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# BMJ Open

## Perioperative Patient-Controlled Regional Analgesia versus Patient-Controlled Intravenous Analgesia for Patients with Critical Limb Ischemia: A Study Protocol for a Randomized Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037879
Article Type:	Protocol
Date Submitted by the Author:	19-Feb-2020
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Keywords:	Vascular surgery < SURGERY, PAIN MANAGEMENT, Pain management < ANAESTHETICS

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Manuscripts



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4 Perioperative Patient-Controlled Regional Analgesia versus  
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6 Patient-Controlled Intravenous Analgesia for Patients  
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8 with Critical Limb Ischemia: A Study Protocol for a  
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12 Randomized Controlled Trial  
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48 Word count: 3158, excluding title page, abstract, references and figures.  
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**Abstract:**

Introduction: Both regional analgesia and intravenous analgesia are frequently used perioperatively for patients with critical limb ischemia (CLI). Nevertheless, the comparison of perioperative effect of regional and intravenous analgesia has not yet been thoroughly illustrated. This study will comprehensively compare patient-controlled regional analgesia (PCRA) and patient-controlled intravenous analgesia (PCIA) as two different perioperative analgesia approaches for patients with CLI. It investigates their effects on analgesia, reperfusion and the quality of recovery perioperatively, also aims to provide clinical evidence to those non-surgical patients with non-reconstructable arteries.

Methods: This trial is a randomized, single-center, open-label, parallel trial with target sample size of 78 in total. Eligible participants will be randomly allocated to the PCRA group (group R) or the PCIA group (group I) after admission. Participants in group R will receive ultrasound-guided subgluteal sciatic catheterization, followed by continuous patient-controlled regional analgesia infusion (0.2% ropivacaine 15ml as loading dose, 8ml/h as background with a patient-controlled bolus of 6ml). Participants in group I will receive patient-controlled intravenous analgesia (morphine is given in boluses of 1mg as needed, background infusion at 1mg/h). Data will be collected at baseline (T0), two hours before revascularization treatment (T1) and two hours before discharge (T2). The primary outcomes include the numerical rating scale (NRS) pain score at T1 and T2. The secondary outcomes include the perioperative transcutaneous oxygen pressure (TcPO<sub>2</sub>), the tissue hemoglobin index (TOI), Hospital Anxiety and

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4 Depression Scale (HADS) at T1 and T2; the Patient Global Impression of Change  
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6 (PGIC) at T1 and T2; the perioperative cumulative morphine consumption, the length  
7  
8 of postoperative hospital stay and adverse events (AEs).  
9

10  
11 Ethics and dissemination: This study received authorization from the Institutional  
12  
13 Review Board of Peking Union Medical College Hospital on 21 March 2017 (approval  
14  
15 no. ZS-1289X). Study findings will be disseminated through presentations at scientific  
16  
17 conferences or publications in peer-reviewed journals.  
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25 Trial registration: Registered on 22 January 2020. Chinese Clinical Trial Registry,  
26  
27 identifier ChiCTR2000029298.  
28

29  
30 Protocol version: V4CP.B1 (18, February, 2020)  
31

32  
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34  
35 Strengths and limitations of this study:  
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- 37 ● Aiming to compare the perioperative efficacy of two different analgesia  
38 approaches, this study will assess their effects on analgesia, reperfusion, as well as  
39 the quality of recovery, rather than their effects on analgesia alone.  
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44
- 45 ● Patient-controlled analgesia is used in this study so that the perioperative pain  
46 management for patients with CLI could be individual and continuous. The  
47 analgesia approaches cover the perioperative period thoroughly.  
48  
49  
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51
- 52 ● Two different-principle-based measuring parameters are used to evaluate the  
53 reperfusion effect. TcPO<sub>2</sub> is by heating skin to a stable hyperemia equilibrium  
54 condition, TOI is by detecting the absorption and reflection of near-infrared light.  
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4 ● As an open-labeled trial, all participants and some of the investigators are aware of  
5  
6 group assignment, their expectation may introduce bias.  
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12 **Keywords:** critical limb ischemia, patient-controlled analgesia, perfusion, analgesia  
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## Introduction

Critical limb ischemia (CLI) presents the end stage of peripheral arterial disease (PAD)

<sup>1</sup>. CLI is clinically defined as ischemic rest pain, ulcers and gangrene in the presence of hemodynamic evidence of arterial insufficiency<sup>2</sup>. The mean annual incidence of CLI was 0.35% reported in a national investigation from the United States<sup>3</sup>. The prevalence is approximately 1% of the adult population, and up to 10% of patients with PAD may have CLI. In recent years, a consensus from Peripheral Academic Research Consortium has provided an objective hemodynamic definition for CLI<sup>4</sup>. In this study, this consensus definition will also be used to diagnose CLI.

The major goal of CLI treatment is to relieve ischemic pain, improve limb perfusion, heal wounds and prevent further tissue loss<sup>5</sup>. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) emphasized the importance of the pain management for CLI patients and recommended a multidisciplinary approach to control pain<sup>1</sup>. Pain control is important not only to improve quality of life, but also reduce the possibility of phantom limb pain<sup>6-7</sup>. For patients with PAD, the general principles of perioperative pain management should be individual, continuous and cover the whole perioperative period thoroughly<sup>8</sup>. Over the past years, the patient-controlled analgesia has become the mainstay for providing postoperative pain relief<sup>9</sup>. Accordingly, we considered to establish patient-controlled analgesia preoperatively in our study. Existing studies suggested that intravenous morphine<sup>10</sup> and ultrasound-guided peripheral nerve block provided satisfactory analgesia effect on patients with CLI<sup>11-14</sup>. However, the analgesia effect of intravenous morphine and ultrasound-guided



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4 regional block has not been compared before. Therefore, in this study, we plan to  
5  
6 compare the perioperative analgesia effect of patient-controlled regional analgesia  
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8 (PCRA) and patient-controlled intravenous analgesia (PCIA) for patients diagnosed  
9  
10 with CLI.  
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14 Additionally, few of the previous studies have studied the effects on reperfusion besides  
15  
16 analgesia. A previous prospective study showed that continuous peridural ropivacaine  
17  
18 infusion provided satisfactory analgesia, dilated vessels, reconstructed collateral  
19  
20 circulation and improved reperfusion remarkably in diabetic patients<sup>15</sup>. Regional  
21  
22 analgesia can cause changes in vascular blood flow, but data regards to CLI patients'  
23  
24 perioperative experiences is limited. Therefore, in this study, the reperfusion effect of  
25  
26 the PCRA and PCIA methods will be further evaluated within participants with CLI.  
27  
28 To compare the effect on reperfusion between the two analgesia approaches, we plan  
29  
30 to use two different-principle-based measuring parameters, namely, the perioperative  
31  
32 transcutaneous oxygen pressure (TcPO<sub>2</sub>) and the tissue hemoglobin index (TOI).  
33  
34 TcPO<sub>2</sub> is a transcutaneous, conventional clinical parameter measured heating a skin  
35  
36 tissue in the range of 37°C to 45°C to reach a stable hyperemia equilibrium condition<sup>16</sup>.  
37  
38 NIRS detects the absorption and reflection of near-infrared light and has the potential  
39  
40 to provide continuous, real-time measurement of both blood volume and cellular  
41  
42 respiration in skin tissue. Other perioperative data regarding the quality of recovery,  
43  
44 such as the patients' emotional state, global impression of change, perioperative  
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46 morphine consumption, length of postoperative hospital stay and adverse events (AEs)  
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48 will be investigated as well.  
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4 We also hope this study offers a reference for the non-surgical patients. Although  
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6 revascularization has been the most effective treatment for patients with CLI, some  
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8 patients' arteries are impossible to revascularize and require other treatments such as  
9  
10 drugs<sup>17</sup>, transcutaneous electrical stimulation<sup>18</sup>, peripheral blood mononuclear cells  
11  
12 therapy<sup>19</sup> or lumbar sympathectomy<sup>20</sup> to relieve pain and/or increase peripheral  
13  
14 perfusion to avoid amputation. For those patients with non-reconstructable arteries,  
15  
16 long-term PCRA may be less invasive and adequate for both analgesia and perfusion.  
17  
18 There are evidences showing that it is safe to discharge patient home with catheter<sup>21</sup>. In  
19  
20 addition, it has been previously reported that continuous sciatic nerve block could be  
21  
22 used at home for long-term pain control<sup>22</sup>. We expect this perioperative study can also  
23  
24 be a future reference for those who lost their opportunity for revascularization, and  
25  
26 whose quality of life may be significantly improved.  
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### Objective

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40 The objectives of this randomized controlled trial are to compare the perioperative  
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42 analgesia efficacy between PCRA and PCIA for patients with CLI. The perioperative  
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44 effect on peripheral inflow perfusion, emotion, patient global impression of change  
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46 (PGIC), morphine consumption, length of postoperative hospital stay and AEs of  
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48 PCRA and PCIA will also be evaluated and compared.  
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### Methods

#### Overall design

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4 This trial is a randomized, single-center, open-label, parallel trial, and will be carried  
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6 out in Peking Union Medical College Hospital (PUMCH). Institutional research ethics  
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8 board approval was obtained from PUMCH Institutional Review Board (No. ZS-1289X,  
9  
10 21 March 2017). An overall flow diagram is provided in Fig.1. The timing of  
11  
12 interventions and data collection is detailed in Fig 2. This protocol was designed in  
13  
14 accordance with the Standard Protocol Items: Recommendations for Interventional  
15  
16 Trials (SPIRIT) guidelines<sup>23</sup>, the checklist can be found in Appendix 1. The trial will  
17  
18 be conducted at PUMCH in accordance with the Good Clinical Practice- International  
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20 Conference on Harmonisation (GCP-ICH) guidelines. This trial was registered with the  
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22 Chinese Clinical Trial Registry (ChiCTR2000029298).  
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### 32 Recruitment

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34 Recruitment for this study will begin on 6 May 2020. Full written informed consents  
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36 will be obtained from each participant by a qualified member of the research team prior  
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38 to any trial-related procedures.  
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### 45 Inclusion criteria

46  
47 Participants who meets the following criteria will be enrolled in this trial:

- 48 ● 18~80 years of age
  - 49 ● Diagnosed with critical limb ischemia<sup>2 4</sup>, admitted in hospital for elective surgery  
50  
51 treatment, either open surgical or endovascular revascularization
  - 52 ● The lesions are mainly unilateral and in the supplied area of sciatic nerve
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- Stage 6 in Rutherford symptom classification system<sup>24</sup>
- American Society of Anesthesiology (ASA) physical status II~III

