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Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

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Abstract

INTRODUCTION: High tibial osteotomy (HTO) is a treatment of choice for active adult with knee osteoarthritis. With advance in 3D scanning, virtual planning and 3D printing, Patient specific instrumentation (PSI) in form of cutting jigs are employed to improve surgical accuracy and outcome of HTO. The aim of this randomized controlled trial (RCT) is to explore the surgical outcomes of HTO for the treatment of medial compartment knee osteoarthritis with or without a 3D printed patient specific jig.

METHODS AND ANALYSIS: A double-blind RCT will be conducted with patients and outcome assessors blinded to treatment allocation. This meant that neither the patients nor the outcome assessors would know the actual treatment allocated during the trial. Thirty-six patients with symptomatic medial compartment knee osteoarthritis fulfilling our inclusion criteria will be invited to participate the study. Participants will be randomly allocated to one of two groups (1:1 ratio): operation with 3D printed patient specific jig or operation without jig. Measurements will be taken before surgery (baseline) and at postoperatively (6, 12, and 24 months). The primary outcome includes radiological accuracy of osteotomy. Secondary outcomes include a change in knee function from baseline to postoperatively as measured by 3 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores and Pain Visual Analog Scale (VAS) score.

ETHICS AND DISSEMINATION: Ethical approval has been obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC no. 2019.050), in accordance with the declaration of Helsinki. The results will be presented at international scientific meetings and through publications in peer-reviewed journals.

TRIAL REGISTRATION NUMBER: NCT04000672; Pre-results.

Strengths and limitations of this study

- To our knowledge, this is the first randomized controlled trial designed to study the accuracy and clinical outcome on using 3D-patient specific instrumentation (PSI) on patients with knee osteoarthritis requiring high tibial osteotomy (HTO).

- Follow-up data will be collected at 3, 6, 12, and 24 months, depending on the date of recruitment for a total timeline of 24 months.

- The trial will provide valuable evidence to surgeons and decision-makers by highlighting the efficacy, benefits and harms of using this new surgical approach.

- The results are expected to have an immediate substantial impact on clinical practice by providing new evidence on the potential of 3D PSI on improving the surgical outcome for patients with knee osteoarthritis.

- A limitation of the study is conducted in a single-center design.

INTRODUCTION

Background

Knee osteoarthritis (OA) is a long-term chronic disease characterized by cartilage degeneration, creating knee pain and impairing movement. It is the single most common cause of disability in older adults according to the World Health Organizations (WHO). According to the United Nations and WHO, by 2050 there will be 130 million people suffering from OA worldwide, of whom 40 million will be severely disabled by the disease. In recent *Lancet* review, osteoarthritis is expected to be the fourth leading cause of disability globally by 2020[1]. The medical cost of osteoarthritis has been estimated to be around 2·5% of the gross domestic product in various high-income countries, with joint replacements representing the major proportion of the cost[1].

Total knee arthroplasty (TKA) is a common and highly effective orthopaedic procedure for treating end-stage knee osteoarthritis with good long-term results when conservative treatment fails. Although TKR has been a successful surgery, up to 20% of patients were unsatisfied with the result[2]. Some of the causes of dissatisfaction have been attributed to the failure of artificial implant to reproduce a normal native knee feeling, and also high functional demand activities after replacement surgery[2]. This has fuelled increasing popularity of joint preserving surgery like high tibial osteotomy (HTO), to preserve the native knee joint and allow better function. Moreover, TKA performed at middle age fails to outlast the patient and is commonly associated with significant bone loss at revision surgery. The functional outcome of revision TKA is worse than TKA after high tibial osteotomy, which has been reported to have excellent long-term survivorship and clinical outcome[3].

HTO can relieve the symptoms and slow down structural damage by unloading the medical knee compartment. It redistributes mechanical load in the knee, hence extending the longevity of native knee joint in this group of moderate OA patients with high daily activity demand. It is also a well-established surgical procedure for medial compartment knee OA with the probability of survival between 85.4% to 91.6% at ten years[4]. In Asia, the number of HTO performed are rising rapidly and the proportion of total knee arthroplasty performed in OA patients fell in recent years. For example, the number of HTO performed

in Korea increased from 2649 cases in 2009 to 8207 cases in 2013, while the number of HTO performed in Japan increased from 261 cases in 2007 to 2152 cases in 2014[5 6]. Recently with the advancement of technology, we started employing Patient Specific Instrumentation (PSI) on HTO. PSI is a surgical advancement made possible by the advancement in 3D scanning, virtual planning and 3D printing. By virtue of close approximation of PSI onto patient's bony surface, PSI HTO cutting jigs are designed to improve surgical accuracy and outcome of HTO. Several groups have reported their results of using PSI jigs on HTO in small case series without a control group. However, without a well-designed randomized trial type of study design, whether there exists scientific significant difference in accuracy and clinical outcome by using PSI on HTO is not known.

Objectives

This trial will explore the surgical outcomes of HTO for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific jig (PSI jig). The primary outcomes will be the radiological differences reflecting difference in surgical accuracy with or without PSI jig and the secondary outcomes will be the postoperative change in knee function from baseline using 3 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores and Pain Visual Analog Scale (VAS) score[7-9].

Trial design

The study is a randomized, double-blind controlled study to compare the surgical outcomes for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific jig, in terms of radiological outcomes, knee scores, range of motion and pain score with a 24-month follow-up.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in online supplemental files). The underlying protocol also follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see CONSORT checklist in online supplemental files. The trial was registered on clinicaltrials.gov). (NCT04000672).

Patient and public involvement

Patients were not involved in the design of this study. However, patients will be a key target of knowledge dissemination following completion.

Participants, interventions and outcomes

Participants and setting

Participants will be primarily recruited from the outpatient clinic of the Department of Orthopaedics and Traumatology at the Alice Ho Miu Ling Nethersole Hospital. Additionally, the Prince of Wales Hospital (affiliated with the Chinese University of Hong Kong) in the same New Territories East Cluster, will also help to refer suitable patients for the trial. Figure 1 shows the overall flowchart of the study.

