

BMJ Open Live birth after in vitro maturation versus standard in vitro fertilisation for women with polycystic ovary syndrome: protocol for a non-inferiority randomised clinical trial

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ABSTRACT

Introduction Polycystic ovary syndrome (PCOS) is the first common cause of anovulatory infertility. Currently, in vitro fertilisation (IVF) is recommended when conventional attempts have failed. In vitro maturation (IVM) of human oocytes is an emerging treatment option in infertile women with PCOS. It is a patient-friendly intervention, avoiding the risk of ovarian hyperstimulation syndrome, which is a serious complication of controlled ovarian stimulation in the standard IVF procedure. We plan a randomised controlled trial (RCT) to evaluate whether IVM is non-inferior to the standard IVF for live birth in women with PCOS.

Methods and analysis This is a single-centre, open-label, non-inferiority RCT performed in a large reproductive medicine centre in China. Infertile women with PCOS will be randomised to receive either IVM or standard IVF in a 1:1 treatment ratio after informed consent. IVF procedures used in our study are all standard treatments and other standard-assisted reproductive technologies will be similar between the two groups. The primary outcome is ongoing pregnancy leading to live birth within 6 months of the first oocyte retrieval cycle after randomisation. Pregnancy outcome, maternal safety and obstetric and perinatal complications will be secondary outcomes. The planned sample size is 350 (175 per group).

Ethics and dissemination Ethical permission was acquired from the Ethics Committee of Peking University Third Hospital. The results will be issued to publications through scientific journals and conference reports.

Trial registration number NCT03463772.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the first common cause of anovulatory infertility and occurs in 5.6% in reproductive-aged women in the Chinese communities¹. It is also a major metabolic disorder associated with insulin resistance, β -cell dysfunction and obesity.² Fifty per cent of women with PCOS present with subfertility. In anovulatory women with PCOS, the first-line treatments are lifestyle

Strengths and limitations of this study

- This is a randomised controlled trial with an adequate sample size to evaluate in vitro maturation (IVM) treatment in infertile women with polycystic ovary syndrome.
- This study will provide evidence on whether the experimental group (IVM) is non-inferior to the standard in vitro fertilisation in terms of live birth.
- The cost-effective analysis is not included in the study, limiting the comprehensiveness of the results.

intervention and ovulation induction with letrozole or clomiphene citrate.³ Laparoscopic ovarian drilling or ovarian induction with gonadotrophin (Gn) is considered as the second-line treatment options. In vitro fertilisation (IVF) is the third-line treatment and is recommended when the above-mentioned treatments have failed.

In standard IVF treatment, women with PCOS are at high risk of ovarian hyperstimulation syndrome (OHSS), which is a serious and common iatrogenic complication of controlled ovarian stimulation (COS). The prevalence of moderate and severe forms of OHSS in women undergoing IVF is 3%–8% and much higher in women with PCOS.⁴ Severe OHSS is defined by the presence of clinical evidence of ascites with severe abdominal pain and pleural effusion. A large amount of pleural and peritoneal effusion can lead to intravascular blood loss, blood concentration, blood hypercoagulability, hypovolemic shock, severe cardiopulmonary dysfunction, electrolyte imbalance, impaired liver and kidney function, thrombosis and even life-threatening.⁵ Therefore, seeking an alternative treatment strategy, avoiding the

risk of OHSS without compromising pregnancy outcomes is crucial for women with PCOS.

In vitro maturation (IVM) has been introduced in 1990. Trounson *et al*⁶ described the first delivery of a healthy baby with the IVM technique in a woman with PCOS. From then on, immature oocyte retrieval followed by IVM had been used widely, resulting in the delivery of thousands of healthy infants worldwide.⁷⁻⁹ In IVM, immature oocytes are collected from antral follicles, typically from unstimulated or minimally stimulated ovaries, then cultured, matured and fertilised in vitro.¹⁰ Compared with standard IVF treatment, IVM is performed without ovarian stimulation, thus preventing the occurrence of OHSS and reducing financial costs.

To date, despite the publication of many studies on IVM, the effectiveness and safety of IVM treatment are still controversial. Some studies showed that the live birth rate was significantly lower in the IVM group than in the IVF group.¹¹⁻¹³ Now mature technology, gradually getting more research results, indicated comparable pregnancy outcomes between IVM and IVF group.^{14 15} Until now, all data available have derived from observational studies.¹⁶ Given the unique advantages of IVM as safer, simpler and cheaper,¹⁷ we need further evidence from well-designed randomised controlled trials (RCTs) on the live birth rate before we draw conclusions on the effectiveness and safety of IVM. Therefore, we plan an RCT to determine whether IVM is non-inferior to standard IVF on live birth for women with PCOS.