#### Exclusion criteria

Participants who meets the following criteria will be excluded:

- Are taking opioids before admission
- Have known allergy to the drugs will be used in the study
- Have severe liver or kidney dysfunction
- Have contraindication for the catheterization (e.g. infection at injection site, coagulation disorders, refuse or be unable to cooperate the procedure)
- The dorsum of the affected foot is not intact
- Are unable to understand the scales or to describe to the investigators

#### Dropout criteria

Participants who meets the following criteria will be withdrawn from the study:

- Not willing to continue their participation
- Cannot follow the initial treatment plan due to any reason

#### Randomization, sequence concealment and blinding

All eligible participants will be randomly allocated to either group R or the group I in a ratio of 1:1 using the R software (R Foundation for Statistical Computing). The random allocation sequence will be computer-generated by an independent researcher

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4 who has no contact with any participant and will not be involved in the following  
5  
6 research. The participants' respective treatment group (group R or group I) will be  
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8 sealed in an opaque envelope and will only be opened after the enrolment of the  
9  
10 participants in the study. An investigator will be responsible for enrolling patients,  
11  
12 obtaining consent form and requesting randomization.  
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16  
17 This study is an open-label study whereby the participants, the personnel who carry out  
18  
19 the intervention and the outcome assessor cannot be blinded because of the nature of  
20  
21 the intervention. However, the researchers who are responsible for the statistical  
22  
23 analysis will be blinded to the allocation.  
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### 30 Interventions

31  
32 Analgesia approaches will be established after the baseline assessment (T0). The  
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34 FORNIA CPE-101 electronic infusion pump will be used as the continuous patient-  
35  
36 controlled analgesia device.  
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### 40 The PCRA group (group R)

41  
42 Ultrasound-guided continuous subgluteal sciatic block will be applied on the  
43  
44 participants enrolled in the group R. Patient will be placed partly lateral and partly  
45  
46 prone, with the legs flexed in the hip and knee. Scanning begins in the depression  
47  
48 between the greater trochanter of femur and the ischial tuberosity using the 8-3MHz  
49  
50 curved probe of the ultrasound equipment (X-porte, SONOSITE, USA). The sciatic  
51  
52 nerve can be identified in the cross-sectional view in between of the two bones, below  
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54 the gluteus muscle. Then rotate the transducer 90° so that the sciatic nerve is imaged in  
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4 the longitudinal view. Insert needle in-plane from the cranial to caudal direction and  
5  
6 underneath the fascia to enter the subgluteal space, then advance the needle until the tip  
7  
8 is adjacent to the nerve. After confirming the needle placement by obtaining a motor  
9  
10 response of the calf and foot using the peripheral nerve stimulator, inject 0.2%  
11  
12 ropivacaine 15ml for loading dose, then insert the catheter 5cm beyond the needle tip  
13  
14 in vicinity of the sciatic nerve. Finally, secure the catheter by tunneling and taping. The  
15  
16 infusion strategy includes 0.2% ropivacaine at 8ml/h as background with a patient-  
17  
18 controlled bolus of 6ml, lockout time 30min, 1-h limit 20ml.  
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24 The PCIA group (group I)

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26  
27 For the participants enrolled in the group I, patient-controlled intravenous analgesia  
28  
29 will be connected after intravenous access is established. The infusion strategy is as  
30  
31 follow. Intravenous morphine is given in boluses of 1mg as needed, background  
32  
33 infusion 1mg/h, with a lockout time of 20min. The 1-h limit is 4mg morphine.  
34  
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37 The intraoperative and postoperative patient management

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39  
40 The continuous patient-controlled analgesia will not be suspended during the  
41  
42 revascularization treatment despite the type of anaesthesia method. After the  
43  
44 revascularization, the device will be paused when patient report it is no longer needed,  
45  
46 which usually takes several days. The device will be on standby for an additional 48  
47  
48 hours before removal. In case of inadequate analgesia is provided perioperatively, the  
49  
50 infusion strategy dosage may be increased for patients in group I, extra-doses of  
51  
52 intravenous morphine may be used and recorded for patients in group R.  
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## Outcomes

### *Primary outcomes*

The primary outcome of this trial is the numerical rating scale (NRS). NRS allows patients to describe the intensity of pain, which is 11-point scale ranging from 0 to 10, with 0 defined as no pain and 10 defined as the worst pain imaginable<sup>25</sup>. The measurement timepoint of the primary outcome will be two hours before revascularization treatment (T1) and two hours before discharge (T2).

### *Secondary outcomes*

The secondary outcomes are as follows:

- The transcutaneous oxygen pressure (TcPO<sub>2</sub>) at T1 and T2. TcPO<sub>2</sub> will be obtained with PeriFlux System 5000 (PERIMED, Sweden) transcutaneously using the TcPO<sub>2</sub> unit-PF 5040. Calibration will be completed before use. When measuring, patients will be in sitting position. The electrode of the PF 5040 will be placed on the dorsum of the affected foot, away from any skin lesion. Wait 10~15min for a stable reading.
- The tissue hemoglobin index (TOI) at T1 and T2. TOI will be obtained with the EGOS-600A near infrared spectroscopy (NIRS, ENGINMED, China). The transducer of NIRS will be placed at the same spot as PF5040 on a sitting position, after the completion of TcPO<sub>2</sub> measurement. Wait 30 sec for each interval to gain five readings. The values at each time point will be calculated as the mean of five consecutive values over 2min.
- Hospital Anxiety and Depression Scale (HADS) at T1 and T2. HADS is a self-

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4 rating patient-reported outcome measure developed to assess depression and  
5  
6 anxiety of patients with illness. The 24-item questionnaire is divided into two  
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8 subscales: anxiety (HADS-A) and depression (HADS-D). The ratings are summed  
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10 to yield a total score (0 to 42), or for each subscale (0 to 21) with special attention<sup>26</sup>.

- 11  
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13  
14 ● Patient Global Impression of Change (PGIC) at T1 and T2. PGIC is a 7-point verbal  
15  
16 scale commonly used to assess patient's perception of pain relief following  
17  
18 treatment, which has been proved its significant relevance and correlations for  
19  
20 peripheral neuropathic pain in daily practice<sup>27</sup>.
- 21  
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23  
24 ● Cumulative morphine consumption perioperatively, the sum will be calculated  
25  
26 before discharge.
- 27  
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30 ● Length of postoperative hospital stay.
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34 ● AEs, such as hematoma, catheter displacement, nausea, vomiting, drowsiness,  
35  
36 dizziness, urinary retention, pruritus, local anaesthesia intoxication, etc. The  
37  
38 occurrence time, nature, duration and severity of AEs will all be collected in detail.

### 41 42 43 Trial safety

44  
45 The establishment, configuration and dispensing of the patient-controlled analgesia  
46  
47 devices will be completed by a dependable anesthesiologist. The continuous  
48  
49 ultrasound-guided subgluteal sciatic block will be performed in an operating room, only  
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51 after intravenous access and standard monitoring is established for the patient.  
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53 Investigators will follow up the patient at least twice a day during the research. All the  
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55 reported AEs and other unintended effects of trial conduct will be collected, assessed,  
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4 reported and managed according to the GCP-ICH guidelines. Any severe AE happens  
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6 perioperatively will be reported to the adverse event registration system of the hospital.  
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#### 10 11 Patient and public involvement

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14 Patients and public were not involved in the development of the research question or in  
15  
16 the design of the study. Patients will receive oral and written information about this  
17  
18 trial. However, they will not be involved in the recruitment and conduct of the study.  
19  
20  
21  
22 The burden of the intervention will be assessed by patients themselves. On completion  
23  
24 of the study, dissemination of the general study results or the anonymized individual  
25  
26 patient data will be made on demand.  
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#### 32 33 Sample size

34  
35 The primary outcome of this trial is the NRS score after analgesia. Sample size was  
36  
37 calculated based on our pilot study which had included ten patients in total (five for  
38  
39 each group). The result of the pilot study showed that the NRS scores in group R and  
40  
41 group I was 1.63 and 3.31, and the standard deviation was 1.85 and 2.12 respectively.  
42  
43  
44 We used the statistical power of 80% and two-sided  $\alpha$  of 0.05. The target sample size  
45  
46 for each group is at least 22 participants. Taking into account a dropout rate of 20%, a  
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48 sample size of 52 (26 for each group) was finally determined.  
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#### 56 57 Data collection, monitoring and confidentiality

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4 Each patient's ID and demographic information (including age, gender, height, weight)  
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6 will be collected. We will document all the AEs related to PCRA or PCIA, including  
7  
8 hematoma, catheter displacement, local anaesthesia intoxication, nausea, dizziness,  
9  
10 urinary retention, pruritus, etc. All the calibration and measurements of TcPO<sub>2</sub> and TOI  
11  
12 will be performed and recorded by one special technician using the same apparatuses.  
13  
14 Collected data will be recorded on paper case report forms (CRFs), then entered into  
15  
16 electronic case report forms (eCRFs) and uploaded to a central server. The CRFs and  
17  
18 eCRFs will be kept for at least five years after publication in case of any inquiry. A  
19  
20 qualified clinical trial expert will be invited in the middle and at the end of the  
21  
22 investigation to ensure that the protocol and GCP-ICH are being followed. No interim  
23  
24 analysis will be performed during the study. Personal information about the enrolled  
25  
26 participants will be safely and confidentially kept. The eCRFs and all the data collected  
27  
28 will be stored anonymously in the password-protected central server and restricted to  
29  
30 relevant members of the research team. Paper copies of the CRFs will be stored in a  
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32 locked cabinet in the relevant research office.  
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#### 47 Statistical analyses

48 Continuous variables will firstly be checked for normality using the visual inspection  
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50 of the histogram. Normally distributed continuous variables will be expressed as the  
51  
52 mean  $\pm$  SD, and non-normally distributed continuous variables will be expressed as the  
53  
54 median and interquartile range (IQR). The categorical variables will be summarized as  
55  
56 frequencies and percentages. The primary outcome, difference of NRS between groups,  
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4 which is generally normally distributed from experience, will be analyzed using  
5  
6 student's *t* test, and the mean difference with corresponding one-sided 95%  
7  
8 confidence interval (CI) will be calculated. For the secondary outcomes including  
9  
10 TcPO<sub>2</sub>, TOI, HADs and PGIC, student's *t* test will be used to compare the group  
11  
12 difference. Data with a skewed distribution, such as cumulative morphine consumption  
13  
14 and length of postoperative hospital stay, will be analyzed using the Mann-Whitney U  
15  
16 test. As categorical variables, AEs will be compared using chi-squared test. The main  
17  
18 analysis will be performed after the study has been completed. Data analysis will be  
19  
20 performed according to the intention to treat principle. The results of this study will be  
21  
22 reported according to the Consolidated Standards of Reporting Trials (CONSORT)  
23  
24 statement<sup>28</sup>. Statistical analyses will be conducted using SPSS 19.0 (Version 22; SPSS  
25  
26 Inc., Chicago, IL, USA). A two-sided  $p < 0.05$  is considered significant.  
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### 38 Trial status and time scale