Eligibility criteria

To be enrolled in this trial, the following eligibility criteria, assessed at screening, will be met:

Inclusion criteria

The inclusion criteria are as follows:

1. Age ≥ 18 years and ≤ 70 years
2. Symptomatic patient with medial compartment knee OA
3. Clinical diagnosis of knee OA (American College of Rheumatology criteria) with radiographic changes (Kellgren-Lawrence [KL] grades 2 or 3)

4. Body mass index (BMI) ≤ 35 kg/m^2.
5. Informed consent obtained

Exclusion criteria

The exclusion criteria are as follows:

1. Lateral compartment OA
2. Symptomatic patellofemoral compartment OA
3. Inflammatory arthritis
4. Significant loss of knee joint range in flexion (less than 100°) or in extension (less than − 10°)
5. Ligamentous instability
6. Obesity with BMI > 35 kg/m^2
7. Significant psychological disorder
8. Inability to communicate in Chinese or English language

Recruitment

Eligible patients will be recruited from the outpatient clinic with written consent in the Alice Ho Miu Ling Nethersole Hospital, based on the inclusion and exclusion criteria. Basic patient demographics, including age, gender, ethnicity, occupation, body mass index and smoking and drinking habits, will be recorded. Medical history will also be confirmed and recorded from the Clinical Management System (CMS), Hospital Authority, which is the central electronic database for public hospitals in Hong Kong. Before signing the consent form, each patient will be explained the objectives, benefits and risks of the study and their rights and responsibilities, as well as privacy and confidentiality information. An information sheet will be distributed, and all patients are asked for their understanding of the trial and encouraged to ask questions at any time.

Sample size calculation

Radiological assessment of accuracy will serve as the study primary outcome. Specifically the average osteotomy cut from joint line will be used as a determinant outcome of this study. As no previous reports guide the expected results, our preliminary pilot data has guided our calculations. Based on our previous cases of high tibial osteotomy, we noted the average osteotomy cut deviation from planning with PSI jig is 0 cm ± 0.3 cm and without PSI jig is 0.76 cm ± 1.2 cm. Therefore, a sample size of 15 per group can achieve an 95% power to detect the difference between the two groups, with an alpha level of 0.05 and effect size of 0.95 using a two-sided two sample t-test. To account for attrition we have increased our sample by 20%. Our sample size of 18 participants per treatment arm (total $n = 36$) will be sufficient to address our primary objective. Our secondary objectives will be considered hypothesis generating information to guide future work. The sample size was calculated using G*Power 3.0 software.

Randomization and allocation concealment

Randomization will be accomplished by computer-generated randomization sequence using serially numbered opaque, sealed envelopes with patients assigned either to intervention or control groups. All investigators, research staff, and patients will be blinded to the group assignment of the subjects, nor will they be aware of the allocation during the study and evaluation periods. However, blinding the surgeon performing the HTO is not feasible because they shall perform surgery either with or without using the jig, but the subsequent assessment and analysis shall be done by blinded research staffs and investigators. A randomization code will be allocated to each included subject to maintain blindness. Randomization code will be broken only after the database had been locked. Patient rehabilitation, post-operative assessment and data analysis are conducted by personnel blinded to the patients' randomization assignment.

Study interventions

Current Standard Practice (Routine HTO surgery)

The controlled arm would be standard medial open-wedge high tibial osteotomy using current standard practice. In brief, an incision is made in the midway between posteromedial border of the tibia and

medial aspect of the tibial tuberosity. Sartorius fascia is cut and retracted medially to expose the medial collateral ligament (MCL). Two to three K-wires are placed 4 cm below the medial joint line toward the proximal tibiofibular joint over lateral tibial cortex under fluoroscopy and osteotomy is done below and parallel to the k-wires using an oscillating saw leaving the lateral 5 mm intact. Thin osteotomes are used to gradually open the osteotomy and finally the desired correction is achieved with the use of navigation checking overall lower limb alignment.

Intervention group:

3D printed patient specific jigs (PSI jig) are created based on the pre-operative CT image. Standard medial open wedge osteotomy similar as described previously is performed with modification. Incision is made in the midway between posteromedial border of the tibia and medial aspect of the tibial tuberosity. Sartorius fascia is cut and retracted medially to expose the medial collateral ligament (MCL). Then the PSI jig is positioned onto the tibia. Due to the patient specific design (individually based on each patient's CT image), it can fit closely to the proximal tibia. The slot opening on the PSI jig corresponds to 4 cm below the medial joint line and the slot design allow the sawblade cut direction toward proximal tibiofibular joint over lateral tibial cortex under fluoroscopy. The PSI Jig is removed after the bone cut completed and would not retain in patient's body. Thin osteotomes are used to gradually open the osteotomy. A 3D printed wedge that corresponds to opening gap size of osteotomy is used to achieve the desired correction, and supersede the navigation (set-up also as part of blinding) values for alignment in case of discrepancy. The rehabilitation and follow-up of the intervention group is the same as the routine patients (Control group) undergoing MOWHTO for knee osteoarthritis.

Outcomes and outcome assessments

Outcome assessments of the patients will be performed at baseline (0 month), immediately before discharge, at 3 months, 6 months, 12 months, and 24-months timepoints. Table 1 shows the overall assessments needed for each timepoint.

Primary Outcome

Radiographic assessment on surgical outcome

The primary outcome is obtained by post-operative radiological assessment of X-ray and computer tomography (CT) images to compare the accuracy of patient specific instrumentation (PSI) jig with freehand bone cut in achieving pre-operative planned bone cut. The planned bone cut is from 4 cm below the medial joint line towards proximal tibiofibular joint near the lateral tibial cortex. It also includes comparison with navigation on overall alignment correction. Anteroposterior full-length lower-limb radiographs are taken with patients in the standing position to assess postoperative lower-limb alignment correction, which is compared with the preoperative planning, based on Miniaci method calculation to achieve target alignment passing through the Fujisawa point[10 11].

Secondary Outcome

Knee Function and Pain Score

Secondary outcomes include the clinical outcome on knee score and knee function. The quality of knee function and pain will be assessed by the previously reported and validated Knee Society Knee Score and Function Score. The Knee Society Score (KSS) was designed to provide a simple and objective scoring system to rate the knee and patient's functional abilities before and after total knee arthroplasty and also employed to assess high tibial osteotomy as well[12 13]. The KSS has a Knee Score section and a Functional Score section, covering on pain, symptom, and activities of daily living. Both sections are scored from 0 to 100 with lower scores being indicative of worse knee conditions and higher scores being indicative of better knee conditions.

Whereas, the Oxford Knee Score (OKS) is a 12-item patient-reported outcome measures (PROMs) originally designed and developed to measure subjective outcome after total knee arthroplasty but later have also been used to assess outcome of high tibial osteotomy[8 14 15]. Each question is scored from 0 to 4 (0

being the worst outcome and 4 being the best). The overall score is the sum of all items and can range from 0 to 48, with higher scores corresponding to better outcomes.

The pain visual analog scale (VAS) is an unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with degenerative knee diseases.