METHODS AND ANALYSIS

Study design

This is a single-centre, non-inferiority RCT with a 1:1 treatment ratio. The programme for enrolment, interventions and evaluation during the study process is shown in [table 1](#). [Figure 1](#) indicates a flowchart showing the registration, allocation, treatment and follow-up of participants.

Study setting

The trial is approved by the Ethics Committee of Peking University Third Hospital (2017sz-066). Women with PCOS and infertility who scheduled for their first IVF attempt at Peking University Third Hospital (Beijing, China) will be recruited. Potentially eligible women will be given information about the study during their first consultation. All the couples provided written informed consent before participation. The trial progress will be monitored by an independent data and safety monitoring board (DSMB).

Eligibility criteria

PCOS outpatient women with infertility who come to the reproductive centre of Peking University Third Hospital will be screened for eligibility by a research team.

Inclusion criteria

- ▶ Married Chinese women with infertility aged between 20 and 38 years.

- ▶ Women with PCOS according to the revised Rotterdam criteria (ie, two of the three following features are present: (1) oligo and/or anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; and (3) polycystic ovaries). Exclusion of other possible related disorders: ovarian or adrenal androgen-secreting tumours, thyroid disease, hyperprolactinaemia, and non-classical adrenal hyperplasia.¹⁸
- ▶ Women scheduled for their first IVF/intracytoplasmic sperm injection (ICSI) cycle. Women must have an indication for assisted reproductive technology (ART), including ovulation dysfunction and failure to become pregnant after ovulation induction treatment; unilateral or bilateral tubal obstruction, adhesion, salpingectomy or tubal ligation; and oligoasthenozoospermia.
- ▶ Written informed consent obtained.

Exclusion criteria

- ▶ Couples with a contraindication for IVF or ICSI (including but not limited to poorly controlled type 1 or type 2 diabetes mellitus; liver disease or dysfunction (based on serum liver enzyme test results); renal disease or abnormal serum renal function; anaemia; history of deep venous thrombosis, pulmonary embolus or cerebrovascular accident; uncontrolled hypertension or known symptomatic heart disease; history of (or suspected) cervical carcinoma, endometrial carcinoma or breast carcinoma; and unexplained colporrhagia).
 - ▶ Couples receiving donor sperm or donor oocytes.
 - ▶ Couples with indications or have the plan to receive preimplantation genetic testing.
 - ▶ Women with a male partner diagnosed with azoospermia.
 - ▶ Either a male partner or female partner with a known abnormal chromosome karyotype (chromosome polymorphisms were not included).
 - ▶ Women who have undergone unilateral ovariectomy.
- Participants can leave the study at any time without any consequences for their clinical treatments.

Recruitment

Potentially eligible women will be informed about the trial during their first consultation. If a woman wants to participate, written informed consent will be acquired in their next scheduled visit. To initiate the IVM or IVF treatment cycle in anovulatory cases, patients were administered oral dydrogesterone (Duphaston, Abbott, OLST, Netherlands) 20 mg daily for 10–14 days/oral contraceptives Diane-35 (cyproterone acetate 2mg, ethinylestradiol 35 mg, Bayer and its generics) for 21 days. After the withdrawal bleeding, eligible participants will be assessed again for the exclusion criteria on day 2 or day 3 following the onset of menstrual bleeding.

Table 1 Schedule of enrolment, interventions and assessments

Content	Study period			Postallocation			Close-out		
	Enrolment	Allocation	Postallocation	Enrolment	Allocation	Postallocation	Enrolment	Allocation	
	Screening and baseline assessment	IVM and IVF randomisation	Oocyte retrieval	Assessment of embryo	Embryo transfer	Evaluation of pregnancy	Follow-up of pregnancy		
Time point	T ₀ -1 month	T ₁ 0 month	T ₂ 10-14 days	T ₃ 1-3-5 days after oocyte pick-up	T ₄ 2-6 months	T ₅ 3-7 months	T ₆ 6-10 months	T ₇ 8-12 months	
Enrolment									
Eligibility screen	x								
Informed consent	x								
Allocation		x							
Interventions									
IVM		x							
Standard IVF		x							
Assessments									
Baseline data	x								
Laboratory tests	x		x		x	x	x	x	
Fertilisation				x					
Embryo quality				x					
Pregnancy tests						x			
Pregnancy outcomes							x	x	
Fetus information							x	x	
Neonate information							x	x	
Safety assessment		x	x		x	x	x	x	

IVF, In vitro fertilisation; IVM, In vitro maturation.