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40 The study was funded and ethically approved in 2017. A pilot study was conducted  
41  
42 subsequently. We had finished the pilot study by 8 July 2018, then the study was  
43  
44 delayed because of the maternity leave of Si Chen until January 2020. The trial was  
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46 registered on 22 January 2020 and will begin to recruit participants on 6 May 2020.  
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### 52 Abbreviations

53  
54 PAD, peripheral artery disease; CLI, critical limb ischemia; PCRA, patient-controlled  
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56 regional analgesia; PCIA, patient-controlled intravenous analgesia; TcPO<sub>2</sub>,  
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4 transcutaneous oxygen pressure; TOI, tissue hemoglobin index; AE, adverse events;  
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6 PUMCH, Peking Union Medical College Hospital; SPIRIT: Standard Protocol Items:  
7  
8 Recommendations for Interventional Trials; GCPs, Good Clinical Practice; ICH,  
9  
10 International Conference on Harmonisation; ASA, American Society of  
11  
12 Anesthesiology; NIRS, near infrared spectroscopy; NRS, numerical rating scale; HAD,  
13  
14 Hospital Anxiety and Depression Scale; PGIC, Patient Global Impression of Change;  
15  
16 VAS, visual analogue scale; CRFs, case report forms, CONSORT, Consolidated  
17  
18 Standards of Reporting Trials; rSO<sub>2</sub>, region tissue oxygenation saturation.  
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#### 27 Acknowledgements

28  
29 We acknowledge Chinese Anesthesiologist Association for funding this study. We  
30  
31 would also like to thank Dujian Wang for her valuable effort on the investigation.  
32  
33  
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37

#### 38 Funding

39  
40 This work was supported by Young Scholar Research Grant of Chinese  
41  
42 Anesthesiologist Association (220160900007). Contact information: +86-0717-  
43  
44 6345093, [mail@ycrenfu.com.cn](mailto:mail@ycrenfu.com.cn). The funders will not participate in the study design  
45  
46 and management; data collection, analysis and interpretation; report writing; or  
47  
48 publication.  
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#### 55 Steering Committee

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4 The Steering Committee carries the ultimate responsibility for the trial and has access  
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6 to the final dataset. Specific tasks of the Steering Committee are: final approval of the  
7  
8 study protocol, approval of the amendments to the study protocol, approval of  
9  
10 manuscripts and publications of the trial. The members of the Steering Committee in  
11  
12 this trial include: Si Chen, anaesthesiologist; Yuehong Zheng, vascular surgery surgeon;  
13  
14  
15  
16  
17 Yuelun Zhang, statistician.  
18  
19  
20  
21

## 22 Author contributions

23  
24 SC and ZHX are joint first authors. SC obtained funding and the ethical approval,  
25  
26 registered and drafted the manuscript. ZHX and YHZ conceived the study and  
27  
28 participated in the design of the study. YGH, HJL and YXC participated in the study  
29  
30 coordination. YLZ contributed to the statistical analysis plan. JZ acquired and analyzed  
31  
32 the data of the work. YHZ is the corresponding author. He critically edited the  
33  
34 manuscript. All authors read and approved the final manuscript.  
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## 43 Ethics approval and consent to participate

44  
45 This research project was approved by the Peking Union Medical College Hospital  
46  
47 Institutional Review Board (ZS-1289X) on 21 March 2017. Important protocol  
48  
49 amendments will be communicated to relevant parties (eg, investigators, IRB, trial  
50  
51 participants, trial registries, journals) by Dr. Yuehong Zheng, trial principal investigator,  
52  
53 as soon as changes are made. Written informed consent (details see Appendix 2) will  
54  
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60 be obtained from all participants.

## Dissemination plan

The result of this study will be presented in national and international meetings and will be submitted for publication to relevant vascular surgery, analgesia or anaesthesia peer-reviewed journals.

## Consent for publication

All authors approved the final manuscript and agreed the submission.

## Competing interests

All authors have completed the ICMJE uniform disclosure form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. There is no conflict of interests.

## Data sharing

No additional data are available.

## References

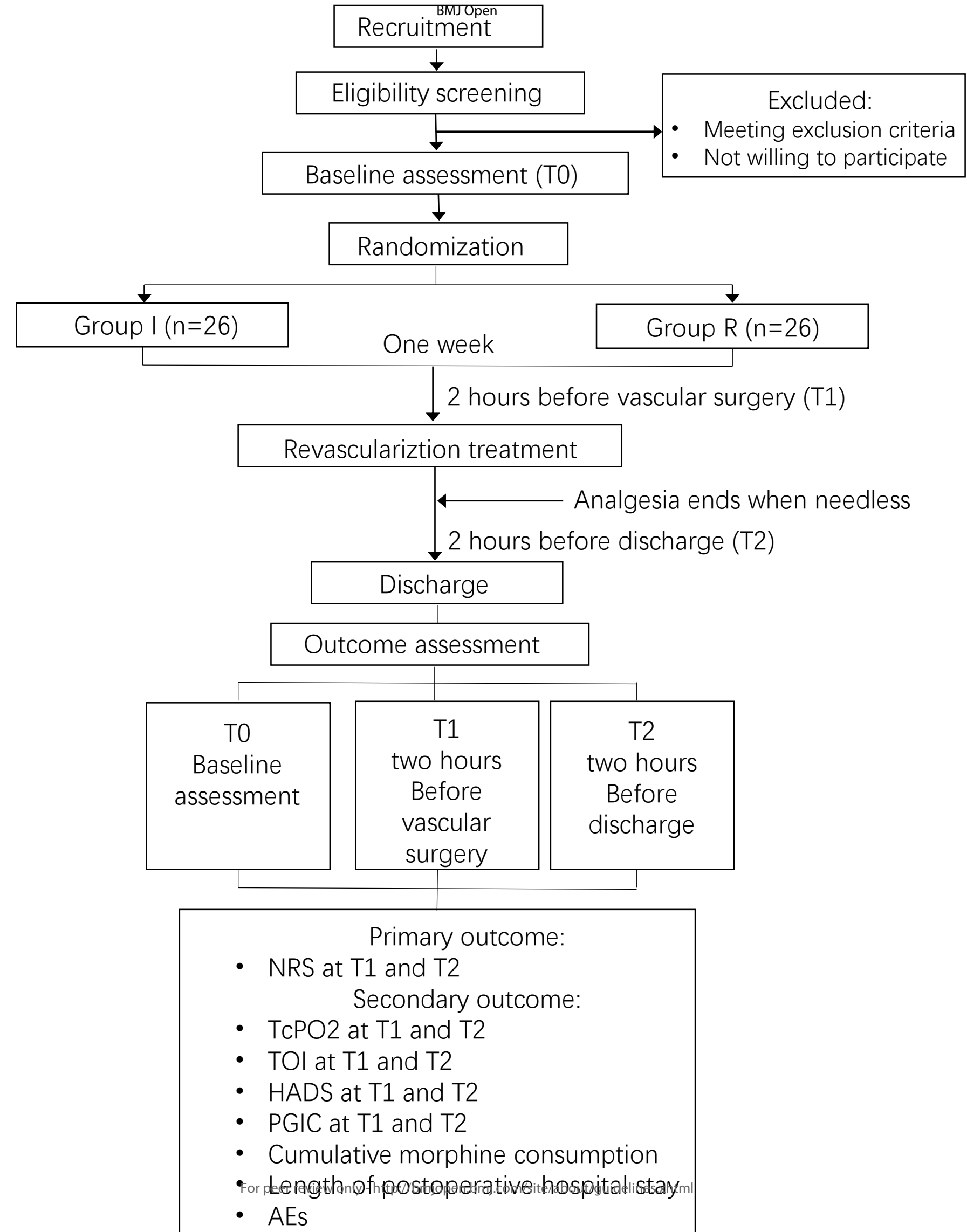
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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2, 8
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	2, 3
Protocol version	<a href="#">#3</a>	Date and version identifier	3
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1, 17

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	17
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	17
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre,	17, 18
17	responsibilities:		steering committee, endpoint adjudication committee, data	
18	committees		management team, and other individuals or groups overseeing the	
19			trial, if applicable (see Item 21a for data monitoring committee)	
20				
21				
22				
23	<b>Introduction</b>			
24				
25	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	5
26	rationale		the trial, including summary of relevant studies (published and	
27			unpublished) examining benefits and harms for each intervention	
28				
29				
30	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	6
31	rationale: choice of			
32	comparators			
33				
34				
35				
36	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
37				
38	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	7, 8
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
43				
44				
45	<b>Methods:</b>			
46	<b>Participants,</b>			
47	<b>interventions, and</b>			
48	<b>outcomes</b>			
49				
50				
51				
52	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	8
53			hospital) and list of countries where data will be collected.	
54			Reference to where list of study sites can be obtained	
55				
56				
57	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable,	8
58			eligibility criteria for study centres and individuals who will	
59				
60				