Adverse Events, safety and compliance assessment

Any postoperative pain, complications and other complaints from the participants will be monitored and taken care of by medical officers. Any adverse event or problems arise during the study will be reported directly to the ethnic committee in the institution. In addition, participants are allowed to quit the study at any time for any reason; if so, they will be asked whether they wish to be followed up according to the trial schedule.

Data management and confidentiality

A research assistant will be trained to ensure accuracy of outcome assessments and data collection. The ethics committee will oversee any issues disturbing quality of research, and corresponding measures will be taken if necessary. Patients are free to withdraw from the study at any time without giving any reasons, and their medical care or legal rights will not be affected. The study will comply with the good clinical practice guideline according to the International Council for Harmonisation. Each patient will be assigned an identification code. The patient identification code list and database will be safeguarded.

Statistical analysis

Data in this study will be analyzed according to the intention-to-treat principle. Only full analysis set and per-protocol set will be used for primary analysis. Any missing data will not be input for calculation. Quantitative variables will be expressed as mean ± standard deviation. Normality tests will be performed to determine whether the data is normally distributed. Analysis of variance tests are used to compare means for continuous variables. Whereas, Chi-square test will be used to compare proportions of categorical

variables and to calculate the differences in the count data. Mixed effects models will be used to analyze the trend of changes in the scores with two factors of groups and time. In addition, a survival analysis on the surgical approach will be shown as a Kaplan-Meier curve. The statistical analysis will be performed using a commercialized statistical software (SPSS, version 25, IBM). All statistical significance is defined as $P < 0.05$.

Ethics and dissemination

Ethics approval and consent to participate have been obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC no. 2019.050), in accordance with the declaration of Helsinki.

Protocol version

This study protocol was approved on 13 March 2019 as detailed in this manuscript.

Study participant consent

1. Surgeon consent: the PI and co-investigators met with potential surgeons individually or as part of faculty meetings to discuss the study and to answer any questions. The surgeons were given a copy of the proposal detailing the assessments to review. Surgeons provided verbal and email consent to the PI to indicate their willingness to participate.
2. Patient consent: Informed written consents for participation into this PROTECTED HTO trial will be obtained from every patient before their operation. Detailed risks and benefits will be explained when obtaining the consent from the patients.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DISCUSSION

High tibial osteotomy (HTO) is a proven effective method to treat relative young and active adults with knee osteoarthritis[16]. In conventional method, HTO is performed using intraoperative fluoroscopy to judge the site and direction of osteotomy, degree of alignment correction and change of posterior slope. However, surgical accuracy with the conventional method is reported to be limited and hence computer navigation has been introduced to improve accuracy in performing HTO. In a recent publication on comparing between computer navigated HTO and conventional HTO, it reported that the risk of outlier in alignment was lower in computer navigated HTO than conventional method[17]. In addition, the tibial slope maintenance was comparable, if not better, in navigated HTO than conventional HTO[17]. Moreover, navigated HTO did not show a discrepancy with conventional HTO on the functional scores[17].

Patient-specific instrumentation (PSI) is a new development in orthopedic field made possible by the advancement in 3D scanning and 3D printing technology, in which an instrument that can couple closely to the targeting bony surface is virtually planned and later produced by 3D printing. The putative benefits of these PSI include increased surgical accuracy, decreased operation time, and elimination of the need for extra devices or reference trackers[18]. The application of PSI on HTO as a cutting jig is reported achieving precise osteotomy and accurate realignment of lower limb in small case series[18]. So far high-quality evidence in form of randomized controlled trial evaluating outcome of HTO performed with PSI is lacking. The current study described in this protocol can fill this gap in knowledge regarding the advantages of PSI use on HTO. A head-to-head comparison with computer navigated HTO was designed in this protocol given previously reported superiority of computer navigated HTO over conventional HTO[17]. Radiological outcome, in terms of discrepancy to planned osteotomy and realignment, and clinical outcome, in terms of functioning score assessment, were reported. Various patient-reported outcome measures (PROMs) or clinical scoring system have been used to gauge the surgical outcome of HTO[19]. And in this study, Knee Society Score (Knee Score and Function Score) and Oxford Knee Score (OKS) will be used. These are also the commonest PROMs and clinical scoring system for unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA), with the former being a common alternative treatment for isolated medial

compartment OA and the latter being the choice of conversion when HTO fails. Moreover, by using the same sets of PROMs and clinical scoring system as in other reports, this would allow seamless and meaningful comparison between different treatment modalities for the same clinical problem.[19]

Enrolment of this trial have commenced on late 2019, and completion is expected to take 36 months. The results from this trial may help to change the current clinical practice, as this will be the first randomized study to evaluate whether patient specific jigs can improve the surgical accuracy and clinical outcome for those requiring HTO. Importantly, we speculate that positive results would allow the incorporation of PSI into multiple orthopedics surgeries to help to improve healthcare for our patients in the future.

Acknowledgements:

None.

Authors' contributions:

LCML and JCHF planned the study. LCLM and GCWM planned the statistical analysis methods. LCWL, YWH, ECSC and KWC designed the jig. All authors contributed to the design and development of the trial (LCML, JCHF, GCWM, YWH, KKWH, ECSC, KWC, SYCW, WWC, PSHY and MB). LCML and GCWM drafted the manuscript. JCHF, KYC, PSHY and MB contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests statement:

None declared.

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Figure and Table Legends

Figure 1. The study flow diagram, including participants' recruitment, eligibility, screening, randomization, allocation concealment and outcome assessments.

Table 1. Study Timeline of Assessment

Table 1. Study Timeline of Assessment

	Enrollment	Assessment period				
	Pre-op	Immediate before discharge	3 months	6 months	12 months	24 months
Enrollment						
Informed consent	✓					
Assessment of eligibility	✓					
Randomization	✓					
Assessments						
Anatomical						
CT Scan	✓	✓				
Scanogram	✓		✓			
Knee X-Rays	✓	✓	✓	✓	✓	✓
Functional						
Knee Society knee score	✓			✓	✓	✓
Knee Society function score	✓			✓	✓	✓
Oxford Knee Score	✓			✓	✓	✓
ROM	✓	✓	✓	✓	✓	✓

VAS score	✓	✓	✓	✓	✓	✓
Others						
Additional use of analgesics		✓				
Postoperative complications and adverse events		✓	✓	✓	✓	✓

PSI, patient specific instrumentation; CT, computed tomography; ROM, range of motion; VAS, visual analog scale

