Abbott Vascular, Santa Clara, California); and Endeavor Resolute or Endeavor Integrity (Medtronic, Minneapolis, Minnesota).

Medication. All patients in the trial are treated with dual antiplatelet therapy for at least one year, according to contemporary guidelines and local practice. A loading dose of aspirin

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(300 mg) and clopidogrel (300 mg), or ticagrelor 180 mg) is recommended at least 6 hours before the PCI procedure. Heparin or an alternative antithrombotic agent (such as bivalirudin) must be used during the procedure to maintain an activated clotting time (ACT) >280 seconds. After the PCI, a lifelong dosage of aspirin at 100 mg/d will be prescribed. The duration of clopidogrel treatment with 75 mg/d (or ticagrelor with 90 mg twice a day) is at least 12 months.

Biomarker assessment. Total creatine kinase (CK), CK-myocardial-band isoenzyme (MB), and troponin T/I are dynamically measured before the procedure and until 72 h post-procedure.

Study endpoints

The primary endpoint in the present trial is TLF at 12 months after the indexed procedure, as defined by the composite of cardiac death, target vessel MI, and clinically driven TLR. The major secondary endpoints include all causes of death, MI, target-vessel revascularization (TVR), in-stent restenosis, stroke, and each individual component of the primary endpoints. The safety endpoint is the risk of Academic Research Consortium (ARC)-defined stent thrombosis. Other endpoints are listed in Table 3. Detailed definitions of the study endpoints are described in the supplemental material.

All endpoints are site-reported in an electronic web-based capture system with the additional submission of supporting medical documents. All clinical events are assessed by an independent committee that was blinded to the study.

Follow-up

After hospital discharge, clinical follow-up is performed with visits (preferred) or telephone contact at 1-, 6-, and 12-month. Follow-up will be continued annually until 5 years after the index procedure. An angiographic follow-up will be encouraged for all patients, and it will be

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conducted 13 months after the index procedure, unless clinically indicated earlier. An independent committee that is blinded to the study assesses all clinical events.

Angiographic analysis

Quantitative coronary angiographic (QCA) analysis at baseline, post-procedure and follow-up is performed by the QCA-laboratories at the Nanjing Heart Center. The images are analyzed by two experienced technicians who are blinded to the study design, with an inter- and intra-observer variability under 5% (Kappa test).

Basic angiograms for all lesions should consist of at least injections after intracoronary injection of 100-200 μg of nitroglycerin. A bifurcation-view must be gained for all patients; there should be an angulation difference between the two baseline angiograms of at least 30°. The diagnostic/guiding catheter should be well visible, near the center of the angiogram and filled with dye. The index lesions should be well visible, near the center of the angiogram and shown without foreshortening. Between the pre- and post-angiograms, all balloon inflations and stent implantations should be documented by short cine-runs.

Statistical analysis

All analyses will be performed on the intent-to-treat (ITT) population, defined as all patients randomized, regardless of the treatment actually received. The primary variable is time from randomization to first occurrence of any event from the TLF. From previous studies, we hypothesized that the rate of a 1-year TLF would be 15% in the systematic two-stent technique group and 25% in the provisional stenting group. Accordingly, a total sample size of 600 is needed to detect a power of 0.8 (Type Ⅱ error = 0.2, α = 0.05, 2-tailed). Because of the considerable uncertainty, the enrollment is extended to 660 patients (10% increment).

The distribution of continuous variables will be assessed by the Kolmogrov-Smirnov test. Categorical variables are expressed as frequencies or percentages and compared by Chi-square statistics or Fisher's exact test. Continuous variables are summarized as the

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means ± standard deviation (SD) or median and compared using Students' t-test (for normal data) and Mann-Whitney U test (for non-normally distributed variables). Survival curves with time-to-event data are generated by the Kaplan-Meier method and compared using the log-rank test. Comparisons between the two groups will be performed using the Cox proportional hazard model. A p value <0.05 is considered statistically significant. All analyses are performed with the use of the statistical program SPSS 24.0 (SPSS Institute Inc, Chicago, Illinois).