		perform the interventions (eg, surgeons, psychotherapists)	
1			
2	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	10
3	description	replication, including how and when they will be administered	
4			
5	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated interventions for a	11
6	modifications	given trial participant (eg, drug dose change in response to harms,	
7		participant request, or improving / worsening disease)	
8			
9	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols, and any	11, 13
10	adherence	procedures for monitoring adherence (eg, drug tablet return;	
11		laboratory tests)	
12	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are permitted or	11
13	concomitant care	prohibited during the trial	
14			
15	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the specific	12, 13
16		measurement variable (eg, systolic blood pressure), analysis metric	
17		(eg, change from baseline, final value, time to event), method of	
18		aggregation (eg, median, proportion), and time point for each	
19		outcome. Explanation of the clinical relevance of chosen efficacy	
20		and harm outcomes is strongly recommended	
21	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any run-ins	8
22		and washouts), assessments, and visits for participants. A	
23		schematic diagram is highly recommended (see Figure)	
24			
25	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	14
26		objectives and how it was determined, including clinical and	
27		statistical assumptions supporting any sample size calculations	
28			
29	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to reach	14
30		target sample size	
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45	<b>Methods: Assignment</b>		
46	<b>of interventions (for</b>		
47	<b>controlled trials)</b>		
48			
49			
50	Allocation: sequence	<a href="#">#16a</a> Method of generating the allocation sequence (eg, computer-	9, 10
51	generation	generated random numbers), and list of any factors for	
52		stratification. To reduce predictability of a random sequence,	
53		details of any planned restriction (eg, blocking) should be provided	
54		in a separate document that is unavailable to those who enrol	
55		participants or assign interventions	
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1	Allocation concealment	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central	10
2	mechanism		telephone; sequentially numbered, opaque, sealed envelopes),	
3			describing any steps to conceal the sequence until interventions are	
4			assigned	
5				
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7				
8	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	9, 10
9	implementation		participants, and who will assign participants to interventions	
10				
11	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial	10
12			participants, care providers, outcome assessors, data analysts), and	
13			how	
14				
15				
16				
17	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,	10
18	emergency unblinding		and procedure for revealing a participant's allocated intervention	
19			during the trial	
20				
21				
22	<b>Methods: Data</b>			
23	<b>collection,</b>			
24	<b>management, and</b>			
25	<b>analysis</b>			
26				
27				
28				
29	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other	14
30			trial data, including any related processes to promote data quality	
31			(eg, duplicate measurements, training of assessors) and a	
32			description of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known. Reference	
34			to where data collection forms can be found, if not in the protocol	
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39	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,	9
40	retention		including list of any outcome data to be collected for participants	
41			who discontinue or deviate from intervention protocols	
42				
43				
44	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any	14, 15
45			related processes to promote data quality (eg, double data entry;	
46			range checks for data values). Reference to where details of data	
47			management procedures can be found, if not in the protocol	
48				
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51	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary outcomes.	15
52			Reference to where other details of the statistical analysis plan can	
53			be found, if not in the protocol	
54				
55				
56	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	N/A
57	analyses		analyses)	
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	N/A
2	population and missing		adherence (eg, as randomised analysis), and any statistical methods	
3	data		to handle missing data (eg, multiple imputation)	
4				
5				
6	<b>Methods: Monitoring</b>			
7				
8	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of its	15
9	formal committee		role and reporting structure; statement of whether it is independent	
10			from the sponsor and competing interests; and reference to where	
11			further details about its charter can be found, if not in the protocol.	
12			Alternatively, an explanation of why a DMC is not needed	
13				
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17	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	15, 16
18	interim analysis		including who will have access to these interim results and make	
19			the final decision to terminate the trial	
20				
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22	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	14
23			and spontaneously reported adverse events and other unintended	
24			effects of trial interventions or trial conduct	
25				
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27	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	17
28			whether the process will be independent from investigators and the	
29			sponsor	
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33	<b>Ethics and</b>			
34	<b>dissemination</b>			
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37	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	3, 18
38	approval		board (REC / IRB) approval	
39				
40				
41	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	18
42			changes to eligibility criteria, outcomes, analyses) to relevant	
43			parties (eg, investigators, REC / IRBs, trial participants, trial	
44			registries, journals, regulators)	
45				
46				
47	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	8,10
48			participants or authorised surrogates, and how (see Item 32)	
49				
50				
51	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant	N/A
52	ancillary studies		data and biological specimens in ancillary studies, if applicable	
53				
54				
55	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants	14, 15
56			will be collected, shared, and maintained in order to protect	
57			confidentiality before, during, and after the trial	
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1	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	17, 19
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5	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17, 18
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10	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13, 14
11				
12				
13				
14	Dissemination policy: trial results	<a href="#">#31a</a>	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	14, 15
15				
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21	Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	17
22				
23				
24	Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
25				
26				
27				
28	<b>Appendices</b>			
29				
30				
31	Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	18
32				
33				
34				
35	Biological specimens	<a href="#">#33</a>	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
36				
37				
38				
39				

40 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND  
 41 3.0. This checklist was completed on 19. February 2020 using <https://www.goodreports.org/>, a tool made by the  
 42 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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## 受试者知情同意书

**研究项目名称：**不同镇痛方式用于重症下肢缺血患者的围术期作用效果研究

**研究负责人：**陈思

**联系电话：**13466364034

**研究单位：**中国医学科学院北京协和医院

- 研究背景、目的：**重症下肢缺血以静息痛、溃疡、坏疽为主要特征。疼痛刺激不仅降低患者的生活质量，还可诱发心脑血管事件、进一步加重神经病理性改变。良好的疼痛管理可帮助患者减轻临床症状、延缓病情发展、改善生活质量、延长生存周期。本研究目的在于比较病人自控周围神经连续阻滞技术(方法1)与病人自控静脉镇痛技术(方法2)在患者围术期的镇痛效果以及其对下肢血流灌注的改善作用。其中，方法1属疼痛介入治疗，通过坐骨神经周围置管完成，优势在于能够扩张下肢血管、减少患者阿片类药物使用量、镇痛效果明确；不足在于属有创操作，导管置于体内，有渗漏、移位、感染等风险。方法2通过静脉持续使用阿片类药物完成，优势在于镇痛效果明确，不足在于有嗜睡、头晕、恶心、呕吐、瘙痒、阿片类药物过量、耐受等风险。
- 研究内容、方法及程序：**入院后将随机为患者选取一种镇痛方式，在镇痛前后分别进行以下内容：
  - 常规疼痛诊疗：**治疗疼痛、协助医生评估镇痛效果；
  - 研究所附加的诊疗项目：**填写调查问卷、测量皮肤温度及患肢血流速度（无创伤）。
- 参加研究的可能风险（或不适、不便）和收益（个人或社会群体受益）：**
  - 可能风险（或不适、不便）：**携带病人自控镇痛装置可能存在轻微不便，
  - 收益：**获得更为确切、舒适的疼痛诊疗体验和更密切的镇痛随访，对于未来此类患者的治疗选择将更加有益。
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研究者姓名：\_\_\_\_\_ 研究者签字：\_\_\_\_\_ 日期：\_\_\_\_\_年\_\_\_\_月\_\_\_\_日

# BMJ Open

## Perioperative Patient-Controlled Regional Analgesia versus Patient-Controlled Intravenous Analgesia for Patients with Critical Limb Ischemia: A Study Protocol for a Randomized Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037879.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Jun-2020
Complete List of Authors:	Chen, Si; Peking Union Medical College Hospital, Department of Anesthesiology Xu, Zhonghuang; Peking Union Medical College Hospital, Department of Anesthesiology Liu, Hongju; Peking Union Medical College Hospital, Department of Anesthesiology Zhang, Yuelun; Peking Union Medical College Hospital, Medical Research Center Zhang, Jiao; Peking Union Medical College Hospital, Department of Anesthesiology Chen, Yuexin; Peking Union Medical College Hospital, Department of Vascular surgery Zheng, Yuehong ; Peking Union Medical College Hospital, Department of Vascular surgery Huang, Yuguang; Peking Union Medical College Hospital, Department of Anesthesiology
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Anaesthesia, Surgery
Keywords:	Vascular surgery < SURGERY, PAIN MANAGEMENT, Pain management < ANAESTHETICS

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4 Perioperative Patient-Controlled Regional Analgesia versus  
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7 Patient-Controlled Intravenous Analgesia for Patients  
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10 with Critical Limb Ischemia: A Study Protocol for a  
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12 Randomized Controlled Trial  
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49 Word count: 3605  
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**Abstract:**

Introduction: Both regional analgesia and intravenous analgesia are frequently used perioperatively for patients with critical limb ischemia (CLI). Nevertheless, the comparison of perioperative effect of regional and intravenous analgesia has not yet been thoroughly illustrated. This study will comprehensively compare patient-controlled regional analgesia (PCRA) and patient-controlled intravenous analgesia (PCIA) as two different perioperative analgesia approaches for patients with CLI. It investigates their effects on analgesia, reperfusion and the quality of recovery perioperatively, also aims to provide clinical evidence to those non-surgical patients with non-reconstructable arteries.

Methods and analysis: This trial is a randomized, single-centre, open-label, parallel trial with target sample size of 78 in total. Eligible participants will be randomly allocated to the PCRA group (group R) or the PCIA group (group I) after admission. Participants in group R will receive ultrasound-guided subgluteal sciatic catheterization, followed by continuous patient-controlled regional analgesia infusion (0.2% ropivacaine 15ml as loading dose, 8ml/h as background with a patient-controlled bolus of 6ml). Participants in group I will receive patient-controlled intravenous analgesia (morphine is given in boluses of 1mg as needed, background infusion at 1mg/h). Data will be collected at baseline (T0), two hours before revascularization treatment (T1) and two hours before discharge (T2). The primary outcomes include the numerical rating scale (NRS) pain score at T1 and T2. The secondary outcomes include the perioperative

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4 transcutaneous oxygen pressure (TcPO<sub>2</sub>), the tissue hemoglobin index (TOI), Hospital  
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6  
7 Anxiety and Depression Scale (HADS) at T1 and T2; the Patient Global Impression of  
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10 Change (PGIC) and patient satisfaction at T1 and T2; the perioperative cumulative  
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12 morphine consumption, the length of postoperative hospital stay and adverse events  
13  
14  
15 (AEs).

16  
17  
18 Ethics and dissemination: This study received authorization from the Institutional  
19  
20  
21 Review Board of Peking Union Medical College Hospital on 21 March 2017 (approval  
22  
23 no. ZS-1289X). Study findings will be disseminated through presentations at scientific  
24  
25  
26 conferences or publications in peer-reviewed journals.

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31 Trial registration: Registered on 22 January 2020. Chinese Clinical Trial Registry,  
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34 identifier ChiCTR2000029298.

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37 Protocol version: V4CP.B2 (15, June, 2020)

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42 Strengths and limitations of this study:

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45 ● Aiming to compare the perioperative efficacy of two different analgesia  
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47 approaches, this study will assess their effects on analgesia, reperfusion, as well as  
48  
49 the quality of recovery, rather than their effects on analgesia alone.  
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51  
52 ● Patient-controlled analgesia is used in this study so that the perioperative pain  
53  
54 management for patients with CLI could be individual and continuous. The  
55  
56 analgesia approaches cover the perioperative period thoroughly.  
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- Two different-principle-based measuring parameters are used to evaluate the reperfusion effect. TcPO<sub>2</sub> is by heating skin to a stable hyperemia equilibrium condition, TOI is by detecting the absorption and reflection of near-infrared light.
- As an open-labeled trial, all participants and some of the investigators are aware of group assignment, their expectation may introduce bias.