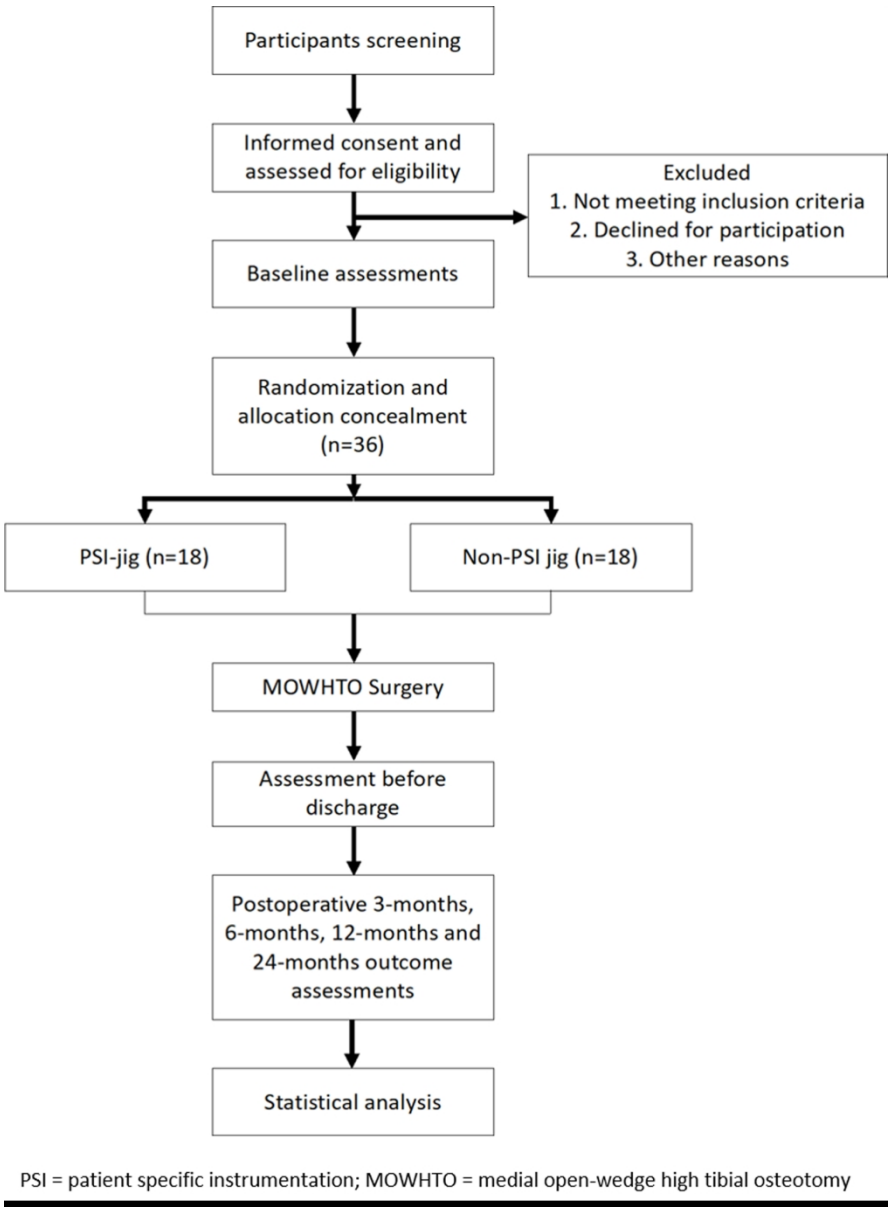

Figure 1. The study flow diagram, including participants' recruitment, eligibility, screening, randomization, allocation concealment and outcome assessments.

141x191mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4, 5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	6, 7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8, 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9, 10, 11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11, 12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11, 12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	✓
Funding	4	Sources and types of financial, material, and other support	✓
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓
	5b	Name and contact information for the trial sponsor	✓
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	✓

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓
	6b	Explanation for choice of comparators	✓
Objectives	7	Specific objectives or hypotheses	✓
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Approval obtained
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

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Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

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Abstract

INTRODUCTION: High tibial osteotomy (HTO) is a treatment of choice for active adult with knee osteoarthritis. With advance in 3D scanning, virtual planning and 3D printing, Patient specific instrumentation (PSI) in form of cutting jigs are employed to improve surgical accuracy and outcome of HTO. The aim of this randomized controlled trial (RCT) is to explore the surgical outcomes of HTO for the treatment of medial compartment knee osteoarthritis with or without a 3D printed patient specific jig.

METHODS AND ANALYSIS: A double-blind RCT will be conducted with patients and outcome assessors blinded to treatment allocation. This meant that neither the patients nor the outcome assessors would know the actual treatment allocated during the trial. Thirty-six patients with symptomatic medial compartment knee osteoarthritis fulfilling our inclusion criteria will be invited to participate the study. Participants will be randomly allocated to one of two groups (1:1 ratio): operation with 3D printed patient specific jig or operation without jig. Measurements will be taken before surgery (baseline) and at postoperatively (6, 12, and 24 months). The primary outcome includes radiological accuracy of osteotomy. Secondary outcomes include a change in knee function from baseline to postoperatively as measured by 3 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores and Pain Visual Analog Scale (VAS) score.

ETHICS AND DISSEMINATION: Ethical approval has been obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC no. 2019.050), in accordance with the declaration of Helsinki. The results will be presented at international scientific meetings and through publications in peer-reviewed journals.

TRIAL REGISTRATION NUMBER: NCT04000672; Pre-results.

Strengths and limitations of this study

- To our knowledge, this is the first randomized controlled trial designed to study the accuracy and clinical outcome on using 3D-patient specific instrumentation (PSI) on patients with knee osteoarthritis requiring high tibial osteotomy (HTO).

- Follow-up data will be collected at 3, 6, 12, and 24 months, depending on the date of recruitment for a total timeline of 24 months.

- The trial will provide valuable evidence to surgeons and decision-makers by highlighting the efficacy, benefits and harms of using this new surgical approach.

- The results are expected to have an immediate substantial impact on clinical practice by providing new evidence on the potential of 3D PSI on improving the surgical outcome for patients with knee osteoarthritis.

- A limitation of the study is conducted in a single-center design.

INTRODUCTION

Background

Knee osteoarthritis (OA) is a long-term chronic disease characterized by cartilage degeneration, creating knee pain and impairing movement. It is the single most common cause of disability in older adults according to the World Health Organizations (WHO). In recent *Lancet* review, osteoarthritis is expected to be the fourth leading cause of disability globally by 2020, with knee OA accounts for approximately 85% of the burden of OA worldwide [1]. The medical cost of osteoarthritis has been estimated to be around 1 - 2·5% of the gross domestic product in various high-income countries, with joint replacements representing the major proportion of the cost[1].