The extensive subgroup analysis will be performed to evaluate variation of treatment effects, as well as a test of interaction with the treatment for each subgroup variable. The sub studies of clinical factors include age (age > 75 years old), sex, diabetes mellitus, hyperlipidemia, hypertension, current smoking, acute coronary syndrome, cardiac dysfunction (left ventricular ejection fraction < 40%), and renal insufficiency (estimated glomerular filtration rate < 60 ml/min/1.73 m^2). In addition, the sub studies of angiographic and procedural factors include an unprotected distal left main bifurcation lesion, the use of IVUS, and complete revascularization. Therefore, there are a total of 12 prespecified subgroup analyses to explore the consistency of effects on two-stent techniques for complex bifurcation lesions.

Ethics and dissemination

The study is performed in accordance with the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practices. The study protocol and informed consent have been reviewed and approved by the Institutional Review Board of Nanjing First Hospital (KY20141128-01-KS-01, in the supplemental material), and accepted by each participating center. Written informed consent for participation in the trial was obtained from all enrolled patients. Dissemination of the results will include conference presentations and publications in peer-reviewed journals.

Trial organization

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The trial was designed by the principal investigator (PI) and the executive committee. The executive committee members are also responsible for reporting the results, and drafting the manuscripts. The executive committee, together with the steering committee, the data and safety monitoring committee, and the independent endpoints adjudication committee are involved in the present trial.

All centers with experience in two-stent techniques (including DK crush and culotte) can participate in the study. Details about trial organization are listed in the supplemental material.

Discussion

Several randomized studies have demonstrated that the PS technique using a jailed wire in the SB is the gold standard treatment for the majority of bifurcation lesions[1-6]; however, the bifurcation lesions enrolled in these studies were not all true bifurcation lesions. They were either moderate narrow or focused lesions at the SB ostium. The DKCRUSH Ⅱ trial[7] demonstrated that the two-stent technique using a DK crush was associated with a lower rate of TVR in true coronary bifurcation lesions with an SB lesion length of 15 mm, compared with PS. A meta-analysis also showed that the two-stent technique remained an optional treatment for true bifurcation lesions with a large SB[16]. In addition, the consensus of the European Bifurcation Club[17] was that true bifurcations with a large SB and ostial disease extending more than 5 mm from the carina are likely to require two-stent techniques. Therefore, a novel bifurcation classification is needed to identify which bifurcation lesions should be treated with two-stent techniques instead of PS.

A practical and easy-to-use classification was proposed in the DEFINITION registry by Shao-Liang Chen[9], which included 2 major criteria and 6 minor criteria. According to the newly established criteria, 70% exhibited simple bifurcation lesions, and the remaining 30% were classified as CBLs in 3660 patients with true coronary bifurcation lesions (Medina 1,1,1 and 0,1,1) and an SB diameter ≥2.5 mm by visual estimation. As was expected, the two-stent technique did not show any benefits over PS for the simple bifurcation lesions.

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However, for CBLs, two-stent techniques were associated with less in-hospital mortality and one-year MACE than PS. This important finding will be further verified in the randomized DEFINITION-Ⅱ trial.

Left main (LM) bifurcation lesions are unique bifurcation lesions. The diameter of the SB is bigger, and the bifurcation angle is also larger compared with that of a non-LM bifurcation. Culotte stenting with bare metal stents has been largely abandoned because of high restenosis rates. Since the introduction of DESs, culotte stenting has regained its popularity. Murasato reported restriction of the stent expansion such as a "napkin ring" in culotte stenting, using close-cell design stents[18]. In our bench study, even using open-cell design stents in T type bifurcations, significant stent under expansion was revealed in culotte stenting, in contrast to DK crush[19]. The DKCRUSH-Ⅲ trial confirmed that DK crush was associated with a lower TLR and stent thrombosis for LM bifurcation, compared with culotte stenting at 3-year follow-up [10,20]. Considering the shortages of culotte stenting, we strongly recommend the use of culotte stenting in non-LM bifurcation instead of LM bifurcations. PS with a jailed balloon is a safer alternative than a jailed wire to protect the SB, especially for a high risk of SB occlusion after MV stenting [14,15]. Given that CBLs will be enrolled in the study if a patient is randomized into the PS group, either the use of a jailed balloon or a jailed wire will be allowed at the discretion of the operators.