**Keywords:** critical limb ischemia, patient-controlled analgesia, perfusion, analgesia

## Introduction

Critical limb ischemia (CLI) presents the end stage of peripheral arterial disease (PAD)

<sup>1</sup>. CLI is clinically defined as ischemic rest pain, ulcers and gangrene in the presence of hemodynamic evidence of arterial insufficiency<sup>2</sup>. The mean annual incidence of CLI was 0.35% reported in a national investigation from the United States<sup>3</sup>. The prevalence is approximately 1% of the adult population, and up to 10% of patients with PAD may have CLI. In recent years, a consensus from Peripheral Academic Research Consortium has provided an objective hemodynamic definition for CLI<sup>4</sup>. In this study, this consensus definition will also be used to diagnose CLI.

The major goal of CLI treatment is to relieve ischemic pain, improve limb perfusion, heal wounds and prevent further tissue loss<sup>5</sup>. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) emphasized the importance of the pain management for CLI patients and recommended a multidisciplinary approach to control pain<sup>1</sup>. Pain control is important not only to improve quality of life, but also reduce the possibility of phantom limb pain<sup>6-7</sup>. For patients with PAD, the general principles of perioperative pain management should be individual, continuous and cover the whole perioperative period thoroughly<sup>8</sup>. Over the past years, the patient-controlled analgesia has become the mainstay for providing postoperative pain relief<sup>9</sup>. Accordingly, we considered to establish patient-controlled analgesia preoperatively in our study. Existing studies suggested that intravenous morphine<sup>10</sup> and ultrasound-guided peripheral nerve block provided satisfactory analgesia effect on patients with



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4 CLI<sup>11-14</sup>. However, the analgesia effect of intravenous morphine and ultrasound-guided  
5  
6 regional block has not been compared before. Therefore, in this study, we plan to  
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8 compare the perioperative analgesia effect of patient-controlled regional analgesia  
9  
10 (PCRA) and patient-controlled intravenous analgesia (PCIA) for patients diagnosed  
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12 with CLI.  
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16  
17 Additionally, few of the previous studies have studied the effects on reperfusion besides  
18  
19 analgesia. A previous prospective study showed that continuous peridural ropivacaine  
20  
21 infusion provided satisfactory analgesia, dilated vessels, reconstructed collateral  
22  
23 circulation and improved reperfusion remarkably in diabetic patients<sup>15</sup>. Regional  
24  
25 analgesia can cause changes in vascular blood flow, but data regards to CLI patients'  
26  
27 perioperative experiences is limited. Therefore, in this study, the reperfusion effect of  
28  
29 the PCRA and PCIA methods will be further evaluated within participants with CLI.  
30  
31 To compare the effect on reperfusion between the two analgesia approaches, we plan  
32  
33 to use two different-principle-based measuring parameters, namely, the perioperative  
34  
35 transcutaneous oxygen pressure (TcPO<sub>2</sub>) and the tissue hemoglobin index (TOI).  
36  
37 TcPO<sub>2</sub> is a transcutaneous, conventional clinical parameter measured heating a skin  
38  
39 tissue in the range of 37°C to 45°C to reach a stable hyperemia equilibrium condition<sup>16</sup>.  
40  
41 NIRS detects the absorption and reflection of near-infrared light and has the potential  
42  
43 to provide continuous, real-time measurement of both blood volume and cellular  
44  
45 respiration in skin tissue. Other perioperative data regarding the quality of recovery,  
46  
47 such as the patients' emotional state, global impression of change, patient satisfaction,  
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4 perioperative morphine consumption, length of postoperative hospital stay and adverse  
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7 events (AEs) will be investigated as well.  
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## 11 Objective

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15 The objectives of this randomized controlled trial are to compare the perioperative  
16  
17 analgesia efficacy between PCRA and PCIA for patients with CLI. The perioperative  
18  
19 effect on peripheral inflow perfusion, emotion, patient global impression of change  
20  
21 (PGIC), patient satisfaction, morphine consumption, length of postoperative hospital  
22  
23 stay and AEs of PCRA and PCIA will also be evaluated and compared.  
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## 31 Methods and analysis

### 32 Overall design

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35 This trial is a randomized, single-centre, open-label, parallel trial, and will be carried  
36  
37 out in Peking Union Medical College Hospital (PUMCH). Institutional research ethics  
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39 board approval was obtained from PUMCH Institutional Review Board (No. ZS-1289X,  
40  
41 21 March 2017). An overall flow diagram is provided in Fig.1. The timing of  
42  
43 interventions and data collection is detailed in Fig 2. This protocol was designed in  
44  
45 accordance with the Standard Protocol Items: Recommendations for Interventional  
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47 Trials (SPIRIT) guidelines<sup>17</sup>, the checklist can be found in Appendix 1. The trial will  
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60 be conducted at PUMCH in accordance with the Good Clinical Practice- International

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4 Conference on Harmonisation (GCP-ICH) guidelines. This trial was registered with the  
5  
6 Chinese Clinical Trial Registry (ChiCTR2000029298).  
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## 10 11 12 Recruitment

13  
14 Recruitment for this study will begin on 27 July 2020. Full written informed consents  
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16 will be obtained from each participant by a qualified member of the research team prior  
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18 to any trial-related procedures.  
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## 25 26 Inclusion criteria

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28 Participants who meets the following criteria will be enrolled in this trial:  
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- 31 ● 18~80 years of age
- 32
- 33 ● Diagnosed with critical limb ischemia<sup>2 4</sup>, admitted in hospital for elective surgery
- 34
- 35 treatment, either open surgical or endovascular revascularization
- 36
- 37
- 38 ● The lesions are mainly unilateral and in the supplied area of sciatic nerve
- 39
- 40 ● Stage 6 in Rutherford symptom classification system<sup>18</sup>
- 41
- 42
- 43 ● American Society of Anesthesiology (ASA) physical status II~III
- 44
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## 50 51 Exclusion criteria

52  
53 Participants who meets the following criteria will be excluded:  
54

- 55 ● Are taking opioids before admission
- 56
- 57 ● Have known allergy to the drugs will be used in the study
- 58
- 59
- 60

- Have severe liver or kidney dysfunction
- Have contraindication for the catheterization (e.g. infection at injection site, coagulation disorders, refuse or be unable to cooperate the procedure)
- The dorsum of the affected foot is not intact
- Are unable to understand the scales or to describe to the investigators

#### Dropout criteria

Participants who meets the following criteria will be withdrawn from the study:

- Not willing to continue their participation or cannot follow the initial treatment plan
- From whom none of the primary outcome data can be obtained due to any reason

#### Randomization, sequence concealment and blinding

All eligible participants will be randomly allocated to either group R or the group I in a ratio of 1:1 using the R software (R Foundation for Statistical Computing). The random allocation sequence will be computer-generated by an independent researcher who has no contact with any participant and will not be involved in the following research. The participants' respective treatment group (group R or group I) will be sealed in an opaque envelope and will only be opened after the enrolment of the participants in the study. An investigator will be responsible for enrolling patients, obtaining consent form and requesting randomization.

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4 This study is an open-label study whereby the participants, the personnel who carry out  
5  
6 the intervention and the outcome assessor cannot be blinded because of the nature of  
7  
8 the intervention. However, the researchers who are responsible for the statistical  
9  
10 analysis will be blinded to the allocation.  
11  
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### 17 Interventions

18  
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20 Analgesia approaches will be established after the baseline assessment (T0) and  
21  
22 randomization, normally three to five days before the revascularization treatment. The  
23  
24 FORNIA CPE-101 electronic infusion pump will be used as the continuous patient-  
25  
26 controlled analgesia device. Relevant concomitant intervention is not involved in this  
27  
28 study. Analgesics outside the intervention plan are prohibited during the trial. Remedial  
29  
30 analgesia therapy will be carried out according to clinical needs for participants who  
31  
32 are dropped out from the trial.  
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### 39 The PCRA group (group R)

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42 Ultrasound-guided continuous subgluteal sciatic block will be applied on the  
43  
44 participants enrolled in the group R. Patient will be placed partly lateral and partly  
45  
46 prone, with the legs flexed in the hip and knee. Scanning begins in the depression  
47  
48 between the greater trochanter of femur and the ischial tuberosity using the 8-3MHz  
49  
50 curved probe of the ultrasound equipment (X-porte, SONOSITE, USA). The sciatic  
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52 nerve can be identified in the cross-sectional view in between of the two bones, below  
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54 the gluteus muscle. Then rotate the transducer 90° so that the sciatic nerve is imaged in  
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4 the longitudinal view. Insert needle in-plane from the cranial to caudal direction and  
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6  
7 underneath the fascia to enter the subgluteal space, then advance the needle until the tip  
8  
9 is adjacent to the nerve. After confirming the needle placement by obtaining a motor  
10  
11 response of the calf and foot using the peripheral nerve stimulator, inject 0.2%  
12  
13 ropivacaine 15ml for loading dose, then insert the catheter 5cm beyond the needle tip  
14  
15 in vicinity of the sciatic nerve. Finally, secure the catheter by tunneling and taping. The  
16  
17 infusion strategy includes 0.2% ropivacaine at 8ml/h as background with a patient-  
18  
19 controlled bolus of 6ml, lockout time 30min, 1-h limit 20ml.  
20  
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25  
26 The PCIA group (group I)

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28 For the participants enrolled in the group I, patient-controlled intravenous analgesia  
29  
30 will be connected after intravenous access is established. The infusion strategy is as  
31  
32 follow. Intravenous morphine is given in boluses of 1mg as needed, background  
33  
34 infusion 1mg/h, with a lockout time of 20min. The 1-h limit is 4mg morphine.  
35  
36  
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38

39 The intraoperative and postoperative patient management

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41  
42 The continuous patient-controlled analgesia will not be suspended during the  
43  
44 revascularization treatment despite the type of anaesthesia method. After the  
45  
46 revascularization, the device will be paused when patient report it is no longer needed,  
47  
48 which usually takes several days. The device will be on standby for an additional 48  
49  
50 hours before removal. In case of inadequate analgesia is provided perioperatively, the  
51  
52 infusion strategy dosage may be increased for patients in group I, extra-doses of  
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4 intravenous morphine may be used and recorded for patients in group R. Ancillary and  
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7 post care will not be involved in this study.  
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## 11 Outcomes