Total knee arthroplasty (TKA) is a common and highly effective orthopaedic procedure for treating end-stage knee osteoarthritis with good long-term results when conservative treatment fails. Although TKR has been a successful surgery, up to 20% of patients were unsatisfied with the result[2]. Some of the causes of dissatisfaction have been attributed to the failure of artificial implant to reproduce a normal native knee feeling, and also high functional demand activities after replacement surgery[2]. This has fuelled increasing popularity of joint preserving surgery like high tibial osteotomy (HTO), to preserve the native knee joint and allow better function. Moreover, TKA performed at middle age fails to outlast the patient and is commonly associated with significant bone loss at revision surgery. The functional outcome of revision TKA is worse than TKA after high tibial osteotomy, which has been reported to have excellent long-term survivorship and clinical outcome[3].

HTO can relieve the symptoms and slow down structural damage by unloading the medial knee compartment. It redistributes mechanical load in the knee, hence extending the longevity of native knee joint in this group of moderate OA patients with high daily activity demand. It is also a well-established surgical procedure for medial compartment knee OA with the probability of survival between 85.4% to 91.6% at ten years[4]. In Asia, HTO is increasingly popular as treatment for knee OA with rising number of HTO performed in conjunction with the fell in number of TKA performed. For example, the annual number of HTO in Korea increased from 2649 cases in 2009 to 8207 cases in 2013, and the annual number of HTO

in Japan increased from 261 cases in 2007 to 2152 cases in 2014[5 6]. Recently with the advancement of technology, we started employing patient specific instrumentation (PSI) on HTO. PSI is a surgical advancement made possible by the advancement in computed tomographic imaging with 3D model reconstruction, virtual planning and 3D printing. By virtue of close approximation of PSI onto patient's bony surface, PSI HTO cutting jigs are designed to improve surgical accuracy and outcome of HTO. Several groups have reported their results of using PSI jigs on HTO in small case series without a control group. However, without a well-designed randomized trial type of study design, whether there exists scientific significant difference in accuracy and clinical outcome by using PSI on HTO is not known.

Objectives

This trial will explore the surgical outcomes of HTO for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific jig (PSI jig). The primary outcomes will be the radiological differences reflecting difference in surgical accuracy with or without PSI jig and the secondary outcomes will be the postoperative change in knee function from baseline using 4 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores, Lysholm Knee Scoring Scale and Pain Visual Analog Scale (VAS) score[7-10].

Trial design

The study is a randomized, double-blind controlled study to compare the surgical outcomes for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific jig, in terms of radiological outcomes, knee scores, range of motion and pain score with a 24-month follow-up.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in online supplemental files). The underlying protocol also follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see CONSORT checklist in online supplemental files. The trial was registered on clinicaltrials.gov). (NCT04000672).

Patient and public involvement

Patients were not involved in the design of this study. However, patients will be a key target of knowledge dissemination following completion.

Participants, interventions and outcomes

Participants and setting

Participants will be primarily recruited from the outpatient clinic of the Department of Orthopaedics and Traumatology at the Alice Ho Miu Ling Nethersole Hospital. Additionally, the Prince of Wales Hospital (affiliated with the Chinese University of Hong Kong) in the same New Territories East Cluster, will also help to refer suitable patients for the trial. Figure 1 shows the overall flowchart of the study.

Eligibility criteria

To be enrolled in this trial, the following eligibility criteria, assessed at screening, will be met:

Inclusion criteria

The inclusion criteria are as follows:

1. Age ≥ 18 years and ≤ 70 years
2. Symptomatic patient with medial compartment knee OA

3. Clinical diagnosis of knee OA (American College of Rheumatology criteria) with radiographic changes (Kellgren-Lawrence [KL] grades 2 or 3)
4. Body mass index (BMI) ≤ 35 kg/m^2.
5. Informed consent obtained

Exclusion criteria

The exclusion criteria are as follows:

1. Lateral compartment OA
2. Symptomatic patellofemoral compartment OA
3. Inflammatory arthritis
4. Significant loss of knee joint range in flexion (less than 100°) or in extension (less than − 10°)
5. Ligamentous instability
6. Obesity with BMI > 35 kg/m^2
7. Significant psychological disorder
8. Inability to communicate in Chinese or English language

Recruitment

Eligible patients will be recruited from the outpatient clinic with written consent in the Alice Ho Miu Ling Nethersole Hospital, based on the inclusion and exclusion criteria. Basic patient demographics, including age, gender, ethnicity, occupation, body mass index and smoking and drinking habits, will be recorded. Medical history will also be confirmed and recorded from the Clinical Management System (CMS), Hospital Authority, which is the central electronic database for public hospitals in Hong Kong. Before signing the consent form, each patient will be explained the objectives, benefits and risks of the study and their rights and responsibilities, as well as privacy and confidentiality information. An information sheet will be distributed, and all patients are asked for their understanding of the trial and encouraged to ask questions at any time.

Sample size calculation

Radiological assessment of accuracy will serve as the study primary outcome. Specifically the average osteotomy cut from joint line will be used as a determinant outcome of this study. As no previous reports guide the expected results, our preliminary pilot data has guided our calculations. Based on our previous cases of high tibial osteotomy, we noted the average osteotomy plane entry point deviation from planning with PSI jig is 0 cm ± 0.3 cm and without PSI jig is 0.76 cm ± 1.2 cm. Therefore, a sample size of 15 per group can achieve an 95% power to detect the difference between the two groups, with an alpha level of 0.05 and effect size of 0.95 using a two-sided two sample t-test. To account for attrition we have increased our sample by 20%. Our sample size of 18 participants per treatment arm (total $n = 36$) will be sufficient to address our primary objective. Our secondary objectives will be considered hypothesis generating information to guide future work. The sample size was calculated using G*Power 3.0 software.

Randomization and allocation concealment

Randomization will be accomplished by computer-generated randomization sequence using serially numbered opaque, sealed envelopes with patients assigned either to intervention or control groups. All investigators, research staff, and patients will be blinded to the group assignment of the subjects, nor will they be aware of the allocation during the study and evaluation periods. However, blinding the surgeon performing the HTO is not feasible because they shall perform surgery either with or without using the jig, but the subsequent assessment and analysis shall be done by blinded research staffs and investigators. A randomization code will be allocated to each included subject to maintain blindness. Randomization code will be broken only after the database had been locked. Patient rehabilitation, post-operative assessment and data analysis are conducted by personnel blinded to the patients' randomization assignment.