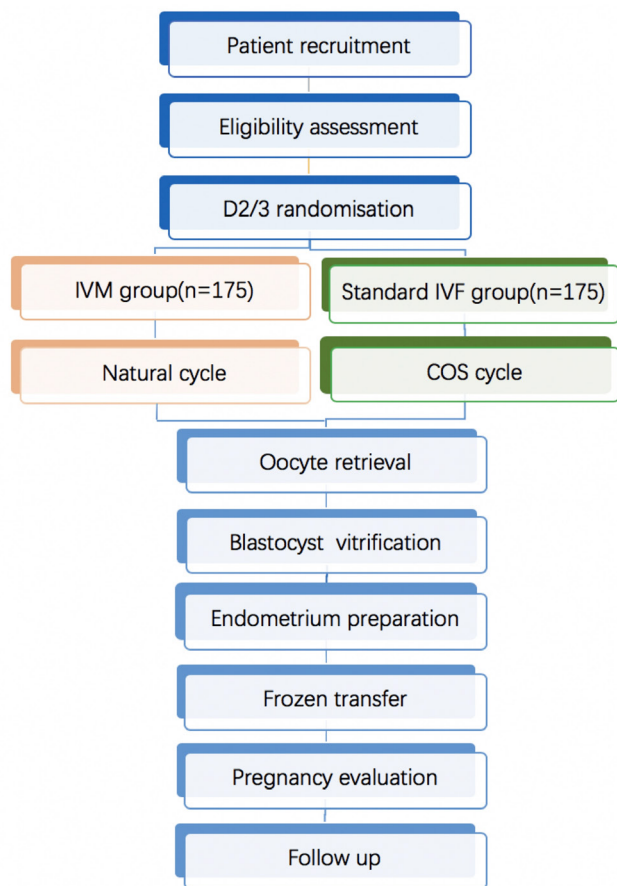


Figure 1 Flowchart of this randomised controlled trial: IVM versus IVF in women with polycystic ovary syndrome. COS, controlled ovarian stimulation; IVF, in vitro fertilisation; IVM, in vitro maturation.

Randomisation and allocation concealment

Randomisation and allocation of qualified participants will be done on day 2/3 of the menstrual cycle. Eligible participants will be allocated to IVM or IVF treatment according to a computer-generated randomisation list in a 1:1 ratio, with a variable block size of 4 or 6. Opaque-sealed envelopes, with participant's screening order printed outside and randomised-assigned group printed inside, will be numbered consecutively. Researchers will enrol the eligible participants after the screening, then open each envelope in a sequence corresponding with the screening order and assign the participant into the IVM or IVF group. Both investigators and participants will be aware of the allocation of the subsequent treatments.

Interventions

IVM protocol

Gns (follicle stimulating hormone (FSH), HMG or human chorionic Gn (hCG)) will not be used in the IVM group. After randomisation, participants will visit the clinic on days 6–8 for a transvaginal ultrasound examination to exclude the development of a dominant follicle. Oocyte retrieval will be scheduled once the endometrium thickness reaches at least 6 mm and there is no appearance of the dominant follicle (follicle diameter >10 mm).

Transvaginal ultrasound-guided oocytes retrieval will be conducted with a single-lumen 19G aspiration needle (K-OPS-7035-REH-ET; Cook, Queensland, Australia) in 90 mm Hg suction pressure. Follicular aspirates will be gathered and filtered through a cell strainer (Cell Strainer 352350, 70 µm nylon; Falcon, Massachusetts, USA). Then the collected aspirates will be washed with prewarmed Hepe's-HTF (CooperSurgical; Trumbull, Connecticut, USA). The mixture will be examined carefully under a stereomicroscope to search for cumulus-oocyte complexes (COCs). All COCs will be transferred into IVM medium (IVM media kit; Sage, Connecticut, USA) supplemented with 0.075 IU/mL FSH and 0.075 IU/mL LH (Menopur; Ferring, Kiel, Germany) in 5% CO₂ incubator at 37°C. All the COCs will be denuded of cumulus cells after 28–32 hours of culture and evaluated the maturation process. The presence of a first polar body indicates that the oocyte enters the metaphase II stage. All the metaphase II (MII) oocytes will be inseminated by means of intracytoplasmic sperm injection (ICSI).