### 12 *Primary outcomes*

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17 The primary outcome of this trial is the numerical rating scale (NRS). NRS allows  
18 patients to describe the intensity of pain, which is 11-point scale ranging from 0 to 10,  
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21  
22  
23 with 0 defined as no pain and 10 defined as the worst pain imaginable<sup>19</sup>. The  
24  
25  
26 measurement timepoint of the primary outcome will be two hours before  
27  
28  
29 revascularization treatment (T1) and two hours before discharge (T2).  
30

### 31 *Secondary outcomes*

32  
33  
34 The secondary outcomes are as follows:

- 35  
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37 ● The transcutaneous oxygen pressure (TcPO<sub>2</sub>) at T1 and T2. TcPO<sub>2</sub> will be obtained  
38  
39 with PeriFlux System 5000 (PERIMED, Sweden) transcutaneously using the  
40  
41 TcPO<sub>2</sub> unit-PF 5040. Calibration will be completed before use. When measuring,  
42  
43 patients will be in sitting position. The electrode of the PF 5040 will be placed on  
44  
45 the dorsum of the affected foot, away from any skin lesion. Wait 10~15min for a  
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47  
48 stable reading.  
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- 51  
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53 ● The tissue hemoglobin index (TOI) at T1 and T2. TOI will be obtained with the  
54  
55 EGOS-600A near infrared spectroscopy (NIRS, ENGINMED, China). The  
56  
57  
58 transducer of NIRS will be placed at the same spot as PF5040 on a sitting position,  
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4 after the completion of TcPO<sub>2</sub> measurement. Wait 30 sec for each interval to gain  
5  
6 five readings. The values at each time point will be calculated as the mean of five  
7  
8 consecutive values over 2min.  
9  
10

- 11 ● Hospital Anxiety and Depression Scale (HADS) at T1 and T2. HADS is a self-  
12 rating patient-reported outcome measure developed to assess depression and  
13 anxiety of patients with illness. The 24-item questionnaire is divided into two  
14 subscales: anxiety (HADS-A) and depression (HADS-D). The ratings are summed  
15 to yield a total score (0 to 42), or for each subscale (0 to 21) with special attention<sup>20</sup>.  
16  
17
- 18 ● Patient Global Impression of Change (PGIC) at T1 and T2. PGIC is a 7-point verbal  
19 scale commonly used to assess patient's perception of pain relief following  
20 treatment, which has been proved its significant relevance and correlations for  
21 peripheral neuropathic pain in daily practice<sup>21</sup>.  
22  
23
- 24 ● Patient satisfaction at T1 and T2. This item allows patients to describe their  
25 satisfaction in medical procedures according to the experience in hospital using a  
26 11-point scale from 0 to 10, with 0 defined as extremely dissatisfied and 10 defined  
27 as vastly satisfied.  
28  
29
- 30 ● Cumulative morphine consumption perioperatively, the sum will be calculated  
31 before discharge.  
32  
33
- 34 ● Length of postoperative hospital stay.  
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36
- 37 ● AEs, such as hematoma, catheter displacement, nausea, vomiting, drowsiness,  
38 dizziness, urinary retention, pruritus, local anaesthesia intoxication, fall, etc. The  
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4 occurrence time, nature, duration and severity of AEs will all be collected in detail.  
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### 9 Trial safety

10  
11 The establishment, configuration and dispensing of the patient-controlled analgesia  
12 devices will be completed by a dependable anesthesiologist. The continuous  
13  
14 ultrasound-guided subgluteal sciatic block will be performed in an operating room, only  
15  
16 after intravenous access and standard monitoring is established for the patient.  
17  
18 Investigators will follow up the patient at least twice a day during the research. Motor  
19  
20 block will be assessed everyday using Bromage motor blockage score<sup>22</sup> in group R to  
21  
22 prevent falling. All the reported AEs and other unintended effects of trial conduct will  
23  
24 be collected, assessed, reported and managed according to the GCP-ICH guidelines.  
25  
26 Any severe AE happens perioperatively will be reported to the adverse event  
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28 registration system of the hospital.  
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### 42 Patient and public involvement

43  
44 Patients and public were not involved in the development of the research question or in  
45  
46 the design of the study. Patients will receive oral and written information about this  
47  
48 trial. However, they will not be involved in the recruitment and conduct of the study.  
49  
50  
51 The burden of the intervention will be assessed by patients themselves. On completion  
52  
53 of the study, dissemination of the general study results or the anonymized individual  
54  
55 patient data will be made on demand.  
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## Sample size

The primary outcome of this trial is the NRS score after analgesia. Sample size was calculated based on our pilot study which had included ten patients in total (five for each group). The result of the pilot study showed that the NRS scores in group R and group I was 1.63 and 3.31, and the standard deviation was 1.85 and 2.12 respectively. We used the statistical power of 80% and two-sided  $\alpha$  of 0.05. The target sample size for each group is at least 22 participants. Taking into account a dropout rate of 20%, a sample size of 52 (26 for each group) was finally determined.

## Data collection, monitoring and confidentiality

Each patient's ID and demographic information (including age, gender, height, weight) will be collected. We will document all the AEs related to PCRA or PCIA, including hematoma, catheter displacement, local anaesthesia intoxication, nausea, dizziness, urinary retention, pruritus, fall, etc. All the calibration and measurements of TcPO<sub>2</sub> and TOI will be performed and recorded by one special technician using the same apparatuses. Participant retention and follow-up engagement is enhanced by communicate verbally and via common instant message app. In the case where primary outcome data is missing at T2, investigators will call the participants within two days of discharge to collect the missing data. Collected data will be recorded on paper case report forms (CRFs), then entered into electronic case report forms (eCRFs) and

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4 uploaded to a central server. The CRFs and eCRFs will be kept for at least five years  
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6 after publication in case of any inquiry. A qualified clinical trial expert will be invited  
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8 in the middle and at the end of the investigation to ensure that the protocol and GCP-  
9  
10 ICH are being followed. No interim analysis will be performed during the study. There  
11  
12 is no planned auditing for the study. Personal information about the enrolled  
13  
14 participants will be safely and confidentially kept. After completion of the study, the  
15  
16 eCRFs and all the data collected will be stored anonymously in the password-protected  
17  
18 central server and restricted to relevant members of the research team. Paper copies of  
19  
20 the CRFs will be stored in a locked cabinet in the relevant research office.  
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### 31 Statistical analyses

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33 Continuous variables will firstly be checked for normality using the visual inspection  
34  
35 of the histogram. Normally distributed continuous variables will be expressed as the  
36  
37 mean  $\pm$  SD, and non-normally distributed continuous variables will be expressed as the  
38  
39 median and interquartile range (IQR). The categorical variables will be summarized as  
40  
41 frequencies and percentages. Variables such as anaesthesia method and surgery type  
42  
43 will be checked in the description of baseline characteristics, unbalanced variables will  
44  
45 be adjusted using a multivariable method. The primary outcome, difference of NRS  
46  
47 between groups, which is generally normally distributed from experience, will be  
48  
49 analyzed using student's *t* test, and the mean difference with corresponding one-sided  
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51 95% confidence interval (CI) will be calculated. For the secondary outcomes including  
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4 TcPO<sub>2</sub>, TOI, HADs and PGIC, student's *t* test will be used to compare the group  
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6 difference. Data with a skewed distribution, such as cumulative morphine consumption  
7  
8 and length of postoperative hospital stay, will be analyzed using the Mann-Whitney U  
9  
10 test. As categorical variables, AEs will be compared using chi-squared test. A post-hoc  
11  
12 subgroup analysis by the type of revascularization treatment (whether endovascular or  
13  
14 open surgical) will be conducted. The main analysis will be performed after the study  
15  
16 has been completed. Data analysis will be performed according to the intention to treat  
17  
18 principle. The results of this study will be reported according to the Consolidated  
19  
20 Standards of Reporting Trials (CONSORT) statement<sup>23</sup>. Statistical analyses will be  
21  
22 conducted using SPSS 19.0 (Version 22; SPSS Inc., Chicago, IL, USA). A two-sided  
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24  $p < 0.05$  is considered significant.  
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### 36 Ethics and dissemination

#### 37 Ethics approval and consent to participate

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39 This research project was approved by the Peking Union Medical College Hospital  
40  
41 Institutional Review Board (ZS-1289X) on 21 March 2017. Important protocol  
42  
43 amendments will be communicated with relevant parties (eg, investigators, IRB, trial  
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45 participants, trial registries, journals) by Dr. Yuehong Zheng, trial principal investigator,  
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47 as soon as changes are made. Written informed consent (details see Appendix 2) will  
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60 be obtained from all participants.

## Trial Organization

### Steering Committee

The Steering Committee carries the ultimate responsibility for the trial and has access to the final dataset. Specific tasks of the Steering Committee are: final approval of the study protocol, approval of the amendments to the study protocol, approval of manuscripts and publications of the trial. The Steering Committee is chaired by Yuehong Zheng, vascular surgery surgeon. Other members include Si Chen, anaesthesiologist and Yuelun Zhang, statistician.

### Data and Safety Monitoring Committee (DSMC)

The DSMC is established to assess the progress of the study, the safety of data and the critical efficacy end points independently from the sponsor and competing interests. Wellbeing of the participants will be monitored by the DSMC, who makes decision on the suspension or termination of the trial to protect the participants under circumstances of severe or unexpected AEs. The DSMC is chaired by Yuguang Huang, Anaesthesiologist. Other members include Hongju Liu, anaesthesiologist and Yuexin Chen, vascular surgery surgeon.

### Trial status and time scale

The study was funded and ethically approved in 2017. A pilot study was conducted subsequently. We had finished the pilot study by 8 July 2018, then the study was

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4 delayed because of the maternity leave of Si Chen until January 2020. The trial was  
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6 registered on 22 January 2020 and will begin to recruit participants on 27 July 2020.  
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## 10 11 12 Dissemination plan

13  
14  
15 The result of this study will be presented in national and international meetings and will  
16  
17 be submitted for publication to relevant vascular surgery, analgesia or anaesthesia peer-  
18  
19 reviewed journals. Authorship eligibility will follow the Good Publication Practice  
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21 (GPP) guideline 3.  
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## 28 29 Discussion

30  
31 The purpose of this study is to compare the analgesia effect of PCRA and PCIA. The  
32  
33 effects on reperfusion and quality of recovery are meanwhile investigated in patients  
34  
35 diagnosed with CLI.  
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39 In this study, a low concentration ropivacaine of 0.2% will be used for patients in group  
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41 R, and a low to median dosage of intravenous morphine will be used for patients of  
42  
43 group I. Morphine is a strong opioid which is well known for its supreme analgesia and  
44  
45 adverse effects such as nausea, vomiting, drowsiness, itching etc. Ropivacaine is a long-  
46  
47 acting regional anesthetic that blocks nerve fibers involved in pain transmission to a  
48  
49 greater degree than those controlling motor functions<sup>24</sup>.  
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55 Regional analgesia can cause changes in vascular blood flow, but data regards to CLI  
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57 patients' perioperative experiences is limited. In this study, we plan to perform two  
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4 different measuring methods to observe the effects on reperfusion of PCRA and PCIA.