Study interventions

Current Standard Practice (Routine HTO surgery)

The controlled arm would be standard medial open-wedge high tibial osteotomy using current standard practice. In brief, an incision is made in the midway between posteromedial border of the tibia and medial aspect of the tibial tuberosity. Sartorius fascia is cut and retracted medially to expose the medial collateral ligament (MCL). Two to three 2.5mm K-wires are placed 4 cm below the medial joint line toward the proximal tibiofibular joint over lateral tibial cortex under fluoroscopy and osteotomy is done below and parallel to the k-wires using an oscillating saw (blade thickness 0.9mm) leaving the lateral 5 mm intact. Thin osteotomes are used to gradually open the osteotomy and finally the desired correction is achieved with the use of computer navigation (Orthomap ASM, Stryker, Michigan) checking overall lower limb alignment.

Intervention group:

3D printed patient specific jigs (PSI jig) (figure 2) are created based on the pre-operative CT image. Before operation, lower limb from hip to ankle center were scanned by CT with slice thickness ≤1 mm covering the proximal tibia and knee joint. CT image data were made available in Digital Imaging and Communications in Medicine (DICOM) format and transferred to a standard desktop computer and loaded to Mimics software (Materialise, Louvain, Belgium) for segmentation. Virtual planning of osteotomy plane and the associated jig was performed on Materialise 3-matic 13.0 (Materialise, Leuven, Belgium) according to TomoFix™ plate (Synthes Medical, Oberdorf, Switzerland) surgical technique manual. PSI jigs were printed in stainless steel by 3D metal printing machine (LUMEX Avance-25, Matsuura, Japan). Standard medial open wedge osteotomy similar as described previously is performed with modification. Incision is made in the midway between posteromedial border of the tibia and medial aspect of the tibial tuberosity. Sartorius fascia is cut and retracted medially to expose the medial collateral ligament (MCL). Then the PSI jig is positioned onto the tibia. Due to the patient specific design (individually based on each patient's CT image), it can fit closely to the proximal tibia. The slot opening on the PSI jig corresponds to 4 cm below the medial joint line and the slot design allow the sawblade (blade thickness 0.9mm) cut direction toward

proximal tibiofibular joint over lateral tibial cortex under fluoroscopy. The PSI jig is removed after the bone cut completed and would not retain in patient's body. Thin osteotomes are used to gradually open the osteotomy. A 3D printed wedge that corresponds to opening gap size of osteotomy is used to achieve the desired correction, and supersede the computer navigation (set-up also as part of blinding) values for alignment in case of discrepancy. The rehabilitation and follow-up of the intervention group is the same as the routine patients (Control group) undergoing MOWHTO for knee osteoarthritis.

Outcomes and outcome assessments

Outcome assessments of the patients will be performed at baseline (0 month), immediately before discharge, at 3 months, 6 months, 12 months, and 24-months timepoints. Table 1 shows the overall assessments needed for each timepoint.

Primary Outcome

Radiographic assessment on surgical outcome

The primary outcome is obtained by post-operative radiological assessment of X-ray and computer tomography (CT) images to compare the accuracy of PSI jig with freehand bone cut in achieving pre-operative planned bone cut. The planned bone cut is from 4 cm below the medial joint line towards proximal tibiofibular joint (PTFJ) near the lateral tibial cortex. Accuracy is measured by comparing the planned versus final position of: the blade entrance point (proximal/distal translation on CT images), osteotomy plane (towards PTFJ) angulation and osteotomy gap opening angle (2D angles in coronal and sagittal plane on CT images) It also includes comparison with navigation on overall alignment correction. Anteroposterior full-length lower-limb radiographs are taken with patients in the standing position to assess postoperative lower-limb alignment correction, which is compared with the preoperative planning, based on Miniaci method calculation to achieve target alignment passing through the Fujisawa point[11 12].

Secondary Outcome

Knee Function and Pain Score

Secondary outcomes include the clinical outcome on knee score and knee function. The quality of knee function and pain will be assessed by the previously reported and validated Knee Society Knee Score and Function Score. The Knee Society Score (KSS) was designed to provide a simple and objective scoring system to rate the knee and patient's functional abilities before and after total knee arthroplasty and also employed to assess high tibial osteotomy as well[13 14]. The KSS has a Knee Score section and a Functional Score section, covering on pain, symptom, and activities of daily living. Both sections are scored from 0 to 100 with lower scores being indicative of worse knee conditions and higher scores being indicative of better knee conditions.

Whereas, the Oxford Knee Score (OKS) is a 12-item patient-reported outcome measures (PROMs) originally designed and developed to measure subjective outcome after total knee arthroplasty but later have also been used to assess outcome of high tibial osteotomy[8 15 16]. Each question is scored from 0 to 4 (0 being the worst outcome and 4 being the best). The overall score is the sum of all items and can range from 0 to 48, with higher scores corresponding to better outcomes. The Lyshom Knee Scoring Scale is a patient-reported instrument that consists of subscales for pain, instability, locking, swelling, limp, stair climbing, squatting, and the need for support. Scores range from 0 (worse disability) to 100 (less disability)[10].

The pain visual analog scale (VAS) is an unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with degenerative knee diseases.

Adverse Events, safety and compliance assessment

Any postoperative pain, complications and other complaints from the participants will be monitored and taken care of by medical officers. Any adverse event or problems arise during the study will be reported directly to the ethnic committee in the institution. In addition, participants are allowed to quit the study at any time for any reason; if so, they will be asked whether they wish to be followed up according to the trial schedule.

Data management and confidentiality

A research assistant will be trained to ensure accuracy of outcome assessments and data collection. The ethics committee will oversee any issues disturbing quality of research, and corresponding measures will be taken if necessary. Patients are free to withdraw from the study at any time without giving any reasons, and their medical care or legal rights will not be affected. The study will comply with the good clinical practice guideline according to the International Council for Harmonisation. Each patient will be assigned an identification code. The patient identification code list and database will be safeguarded.

Statistical analysis

Data in this study will be analyzed according to the intention-to-treat principle. Only full analysis set and per-protocol set will be used for primary analysis. Any missing data will not be input for calculation. Quantitative variables will be expressed as mean ± standard deviation. Normality tests will be performed to determine whether the data is normally distributed. Analysis of variance tests are used to compare means for continuous variables. Whereas, Chi-square test will be used to compare proportions of categorical variables and to calculate the differences in the count data. Mixed effects models will be used to analyze the trend of changes in the scores with two factors of groups and time. In addition, a survival analysis on the surgical approach will be shown as a Kaplan-Meier curve. The statistical analysis will be performed using a commercialized statistical software (SPSS, version 25, IBM). All statistical significance is defined as $P < 0.05$.