IVF protocol

For participants in the IVF group, COS will be performed by a flexible protocol using Gn-releasing hormone antagonist (GnRH-ant) with recombinant FSH (rFSH) and recombinant human chorionic Gn (rhCG). Treatment will start on day 2/3 of the menstrual cycle. All participants will be subcutaneous injected rFSH (Gonal-F; Serono, Geneva, Switzerland) with 100–225 IU/day initial dosage. Transvaginal ultrasound, serum luteinising hormone (LH), serum oestrogen (E2) and progesterone (P4) will be tested to monitor follicle growth. rFSH doses will be adjusted according to ovarian response. GnRH antagonist-cetrorelix (Cetrotide; Serono, Darmstadt, Germany) 0.25 mg daily by subcutaneous injection will begin when at least one follicle has reached a diameter of 12 mm which is usually between day 5 and day 8 of ovarian stimulation, until the trigger day (include the trigger day). After two or more follicles reach a diameter ≥17 mm, 250 µg of rhCG (Ovidrel; Serono, Aubonne, Germany) will be once injected on trigger day. Oocyte retrieval will be performed 36 (±2) hours after rhCG injection. Oocyte collection is conducted via 17G oocyte aspiration needle with the use of intravenous sedation. All COCs will be cultured in human tubal fluid medium and incubated in a humidified 37°C incubator 5% CO₂, after oocyte retrieval immediately. The fertilisation method will be selected according to the semen analysis.

Assessment of fertilisation and embryo culture

Fertilisation will be considered normal when two pronuclei are present between 16 and 18 hours after ICSI or IVF. Normal fertilisation rate will be calculated as the number 2PN over the number of MII in ICSI patients or the number 2PN over the number of COCs for conventional IVF. All zygotes will be cultured in cleavage medium (G-1plus, Vitrolife, USA) for further 48–52 hour after fertilisation. Cleavage embryonic development will

be assessed according to the developmental stage and degree of cytoplasmic fragmentation. All day 3 embryos will be cultured up to 2–3 days (G-2 plus, Vitrolife, USA). From day 5 to day 6, those embryos achieving the blastocyst stage will be evaluated morphologically using Gardner's grading system.

For all participants, a freeze-only blastocyst transfer strategy will be applied. All usable blastocysts (embryos that can grow to expanded or hatching blastocysts earn a score above grade CC) will be cryopreserved by vitrification methods.

Blastocyst vitrification and warm

The expanded blastocysts collapsed after artificial shrinkage will be vitrified and warmed as previously demonstrated.¹⁹ In brief, the blastocysts will be transferred in equilibration medium, which included 7.5% (v/v) dimethyl sulfoxide (DMSO, Sigma Chemical Co., Missouri, USA) and 7.5% (v/v) ethylene glycol (EG, Sigma Chemical Co), at 37°C for 2 min, then placed in vitrification solution for 30 s that containing 15% DMSO, 15% EG and 0.65 mol/L sucrose. During this period, shrinkage blastocyst will be loaded on the cryotop strip (Kitazato, Fuji, Japan), next plunged into liquid nitrogen immediately. For warming, the cryotop will be quickly placed in 0.33 mol/L sucrose at 37°C and searching for the floated blastocyst under the microscope. The blastocyst will be washed several times and placed for 2 min. Then it will be transferred into 0.2 mol/L sucrose for 3 min and in a N-2-hydroxyethylpiperazine-N-ethanesulphonic acid (HEPES)-buffered medium for 5 min in turn. After 2 hours, the blastocysts will be evaluated the quality. The re-expanded blastocysts will be considered to survive and will be transferred to the patients.

Endometrium preparation, blastocyst transfer and luteal support

In vitrified-warmed blastocyst transferred cycles, participants will undergo hormone replacement therapy (HRT) for their endometrial preparation. All participants' once endometrial thickness reaches 6 mm and no ovarian cyst is observed on ultrasound, oral oestradiol valerate (Progynova, Delpharm Lille, Lys-Lez-Lannoy, France) at a dose of 3 mg two times per day will be started on day 1–3 of the menstrual cycle. And then an ultrasound will be repeated after more than 10 days after administration of HRT, vaginal progesterone gel (Crinone, Merck Serono, Watford, UK) 90 mg per day and oral dydrogesterone (Duphaston, Abbott) 20 mg two times per day will be added when the endometrial thickness was ≥ 8 mm. All the ultrasound scans and measurements will be performed with the digital platform Voluson E8 system. Only one blastocyst will be transferred on day 7 after progesterone administration. Luteal phase support was continued until 12 weeks gestation.