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6  
7 In previous researches, the parameter TOI was also known as the region tissue  
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9 oxygenation saturation (rSO<sub>2</sub>). A recent study has revealed a significant correlation  
10  
11 between TcPO<sub>2</sub> and rSO<sub>2</sub> measured by NIRS to evaluate limb ischemia in patients with  
12  
13 peripheral arterial disease<sup>25</sup>. We expect the outcomes of this study provide clinical  
14  
15 evidence for the efficacy of the two different analgesia approaches perioperatively.  
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19  
20 We also hope this study offers a reference for the non-surgical patients. Although  
21  
22 revascularization has been the most effective treatment for patients with CLI, some  
23  
24 patients' arteries are impossible to revascularize and require other treatments such as  
25  
26 drugs<sup>26</sup>, transcutaneous electrical stimulation<sup>27</sup>, peripheral blood mononuclear cells  
27  
28 therapy<sup>28</sup> or lumbar sympathectomy<sup>29</sup> to relieve pain and/or increase peripheral  
29  
30 perfusion to avoid amputation. For those patients with non-reconstructable arteries,  
31  
32 long-term PCRA may be less invasive and adequate for both analgesia and perfusion.  
33  
34 There are evidences showing that it is safe to discharge patient home with catheter<sup>30</sup>. In  
35  
36 addition, it has been previously reported that continuous sciatic nerve block could be  
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38 used at home for long-term pain control<sup>31</sup>. We expect this perioperative study can also  
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improve their quality of life.

## Abbreviations

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4 PAD, peripheral artery disease; CLI, critical limb ischemia; PCRA, patient-controlled  
5  
6 regional analgesia; PCIA, patient-controlled intravenous analgesia; TcPO<sub>2</sub>,  
7  
8 transcutaneous oxygen pressure; TOI, tissue hemoglobin index; AE, adverse events;  
9  
10 PUMCH, Peking Union Medical College Hospital; SPIRIT: Standard Protocol Items:  
11  
12 Recommendations for Interventional Trials; GCPs, Good Clinical Practice; ICH,  
13  
14 International Conference on Harmonisation; ASA, American Society of  
15  
16 Anesthesiology; NIRS, near infrared spectroscopy; NRS, numerical rating scale; HAD,  
17  
18 Hospital Anxiety and Depression Scale; PGIC, Patient Global Impression of Change;  
19  
20 VAS, visual analogue scale; CRFs, case report forms, CONSORT, Consolidated  
21  
22 Standards of Reporting Trials; rSO<sub>2</sub>, region tissue oxygenation saturation; DSMC, Data  
23  
24 and Safety Monitoring Committee; GPP, Good Publication Practice.  
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### 38 Acknowledgements

39 We acknowledge Chinese Anesthesiologist Association for funding this study. We  
40  
41 would also like to thank Dujian Wang for her valuable effort on the investigation.  
42  
43  
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47

### 48 Funding

49 This work was supported by Young Scholar Research Grant of Chinese  
50  
51 Anesthesiologist Association (220160900007). Contact information: +86-0717-  
52  
53 6345093, [mail@ycrfu.com.cn](mailto:mail@ycrfu.com.cn). The funders will not participate in the study design  
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3  
4 and management; data collection, analysis and interpretation; report writing; or  
5  
6  
7 publication.

#### 11 12 Authors' contributions

13  
14 SC and ZHX are joint first authors. SC obtained funding and the ethical approval,  
15  
16 registered and drafted the manuscript. ZHX and YHZ conceived the study and  
17  
18 participated in the design of the study. YGH, HJL and YXC participated in the study  
19  
20 coordination. YLZ contributed to the statistical analysis plan. JZ acquired and analyzed  
21  
22 the data of the work. YHZ is the corresponding author. He critically edited the  
23  
24 manuscript. All authors read and approved the final manuscript and agreed the  
25  
26 submission.  
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#### 37 38 Competing interests

39  
40 All authors have completed the ICMJE uniform disclosure form at  
41  
42 [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no financial relationships with  
43  
44 any organization that might have an interest in the submitted work in the previous three  
45  
46 years, no other relationships of activities that could appear to have influenced the  
47  
48 submitted work. There is no conflict of interests.  
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#### 55 56 Data sharing

57  
58 No additional data are available.  
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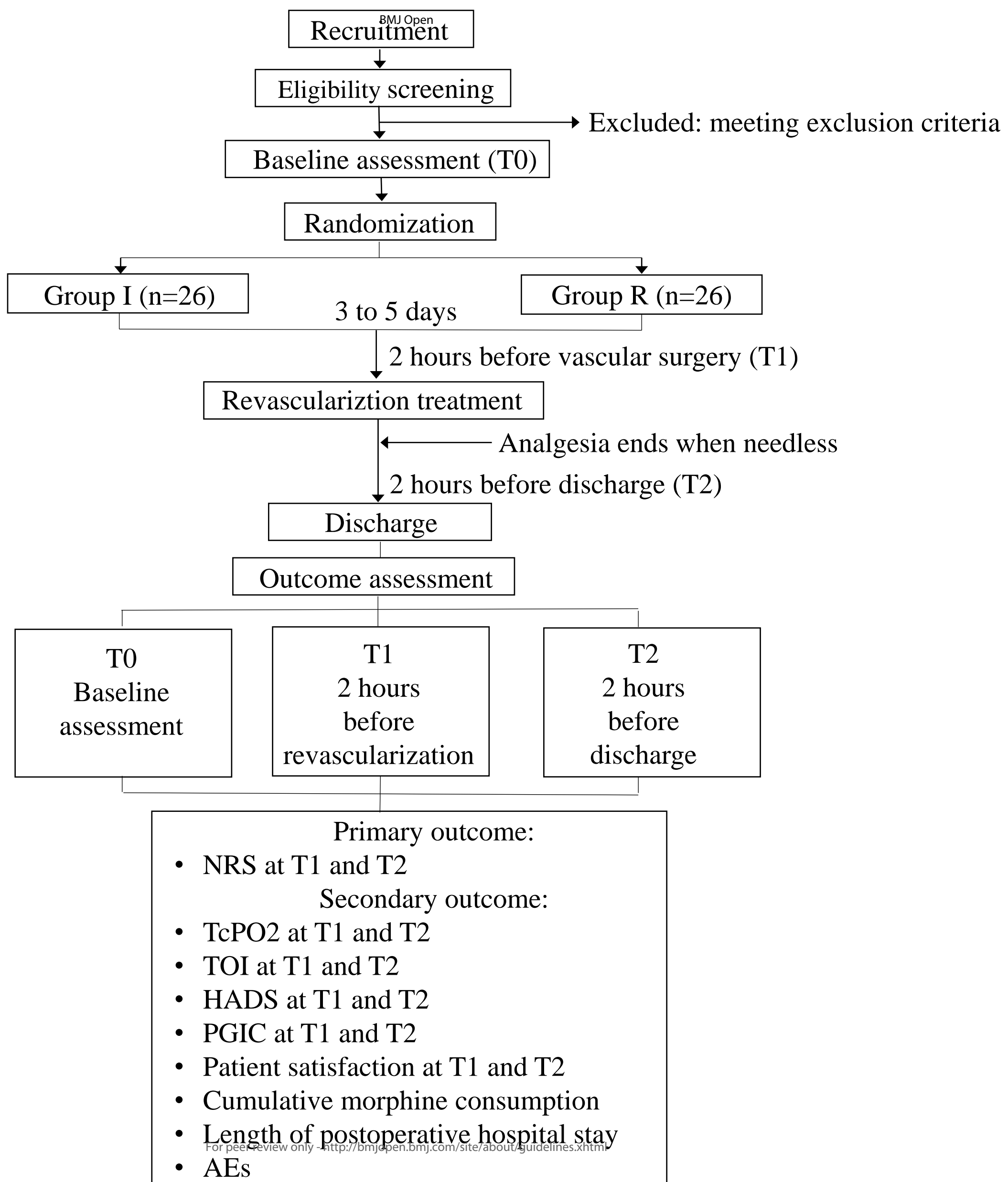
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## 57 Figure Legends

58  
59 Fig 1. Study process diagram

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4 Fig 2. Schedule of the enrollment, interventions and assessments  
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For peer review only



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	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT		T0	T1		T2
<b>ENROLMENT:</b>					
<i>Eligibility screen</i>	x				
<i>Informed consent</i>	x				
<i>Randomization</i>		x			
<b>INTERVENTIONS:</b>					
<i>Group I</i>		←————→			
<i>Group R</i>		←————→			
<b>ASSESSMENTS:</b>					
<i>Demographic data</i>	x				
<i>NRS</i>		x	x		x
<i>TcPO2</i>		x	x		x
<i>TOI</i>		x	x		x
<i>HADS</i>		x	x		x
<i>PGIC</i>			x		x
<i>Patient satisfaction</i>			x		x
<i>Cumulative morphine consumption</i>					x
<i>Length of postoperative hospital stay</i>					x
<i>Adverse events</i>	For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>				x

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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

	Reporting Item	Page Number
<b>Administrative information</b>		
Title	<a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a> Trial identifier and registry name. If not yet registered, name of intended registry	3, 8
Trial registration: data set	<a href="#">#2b</a> All items from the World Health Organization Trial Registration Data Set	3
Protocol version	<a href="#">#3</a> Date and version identifier	3
Funding	<a href="#">#4</a> Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	<a href="#">#5a</a> Names, affiliations, and roles of protocol contributors	1, 22

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	21
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study	21
8	responsibilities:		design; collection, management, analysis, and	
9	sponsor and funder		interpretation of data; writing of the report; and the	
10			decision to submit the report for publication, including	
11			whether they will have ultimate authority over any of	
12			these activities	
13				
14				
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16				
17	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the	21
18	responsibilities:		coordinating centre, steering committee, endpoint	
19	committees		adjudication committee, data management team, and	
20			other individuals or groups overseeing the trial, if	
21			applicable (see Item 21a for data monitoring committee)	
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26	<b>Introduction</b>			
27				
28	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining benefits	
31			and harms for each intervention	
32				
33				
34				
35	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	5, 6, 7
36	rationale: choice of			
37	comparators			
38				
39				
40	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
41				
42				
43	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	7, 8
44			parallel group, crossover, factorial, single group),	
45			allocation ratio, and framework (eg, superiority,	
46			equivalence, non-inferiority, exploratory)	
47				
48				
49	<b>Methods:</b>			
50	<b>Participants,</b>			
51	<b>interventions, and</b>			
52	<b>outcomes</b>			
53				
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55				
56	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	7, 8
57			academic hospital) and list of countries where data will	
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be collected. Reference to where list of study sites can be obtained