Ethics and dissemination

Ethics approval and consent to participate have been obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC no. 2019.050), in accordance with the declaration of Helsinki. The results will be presented at international scientific meetings and through publications in peer-reviewed journals

Protocol version

This study protocol was approved on 13 March 2019 as detailed in this manuscript.

Study participant consent

1. Surgeon consent: the PI and co-investigators met with potential surgeons (with ≥ 5 year of experience in performing HTO) individually or as part of faculty meetings to discuss the study and to answer any questions. The surgeons were given a copy of the proposal detailing the assessments to review. Surgeons provided verbal and email consent to the PI to indicate their willingness to participate.
2. Patient consent: Informed written consents for participation into this PROTECTED HTO trial will be obtained from every patient before their operation. Detailed risks and benefits will be explained when obtaining the consent from the patients.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

DISCUSSION

As previously shown, HTO is a proven effective method to treat relative young and active adults with knee osteoarthritis[17]. In conventional method, HTO is performed using intraoperative fluoroscopy to judge the site and direction of osteotomy, degree of alignment correction and change of posterior slope. However, surgical accuracy with the conventional method is reported to be limited and hence computer navigation has been introduced to improve accuracy in performing HTO. In a recent publication on comparing between computer navigated HTO and conventional HTO, it reported that the risk of outlier in alignment was lower in computer navigated HTO than conventional method[18]. In addition, the tibial slope maintenance was comparable, if not better, in navigated HTO than conventional HTO[18]. Moreover, navigated HTO did not show a discrepancy with conventional HTO on the functional scores[18].

PSI is a development in orthopedic field made possible by the advancement in 3D scanning and 3D printing technology, in which an instrument that can couple closely to the targeting bony surface is virtually planned and later produced by 3D printing. The putative benefits of these PSI include increased surgical accuracy, decreased operation time, and elimination of the need for extra devices or reference trackers[19 20]. The application of PSI on HTO as a cutting jig is reported achieving precise osteotomy and accurate realignment of lower limb in case series[19]. However, evidence in form of randomized controlled trial evaluating outcome of HTO performed with PSI is lacking. The current study described in this protocol can fill this gap in knowledge regarding the advantages of PSI use on HTO. A head-to-head comparison with computer navigated HTO was designed in this protocol given previously reported superiority of computer navigated HTO over conventional HTO[18]. Radiological outcome, in terms of discrepancy to planned osteotomy and realignment, and clinical outcome, in terms of functioning score assessment, were reported. Various patient-reported outcome measures (PROMs) or clinical scoring system have been used to gauge the surgical outcome of HTO[21]. And in this study, Knee Society Score (Knee Score and Function Score) and Oxford Knee Score (OKS) will be used. These are also the commonest PROMs and clinical scoring system for unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA), with the former being a common alternative treatment for isolated medial compartment OA and the latter being the choice of conversion when HTO fails. Moreover, by using the same sets of PROMs and clinical scoring system as in other reports, this would allow seamless and meaningful comparison between different treatment modalities for the same clinical problem.[21]

Enrolment of this trial have commenced on late 2019, and completion is expected to take 36 months. The results from this trial may help to change the current clinical practice, as this will be the first randomized study to evaluate whether patient specific jigs can improve the surgical accuracy and clinical outcome for those requiring HTO. Importantly, we speculate that positive results would allow the incorporation of PSI into multiple orthopedics surgeries to help to improve healthcare for our patients in the future.

Acknowledgements:

None.

Authors' contributions:

LCML and ECSC planned the study. LCML and GCWM planned the statistical analysis methods. LCML, YWH and ECSC designed the jig. All authors contributed to the design and development of the trial (LCML, JCHF, GCWM, YWH, KKWH, ECSC, KYC, SYCW, JWWC, PSHY and MB). LCML and GCWM drafted the manuscript. LCML, KYC, PSHY and MB contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests statement:

None declared.

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Figure and Table Legends

Figure 1. The study flow diagram, including participants' recruitment, eligibility, screening, randomization, allocation concealment and outcome assessments.

Figure 2. Image of PSI jig.

Table 1. Study Timeline of Assessment

Table 1. Study Timeline of Assessment

	Enrollment	Assessment period				
	Pre-op	**Immediate before discharge**	**3 months**	**6 months**	**12 months**	**24 months**
Enrollment						
Informed consent	✓					
Assessment of eligibility	✓					
Randomization	✓					
Assessments						
Anatomical						
CT Scan	✓	✓	✓			
Scanogram	✓		✓			
Knee X-Rays	✓	✓	✓	✓	✓	✓
Functional						
Knee Society knee score	✓			✓	✓	✓
Knee Society function score	✓			✓	✓	✓
Oxford Knee Score	✓			✓	✓	✓
Lysholm Knee Scoring Scale	✓			✓	✓	✓

ROM	✓	✓	✓	✓	✓	✓
VAS score	✓	✓	✓	✓	✓	✓
Others						
Additional use of analgesics		✓				
Postoperative complications and adverse events		✓	✓	✓	✓	✓

PSI, patient specific instrumentation; CT, computed tomography; ROM, range of motion; VAS, visual analog scale