Follow-up

All participants will measure the hCG of urine and blood at the 12 days after blastocyst transfer, in which positive

results indicate biochemical pregnancy. On 28 days after transfer, if the gestational sac is observed with ultrasonography, participants will be diagnosed with clinical pregnancy. Ongoing pregnancy is defined as a sac with the fetal heartbeat and occurs after 12 weeks of pregnancy. Ongoing pregnancy leading to live birth is defined by the live fetus in the uterine after 22 weeks of gestation. We will collect the following information within 6 weeks after delivery, prenatal testing information (pregnancy complications and fetal information), delivery information (gestational age, mode of delivery, placental condition and birth complications) and newborn information (fetal sex, birth weight and birth defects).

Outcome measures

Primary outcome

Our primary study endpoint is ongoing pregnancy leading to live birth (gestation age ≥ 22 weeks) within 6 months of the first oocyte retrieval cycle after randomisation.²⁰

Secondary outcomes

Secondary outcomes of our trial include pregnancy outcomes, maternal safety and obstetric and perinatal complications. Detailed information is provided in [table 2](#). Maternal safety is an important part of the secondary outcomes. The incidence of OHSS is the key indicator of maternal safety. Routine evaluation for OHSS will be performed on oocyte retrieval day and on day 3 after fertilisation with ultrasound scanning and hormonal result in all participants. It is classified as mild, moderate or severe according to the Royal College of Obstetricians & Gynaecologists guideline.²¹

Safety reporting

Adverse events (AE) are defined as any undesirable experience occurring to a subject during the trial. A serious AE (SAE) is any untoward medical events, that results in death; is life-threatening (at the time of the event); requires hospitalisation or prolongation of existing inpatients' hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; and is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction.

SAE in this study includes: moderate/severe OHSS; intraperitoneal haemorrhage or ovarian torsion after oocyte retrieval; ectopic pregnancy; severe pre-eclampsia; pregnancy complications leading to hospitalisation; still-birth; birth defects; other serious medical events judged by researchers to meet the criteria of SAE.

All SAEs will be reported to the DSMB and accredited Medical Education Technology Committee (METC) that approved the protocol, according to the requirements of that METC.

Statistical analysis

Sample size calculation

The primary hypothesis of this study is that the experimental group (IVM) is non-inferior to the control group

**Table 2** Secondary outcomes and related definition

Secondary outcomes	Definition
Pregnancy outcomes	
Implantation	Number of gestational sacs observed per embryo transferred
Clinical pregnancy	One or more observed gestational sac or definitive clinical signs of pregnancy under ultrasonography at 7 weeks of gestation (including clinical documented ectopic pregnancy)
Ongoing pregnancy	Presence of a gestational sac and fetal heartbeat after 12 weeks of gestation
Time to ongoing pregnancy leading to live birth*	Time from randomisation to detection of ongoing pregnancy after completion of the transfer
Maternal safety outcomes	
OHSS	Exaggerated systemic response to ovarian stimulation characterised by a wide spectrum of clinical and laboratory manifestations. It is classified as mild, moderate, or severe according to the degree of abdominal distention, ovarian enlargement and respiratory haemodynamic, and metabolic complications. Diagnosed by ultrasound, blood testing and physical examination according to the RCOG Guideline. ²¹
Miscarriage	Spontaneous loss of an intra-uterine pregnancy prior to 28 completed weeks of gestational age
Ectopic pregnancy	A pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualisation or histopathology
Obstetric and perinatal complications	
Gestational diabetes mellitus	Development of diabetes during pregnancy
Hypertensive disorders of pregnancy	Including pregnancy-induced hypertension, pre-eclampsia and eclampsia
Antepartum haemorrhage	Including placenta previa, placenta accreta and unexplained
Birth weight	Including low birth weight (weight <2500 g at birth), very low birth weight (<1500 g at birth), high birth weight (>4000 g at birth) and very high birth weight (>4500 g at birth)
Large for gestational age	A birth weight greater than the 90th centile of the sex-specific birth weight for a given gestational age reference
Small for gestational age	A birth weight less than the 10th centile for the sex-specific birth weight for a given gestational age reference
Preterm birth	Birth of a fetus delivered after 28 and before 37 completed weeks of gestational age in participants confirmed ongoing pregnancy
Congenital anomaly	Structural or functional disorders that occur during intrauterine life and can be identified prenatally, at birth or later in life, including trisomy 21 syndrome, neural tube defect, congenital heart disease, cleft lip, excessive numbers of fingers or toes, hydrocephalus.
Perinatal mortality	Fetal or neonatal death occurring during late pregnancy (at 28 completed weeks of gestational age and later), during childbirth, or up to seven completed days after birth)

*Only ongoing pregnancy leading to live birth within 6 months of the first oocyte retrieval cycle after randomisation will be counted.