Conclusions

Strategies for coronary bifurcation lesions should be individualized. PS is the default approach for simple bifurcation lesions. The DEFINITION Ⅱ study is investigating whether systematic two-stent technique will be superior to PS in CBLs, regarding the incidence of TLF at 12 months.

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Table 1. Criteria of complex bifurcation lesions

Criteria	Lesion characteristics
Major 1	Distal LM bifurcation: SB-DS ≥70% and SB lesion length ≥10 mm
Major 2	Non-LM bifurcation: SB-DS ≥90% and SB lesion length ≥10 mm
Minor 1	Moderate to severe calcification
Minor 2	Multiple lesions
Minor 3	Bifurcation angle <45° or >70°
Minor 4:	Main vessel RVD <2.5 mm
Minor 5	Thrombus-containing lesions
Minor 6	MV lesion length ≥25 mm
Major 1 + any 2 minor 1–6 = complex bifurcation lesion	
Major 2 + any 2 minor 1–6 = complex bifurcation lesion	

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Table 2 Inclusion and exclusion criteria

Inclusion Criteria:
1. Provision of informed consent prior to any study specific procedures; 2. Men and women 18 years and older; 3. Established indication for PCI according to the guidelines of American Heart Association and American College of Cardiology; 4. Native coronary lesion suitable for drug-eluting stent placement; 5. True bifurcation lesions (Medina 0,1,1/1,1,1 /1,0,1); 6. Reference vessel diameter in side branch ≥2.5 mm by visual estimation.
Exclusion Criteria:
1. Pregnancy or breast-feeding mother; 2. Co-morbidity with an estimated life expectancy of < 50% at 12 months; 3. Scheduled major surgery in the next 12 months; 4. Inability to follow the protocol and comply with follow-up requirements or any other reason that the investigator feels would place the patient at increased risk; 5. Previous enrolment in this study or treatment with an investigational drug or device under another study protocol in the past 30 days; 6. Known allergy to ticagrelor clopidogrel, or aspirin, history of major hemorrhage (intracranial, gastrointestinal, etc.); 7. Chronic total occlusion lesion in either LAD, or LCX or RCA not re-canalized; 8. Severe calcification needing rotational atherectomy； 9. Patient with STEMI (within 24-hour from the onset of chest pain to admission).

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Table 3. Study endpoints.

Primary endpoint ● Target lesion failure: composite of cardiac death, target vessel myocardial infarction (MI), and target lesion revascularization (TLR) at 12 months
Secondary endpoints ● All-cause death: cardiac death, non-cardiac death ● MI: periprocedural MI, spontaneous MI ● Revascularization: TLR, target vessel revascularization (TVR) ● Stroke: ischemic stroke, hemorrhagic stroke ● Combined endpoint of all-cause death, MI, TVR ● In-stent restenosis ● Other outcome parameters: NYHA functional class, Braunwald class, net gain of lumen diameter, contrast volume, procedural time, devices consumed during indexed procedure, X-ray exposure time, X-ray dose, DAP-total, DAP-record, DAP-fluoro
Safety endpoints ● Stent thrombosis ● Bleeding complications

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Acknowledgements The authors appreciate the contributions of Ling Lin, Hai-Mei Xu, and Ying-Ying Zhao to data collection. They also acknowledge Bao-Xiang Duan, Lin Lin, Ji Yong, and Linda Lison for their contribution in the data and safety monitoring.

Contributiors

SLC made substantial contributions to study conception and design, and to the drafting and critical revision of the manuscript. JJZ and XFG wrote the first draft. YLH, JK, LT, and ZG provided data management and statistical expertise. DT, SL, LKM, FL, SY, JZ, MM, LL, RYZ, HSZ, TS, PX, ZNJ, LH, WHY, XSQ, QHL, LH, CP, YW, LJL, LZ, XMW, SYW, QHL, JQY, LLC, FL, AER, LMZ, SQD, KV, YSZ, MYY, CC, IS, YX, YLT, ZLS, QJ, YHZ, XW, FY, NLT, SL, and ZZL provided comments and suggestions in critical revision of the article. All authors approved the final version of the article.

Funding The present trial was support by National Science Foundation of China (NSFC 81270191, NSFC 91439118) and Health and Family Planning Commission Foundation of Nanjing (YKK16124)

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study protocol and informed consent have been reviewed and approved by the Institutional Review Board of Nanjing First Hospital (KY20141128-01-KS-01), and accepted by each participating center. Version of this protocol was 1.2, and was approved on March 9, 2016 (in the supplemental material).