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4	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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11	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
12	description		
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15			
16	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)
17	modifications		
18			
19			
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23	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
24	adherence		
25			
26			
27			
28	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29	concomitant care		
30			
31			
32	Outcomes	<a href="#">#12</a>	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
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43	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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50	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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57	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size
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1 **Methods:**

2 **Assignment of**  
3 **interventions (for**  
4 **controlled trials)**  
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8	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,
9	generation		computer-generated random numbers), and list of any
10			factors for stratification. To reduce predictability of a
11			random sequence, details of any planned restriction (eg,
12			blocking) should be provided in a separate document
13			that is unavailable to those who enrol participants or
14			assign interventions
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19	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence
20	concealment		(eg, central telephone; sequentially numbered, opaque,
21	mechanism		sealed envelopes), describing any steps to conceal the
22			sequence until interventions are assigned
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26	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will
27	implementation		enrol participants, and who will assign participants to
28			interventions
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30			
31	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions
32			(eg, trial participants, care providers, outcome
33			assessors, data analysts), and how
34			
35			
36	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is
37	emergency unblinding		permissible, and procedure for revealing a participant's
38			allocated intervention during the trial
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41 **Methods: Data**  
42 **collection,**  
43 **management, and**  
44 **analysis**  
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49	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome,
50			baseline, and other trial data, including any related
51			processes to promote data quality (eg, duplicate
52			measurements, training of assessors) and a description
53			of study instruments (eg, questionnaires, laboratory
54			tests) along with their reliability and validity, if known.
55			Reference to where data collection forms can be found,
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if not in the protocol

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3	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete
4	retention		follow-up, including list of any outcome data to be
5			collected for participants who discontinue or deviate
6			from intervention protocols
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9	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,
10			including any related processes to promote data quality
11			(eg, double data entry; range checks for data values).
12			Reference to where details of data management
13			procedures can be found, if not in the protocol
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17	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
18			outcomes. Reference to where other details of the
19			statistical analysis plan can be found, if not in the
20			protocol
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24	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and
25	analyses		adjusted analyses)
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28	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-
29	population and		adherence (eg, as randomised analysis), and any
30	missing data		statistical methods to handle missing data (eg, multiple
31			imputation)
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35	<b>Methods: Monitoring</b>		
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37	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);
38	formal committee		summary of its role and reporting structure; statement of
39			whether it is independent from the sponsor and
40			competing interests; and reference to where further
41			details about its charter can be found, if not in the
42			protocol. Alternatively, an explanation of why a DMC is
43			not needed
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48	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping
49	interim analysis		guidelines, including who will have access to these
50			interim results and make the final decision to terminate
51			the trial
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55	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing
56			solicited and spontaneously reported adverse events
57			and other unintended effects of trial interventions or trial
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		conduct	
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2	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if	16
3		any, and whether the process will be independent from	
4		investigators and the sponsor	
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8	<b>Ethics and</b>		
9	<b>dissemination</b>		
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11	Research ethics	<a href="#">#24</a> Plans for seeking research ethics committee /	17
12	approval	institutional review board (REC / IRB) approval	
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15	Protocol amendments	<a href="#">#25</a> Plans for communicating important protocol	17
16		modifications (eg, changes to eligibility criteria,	
17		outcomes, analyses) to relevant parties (eg,	
18		investigators, REC / IRBs, trial participants, trial	
19		registries, journals, regulators)	
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24	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or assent from	8, 9, 17
25		potential trial participants or authorised surrogates, and	
26		how (see Item 32)	
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29	Consent or assent:	<a href="#">#26b</a> Additional consent provisions for collection and use of	N/A
30	ancillary studies	participant data and biological specimens in ancillary	
31		studies, if applicable	
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34	Confidentiality	<a href="#">#27</a> How personal information about potential and enrolled	15, 16
35		participants will be collected, shared, and maintained in	
36		order to protect confidentiality before, during, and after	
37		the trial	
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41	Declaration of	<a href="#">#28</a> Financial and other competing interests for principal	22
42	interests	investigators for the overall trial and each study site	
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44			
45	Data access	<a href="#">#29</a> Statement of who will have access to the final trial	16
46		dataset, and disclosure of contractual agreements that	
47		limit such access for investigators	
48			
49			
50	Ancillary and post trial	<a href="#">#30</a> Provisions, if any, for ancillary and post-trial care, and	12
51	care	for compensation to those who suffer harm from trial	
52		participation	
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56	Dissemination policy:	<a href="#">#31a</a> Plans for investigators and sponsor to communicate trial	19
57	trial results	results to participants, healthcare professionals, the	
58		public, and other relevant groups (eg, via publication,	
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reporting in results databases, or other data sharing arrangements), including any publication restrictions

Dissemination policy: authorship	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15

## Appendices

Informed consent materials	<a href="#">#32</a>	Model consent form and other related documentation given to participants and authorised surrogates	17, Appendix 2
Biological specimens	<a href="#">#33</a>	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

The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 19. February 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

## 受试者知情同意书

**研究项目名称：**不同镇痛方式用于重症下肢缺血患者的围术期作用效果研究

**研究负责人：**陈思

**联系电话：**13466364034

**研究单位：**中国医学科学院北京协和医院

1. **研究背景、目的：**重症下肢缺血以静息痛、溃疡、坏疽为主要特征。疼痛刺激不仅降低患者的生活质量，还可诱发心脑血管事件、进一步加重神经病理性改变。良好的疼痛管理可帮助患者减轻临床症状、延缓病情发展、改善生活质量、延长生存周期。本研究目的在于比较病人自控周围神经连续阻滞技术(方法 1)与病人自控静脉镇痛技术(方法 2)在患者围术期的镇痛效果以及其对下肢血流灌注的改善作用。其中，方法 1 属疼痛介入治疗，通过坐骨神经周围置管完成，优势在于能够扩张下肢血管、减少患者阿片类药物使用量、镇痛效果明确；不足在于属有创操作，导管置于体内，有渗漏、移位、感染等风险。方法 2 通过静脉持续使用阿片类药物完成，优势在于镇痛效果明确，不足在于有嗜睡、头晕、恶心、呕吐、瘙痒、阿片类药物过量、耐受等风险。本研究于 2017 年 3 月 21 日通过北京协和医院伦理委员会审查（编号 ZS-1289X）。
2. **受试者纳入标准：**
  - a) 18~80 岁；
  - b) 诊断为重症下肢缺血，入院行血管开通治疗；
  - c) 单侧为主，疼痛部位主要在坐骨神经支配区域；
  - d) Rutherford 症状分级 6 级；
  - e) ASA（美国麻醉医师协会）分级 II~III 级。**受试者排除标准：**
  - a) 入院前使用阿片类药物止痛；
  - b) 对研究中可能使用的药物有明确的过敏史；
  - c) 严重肝肾功能不全；
  - d) 神经周围置管禁忌（如穿刺部位感染、凝血功能异常、无法配合体位或拒绝穿刺）；
  - e) 患侧足背皮肤不完整；
  - f) 无法理解调查量表或无法表述自己的感受。
3. **研究内容、方法及程序：**入院后将随机为患者选取一种镇痛方式，在镇痛前后分别进行以下内容：
  - a) **常规疼痛诊疗：**治疗疼痛、协助医生评估镇痛效果；
  - b) **研究所附加的诊疗项目：**填写调查问卷、测量皮肤温度及患肢血流速度（无创伤）。
4. **参加研究的可能风险（或不适、不便）和收益（个人或社会群体受益）：**
  - a) **可能风险（或不适、不便）：**携带病人自控镇痛装置可能存在轻微不便，
  - b) **收益：**获得更为确切、舒适的疼痛诊疗体验和更密切的镇痛随访，对于未来此类患者的治疗选择将更加有益。
5. **有关内容的咨询：**您有权就有关研究内容进行咨询，咨询电话（主要研究者）：010-69152020 或 13466364034，电子邮箱：yuehongzheng@yahoo.com；您有权就有关您的权利或相关风险等问题进行咨询，咨询电话（伦理审查委员会电话）：010-69154494，电子邮箱：pumchkyc@126.com。
6. **退出研究的权利：**您参加此项研究是完全自愿的。无需任何原因，您不愿意参加或不愿

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3 继续参加此研究，并不会对您的权益有任何影响。此外，您有权在任何时间退出此研  
4 究。（如果您没有按医生指示，或医生为您的健康和益处着想，医生或研究者也可能要  
5 求您退出。）  
6

- 7 7. 研究的费用及赔偿问题：常规疼痛诊疗产生的费用由您及患者自行缴纳的医疗保险承担  
8 及赔付；研究所附加的诊疗项目产生的费用由课题组经费承担，如果您由于参加此研  
9 究所附加的项目而使健康受到损害，将由北京协和医院麻醉科及血管外科负责提供补  
10 偿费用。  
11  
12 8. 保密制度：您参加此研究所获得的医疗信息将得到保密。研究结果在学术刊物上发表时  
13 也不会泄露任何可识别您个人身份的信息。北京协和医院将保存您在这项研究中的全  
14 部记录以及有关的医院和办公室记录，未经授权任何人不得获取这些信息。  
15  
16 9. 本知情同意书一式两份，受试者和研究者各一份，双方签字后有效。  
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19 **受试者的知情同意：**

20 我已详细阅读并充分了解以上内容，并对以上内容，特别是我参与此研究的权利、风险  
21 和受益进行了认真考虑。我自愿参加这项研究，愿意与研究人员合作。同时声明我可以任  
22 何时候因任何原因退出此研究，而不会丧失任何合法权利。  
23  
24  
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26 受试者姓名：\_\_\_\_\_ 受试者签字：\_\_\_\_\_ 日期：\_\_\_\_\_ 年 \_\_\_\_\_ 月 \_\_\_\_\_ 日  
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29 研究者姓名：\_\_\_\_\_ 研究者签字：\_\_\_\_\_ 日期：\_\_\_\_\_ 年 \_\_\_\_\_ 月 \_\_\_\_\_ 日  
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