(IVF) in terms of ongoing pregnancy leading to live birth. On the basis of actual data on the women with PCOS who underwent IVM or IVF-ET in our reproductive medicine centre, we assume that after IVF the proportions of ongoing pregnancy leading to live birth for the PCOS women are 35% per transferred cycle.^{22 23} With a non-inferiority margin of 15%, power of 80% and one-sided α 0.025, we will need to enrol 159 participants in each group (the ratio between groups will be 1:1). Taking consideration of dropout rate as 10% (such as cancellation during trial procedures), each group will include 175 participants (a total of 350 participants).

Statistical analysis

The result will be analysed according to the intention-to-treat principle. Preprotocol (PP) analysis will also be conducted as a sensitivity analysis. Baseline characteristics will be described by descriptive analysis, and the balance among groups or subgroups will be assessed by analysis for different kinds of data. For continuous variables,

the normality distribution will be estimated by using frequency histograms and the Kolmogorov-Smirnov test initially. If the continuous variables are normally distributed, they will be presented as means with SDs. If the continuous variables are non-normally distributed, their medians and inter-quantile ranges will be reported. For categorical variables, we will present the proportion between each group. In addition, the recruitment numbers, those participants lost to follow-up, protocols violations and other relevant data will also be reported. A comparison between groups will be performed using the independent sample t-test, Mann-Whitney U test for continuous variables or Pearson's χ^2 test/Fisher's exact test for categorical variables as appropriate. The primary outcome, ongoing pregnancy leading to live birth, will be compared using Pearson's χ^2 test or Fisher's exact test as appropriate. Categorical secondary outcomes will be compared between two groups using a similar approach as the primary outcome. Student's t-test or Wilcoxon test

will be used as appropriate for continuous secondary outcomes, such as birth weight and etc. The relative risks (RR) and absolute rate differences (ARD) and their 95% CI between the two groups will be calculated. And the 95% CI of the ARDs will be used to evaluate if the experimental group (IVM) is non-inferior to the control group (IVF-ET). For the time-to-event outcome, the Kaplan-Meier curve will be used. Multiple variable logistic regression models will be used to assess the treatment effect adjusting for other potential confounding variables that are unbalanced in the baseline.

Missing data will be treated as missing at random and will be imputed using the last observation carried forward method. For the missing values, a sensitivity analysis will be done under the hypothesis of the worst and the best outcomes for each missing individual. Therefore, all secondary outcomes will be considered exploratory. All statistical analyses will be done using the statistical package SPSS V.25.0 (SPSS). Statistical significance is defined as $p < 0.05$ with two-sided testing except for the non-inferiority test for the primary outcome.

TRIAL STATUS

The study was designed in 2017. The first participant was recruited in March 2018 and the last participant was recruited in July 2019. The follow-up is ongoing. It is expected that data collection will be completed in October 2020.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient or public involvement. Neither patients nor the public was involved in the development of the research question, study design or implementation of this trial. Patients will not be invited to develop patient-relevant outcomes or interpret the results, as well as the writing or editing of the final manuscript for readability or accuracy. As interventions in our study are both routine procedures during clinical work, the burden of the intervention is assessed by patients themselves.

ETHICS AND DISSEMINATION

The trial had been reviewed and approved by the Science Research Ethics Committee of Peking University Third Hospital (2017sz-066). Informed consent will be obtained from each participant before randomisation. The researchers will permit trial-related monitoring, audits, regulatory inspections, providing direct access to source data and documents. There are no additional data available in this study protocol.

Contributors JQ and RL conceived the study idea. JQ, RL, RW, BWM, XZ and WG participated in the design of the study and drafting of the manuscript. XZ, WG, SY and LW participated in the recruitment of participants and the assessment of clinical outcomes. LZ and DZ coordinated for data collection and will perform

data analysis. All authors critically reviewed the article and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

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