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure legend

Figure 1 Flowchart of study design.

SB: side branch; RVD: reference vessel diameter; DS: diameter stenosis; LMd: left main distal bifurcation; MV: main vessel; PS: provisional stenting; TLF: target lesion failure; TV-MI: target-vessel myocardial infarction; TLR: target lesion revascularization.

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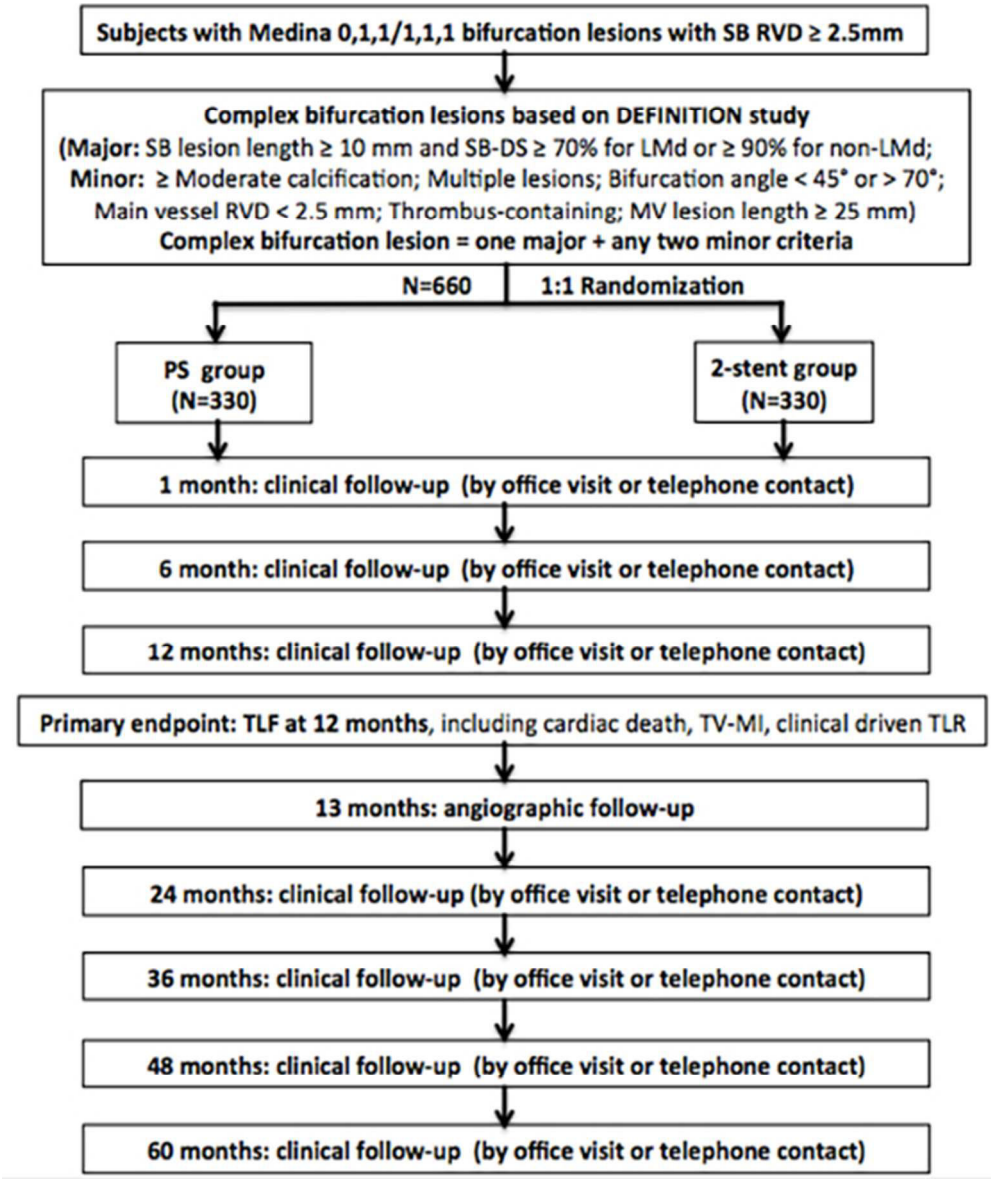

Flowchart of study design.

50x58mm (300 x 300 DPI)

Supplemental material

The treatment effects of systematic two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: Rationale and design of a prospective, randomized, and multicenter DEFINITION II Trial

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Appendix 1. Definitions of major study endpoints

Endpoint	Definition
Death	● **Cardiovascular death** includes sudden cardiac death, death due to acute myocardial infarction (MI), arrhythmia, heart failure, stroke, other cardiovascular causes, or bleeding ● **Non-cardiovascular death** is defined as any death with known cause not of cardiac or vascular cause ● All deaths are considered cardiac in origin unless a non-cardiac cause is confirmed clinically or at autopsy.
Myocardial infarction	**Post-procedure MI**: occurrence within 48 hours after PCI ● Patients with normal baseline CK-MB: the peak CK-MB measured within 48 hours of the procedure rises to ≥ 10 × upper reference limit (URL), or to ≥ 5 × URL with new pathologic Q-waves in at least 2 contiguous leads or new persistent left bundle branch block (LBBB) ● Patients with elevated baseline CK-MB in whom the biomarker levels are stable or falling: the CK-MB rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level **Spontaneous MI**: occurrence more than 48 hours after PCI ● The rise of cardiac biomarkers (CK-MB or troponin) > 1x URL, with one of the follows: ➢ Evidence of prolonged ischemia as demonstrated by prolonged chest pain ➢ Ischemic ST-segment changes or new pathological Q waves ➢ Angiographic evidence of a flow limiting complication ➢ Imaging evidence of new loos of viable myocardium or new regional wall motion abnormality **Target vessel MI:** spontaneous MI associated with target vessel (including main vessel [MV] and side branch [SB]), which was identified by electrocardiographic changes or coronary angiography. Each MI will also be classified as ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI)
Revascularization	**Target lesion revascularization (TLR)** ● Repeat revascularization (including PCI and coronary artery bypass grafting) for target lesions (including MV and SB), in the presence of symptoms or objective signs of ischemia **Target vessel revascularization (TVR)** ● Repeat revascularization (including PCI and coronary artery bypass grafting) for target vessels (including MV and SB), in the presence of symptoms or objective signs of ischemia **Target vessel non-target lesion revascularization** ● Target vessel non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography
Stent thrombosis	Academic Research Consortium (ARC) classification **Definite stent thrombosis** ● Symptoms suggestive of an acute coronary syndrome and angiographic or pathological confirmation of stent thrombosis

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	Probable stent thrombosis ● Unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis **Possible stent thrombosis** ● Any unexplained death after 30 days Stent thrombosis will also be classified as acute stent thrombosis (0–24 hours after PCI), subacute stent thrombosis (24 hours-30 days), late stent thrombosis (31 days–1 year), or very late stent thrombosis (>1 year)
Bleeding	Bleeding Academic Research Consortium (BARC) classification **Type 0**: no bleeding **Type 1**: bleeding that is not actionable and doses not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment **Type 2**: any overt, actionable sign of hemorrhage that doses not fit the criteria for 3, 4, or 5 **Type 3**: ● **Type 3a**: overt bleeding with hemoglobin drop of 3 to 5 g/dl; any transfusion with overt bleeding ● **Type 3b**: overt bleeding with hemoglobin drop ≥ 5g/dl; cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring intravenous vasoactive agents ● **Type 3c**: intracranial hemorrhage; intraocular bleeding compromising vision **Type 4**: CABG-related bleeding **Type 5**: fatal bleeding
Stroke	Global or focal cerebral, spinal cord, or retinal injury resulting in acute neurological dysfunction and was further classified into ischemic and hemorrhagic stroke

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Appendix 2. Trial organization

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Study statistician:

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Data and safety monitoring committee:

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12. Shanghai Ruijin Hospital, Shanghai, China;
13. Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;
14. Medistra Hospital, University of Indonesia, Jakarta, Indonesia;
15. Gansu Provincial Hospital, Lanzhou, China;
16. Beijing Anzhen Hospital, Capital Medical University, Beijing, China;
17. Changshu First People's Hospital, Changshu, China;
18. Cheng-Hsin General Hospital, Taipei, China;
19. Zhangjiagang First People's Hospital, ZhangjiaGang, China;
20. Changzhou Hospital of Traditional Chinese Medicine, Changzhou, China;
21. Jiangxi Provincial People's Hospital, Nanchang, China;
22. Bangkok General Hospital, Bangkok, Thailand;
23. Xia'Men Zhongshan Hospital, Xia'Men, China;
24. Huainan First People's Hospital, Huainan, China;
25. Jintan People's Hospital, Jintan, China;
26. Wuxi Third People 's Hospital, Wuxi, China;
27. Daqing Oil General Hospital, Daqing, China;
28. The Second Hospital of Shandong University, Ji'nan, China;

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29. Xinyang Central Hospital, Xinyang, China;
30. Fujian Union Hospital, Fuzhou, China;
31. Jilin Heart Hospital, Changchun, China;
32. Otamendi Hospital, Buenos Aires, Argentina;
33. Chuzhou First People 's Hospital, Chuzhou, China;
34. Huainan Xinhua Hospital, Huainan, China;
35. Bangle Hospital, Bangkok, Thailand;
36. Huai'an Second People's Hospital, Huai'an, China;
37. Qingdao Fuwai Hospital, Qingdao, China;
38. The Affiliated Hospital of Guangdong Medical University, Guangdong, China;
39. University of Turin, Turin, Italy;
40. The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China;
41. Xuyi People's Hospital, Xuyi, China;
42. Wuxi Huishan District People's Hospital, Wuxi, China;
43. Anqing First People's Hospital, Anqing, China;
44. Liyang Hospital of Traditional Chinese Medicine, Liyang, China;
45. Lianyungang Hospital of Traditional Chinese Medicine, Lianyungang, China;

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Appendix 3. Institutional Review Boards

南京市第一医院伦理委员会审批件

编号：KY20141128-01

科研项目名称	比较 DK Crush 技术和 Provision Stenting 技术处理复杂分叉病变的前瞻性、随机对照研究（DEFINATION-2）		
项目来源	中办者发起	CRO	无
申请科室	心内科	项目负责人	陈绍良
审查时间	2014 年 11 月 28 日	审查地点	南京市第一医院多媒体教室
审查方式	■会议审查 □快速审查		
审批材料	详见附件审批材料目录		

伦理委员会成员

姓名	性别	单位部门	职称	伦理职务	签到
沈海琦	男	南京市第一医院骨科	主任医师	主任委员	
马俊	男	南京市第一医院党委	政工师	副主任委员	
陈亚新	女	南京医科大学医政学院	副教授	副主任委员	
刘晓东	男	中国药科大学	教授	副主任委员	
夏京胜	男	江苏三法律师事务所	律师	委员	
孙辉	男	南京市建邺区信访局	公务员	委员	
娄晟	女	南京市第一医院药剂科	主任药师	委员	
张林	男	南京市第一医院科技处	主治医师	委员	
朱怀刚	男	南京市第一医院教育处	主管技师	委员	
赵太宏	男	南京市第一医院医务处	副主任医师	委员	
陈玉红	女	南京市第一医院护理部	主任护师	委员	

出席人数	应到人数 11 人、实到人数 9 人，其中：投票人数 9 人，回避人数 0 人。
投票结果	同意（ 8 ）修改后同意（ 1 ）修改后重审（ 0 ） 不同意（ 0 ） 终止或暂停（ 0 ）

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审查意见：

本伦理委员会的职责、人员组成、操作程序及记录遵循 ICH-GCP、中国 GCP 和中国相关法律。根据卫生部《涉及人的生物医学研究伦理审查办法(试行 (2007))》、SFDA 《药物临床试验质量管理规范(2003)》、《医疗器械临床试验规定 (2004)》、《赫尔辛基宣言》和 《人体生物医学研究国际道德指南》的伦理原则进行审查。

□非同意性意见：

按审查意见修改后的文件，或对审查意见不同观点的陈诉，请提交"复审申请"，方案/知情同意书 请注明新的版本号和版本日期，并以下划线方式标注修改部分，报伦理委员会审查，经批准后执行。

具体修改意见：

☑同意性意见：

经本伦理委员会审查，同意按所批准的临床研究方案、知情同意书、招募材料开展本项研究。

请遵循 GCP 原则、遵循伦理委员会批准的方案开展临床研究，保护受试者的健康与权利。

研究开始前，请申请人完成临床试验注册。

研究过程中若变更主要研究者，对临床研究方案、知情同意书、招募材料等的任何修改，请申请人提交修正案审查申请。

发生严重不良事件，请申请人及时提交严重不良事件报告。

请按照伦理委员会规定的年度跟踪审查频率申请人在截止日期前 1 个月提交研究进展报告

申办者应当向组长单位伦理委员会提交各中心研究进展的汇总报告，当出现任何可能显著影响试验进行或增加受试者危险的情况时，请申请人及时向伦理委员会提交书面报告。

研究纳入了不符合纳入标准或符合排除标准的受试者，符合中止试验规定而未让受试者退出研究，给予错误治疗或剂量，给予方案禁止的合并用药等没有遵从方案开展研究的情况;或可能对受试者的权益/健康以及研究的科学性造成不良影响等违背 GCP 原则的情况，请监查员/研究者提交违背方案报告。

申请人暂停或提前终止临床研究，请及时提交暂停/终止研究报告。 完成临床研究，请申请人提交结题报告。

具体审查意见：

跟踪审查频率：□半年 ☑一年 □其他

本批件有效期为1年（自批准之日起），逾期未实施的，则自行废止。

联系电话：025-52271039

审 批 结 论

同意(✓) 修改后同意( )修改后重审( ) 不同意( ) 终止或暂停( )

主任委员（签名）：

2014年1月28日

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南京市第一医院伦理委员会快速审批件

编号：KY20141128-01-KS-01

科研项目名称	比较双支架术和必要时分支支架术治疗冠状动脉复杂分叉病变的一项前瞻性，多中心，随机对照研究（DEFINATION-2）		
项目来源	申办者发起	CRO	无
申请科室	心内科	项目负责人	陈绍良
审批材料	1、修正案审查申请表 2、研究方案（版本 1.1，日期 2015-12-08） 3、病例报告表（版本 1.1，日期 2015-12-08） 4、知情同意书（版本 1.1，日期 2015-12-08）		
快审人员签名			
签名			
职务	主任委员	委员	
审批结论			
同意(√) 修改后同意( ) 不同意( ) 终止或暂停( ) 转为会审 ( ) 说明： 主任委员或授权人（签名）： 2015年12月16日			
声明	本伦理委员会的职责、人员组成、操作程序及记录遵循 ICH-GCP、中国 GCP 和中国相关法律。		

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南京市第一医院伦理委员会快速审批件

编号：KY20141128-01-KS-01

科研项目名称	比较双支架术和必要时分支支架术治疗冠状动脉复杂分叉病变的一项前瞻性，多中心，随机对照研究（DEFINATION-2）		
项目来源	申办者发起	CRO	无
申请科室	心内科	项目负责人	陈绍良
审批材料	1、修正案审查申请表 2、研究方案（版本 1.2，日期 2016-02-25） 3、病例报告表（版本 1.2，日期 2016-02-25） 4、知情同意书（版本 1.2，日期 2016-02-25）		
快审人员签名			
签名			
职务			
审批结论			
同意（√） 修改后同意（ ） 不同意（ ） 终止或暂停（ ） 转为会审（ ） 说明： 主任委员或授权人（签名）： 2016年3月9日			
声明	本伦理委员会的职责、人员组成、操作程序及记录遵循 ICH-GCP、中国 GCP 和中国相关法律。		

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Appendix 4. SPIRIT 2013 Checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15-16
	5b	Name and contact information for the trial sponsor	16
	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	16
	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)	9-10
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	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	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)	5
Methods: Participants, interventions, and outcomes			

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Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___5_____
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)	____5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___5-6____
	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)	____6_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____6_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___6-7____
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	____7_____
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)	____7_____
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	____8_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___n/a____
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	____5_____
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	___5_____

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Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5,7
	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	7
	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	n/a
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	n/a
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	8-9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	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)	8-9
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	9
	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	n/a

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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	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)	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)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
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	16
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	9,16
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	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	9,16
	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	9
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.

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