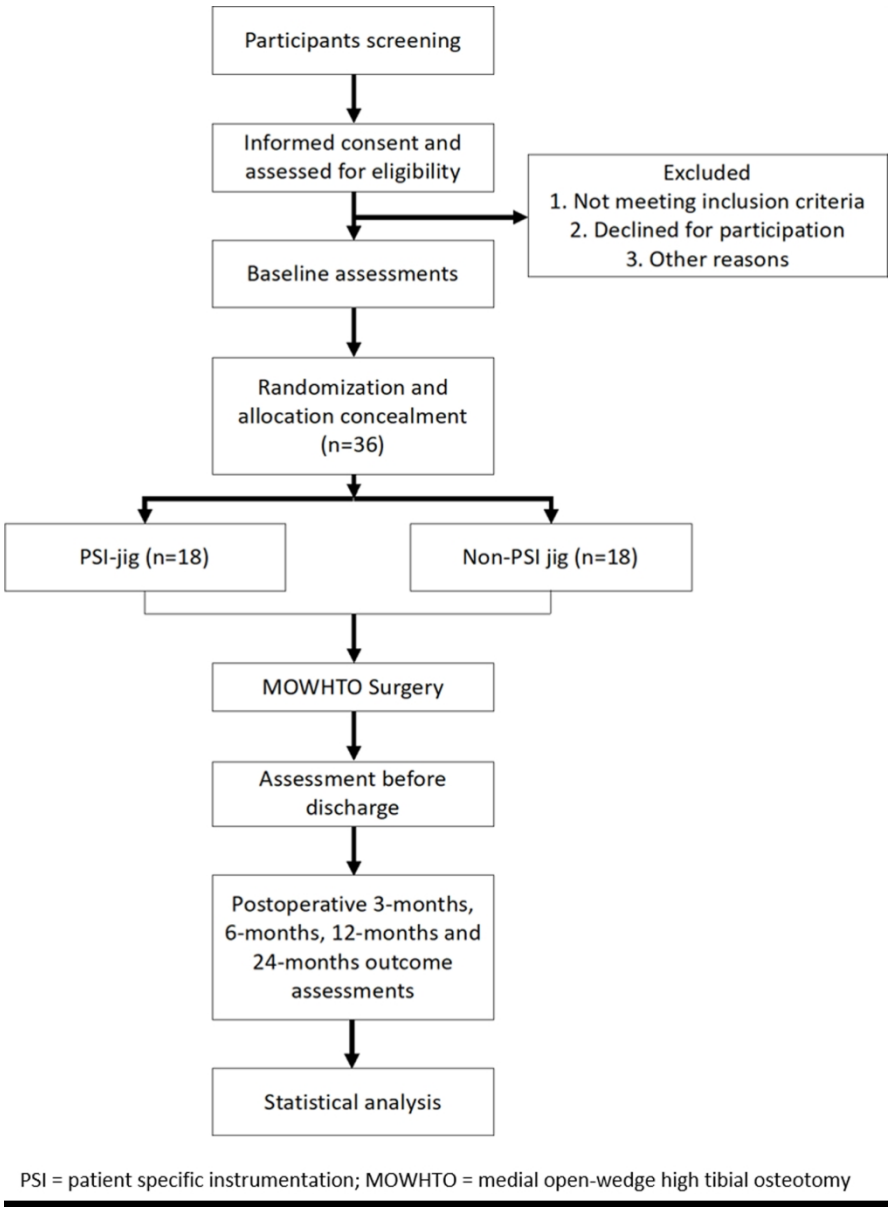

Figure 1. The study flow diagram, including participants' recruitment, eligibility, screening, randomization, allocation concealment and outcome assessments.

141x191mm (300 x 300 DPI)

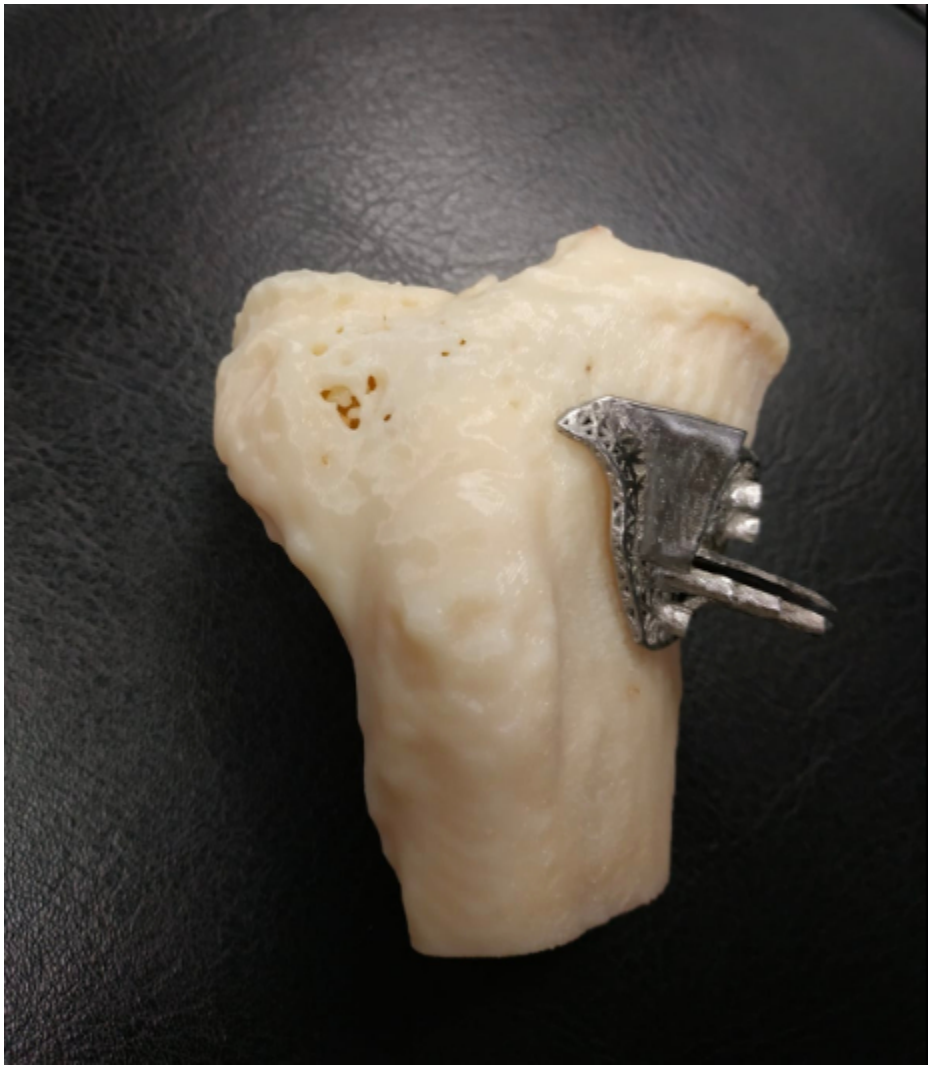

Figure 2. Image of PSI jig

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4, 5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	6, 7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8, 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9, 10, 11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11, 12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11, 12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

Section/item	ItemNo	Description	line/page numbers
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ Page 1 Line 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ Page 2 Line 25
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	✓ Page 13 Line 1
Funding	4	Sources and types of financial, material, and other support	✓Page 15 Line 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ Page 1 Line 5-7
	5b	Name and contact information for the trial sponsor	No sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No sponsor

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓ Page 11 Line 20-24
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ Page 4-5
	6b	Explanation for choice of comparators	✓ Page 9 Line 1-26
Objectives	7	Specific objectives or hypotheses	✓ Page 5 Line 11-16
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ Page 5 Line 19-21
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ Page 6 Line 14-17
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ Page 6 Line 22-25 and Page 7 Line 1-15
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓Page 91-26 and Page 7 1-5

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not relevant. Surgery done
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not relevant. Surgery done
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A. Unrestricted
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ Page 10 Line 7-26, Page 11 Line 1-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ Page 10 Line 7-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ Page 8 Line 2-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ Page 8 Line 8-12

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ Page 8 Line 15-23
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ Page 8 Line 15-22
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ Page 8 Line 15-16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 8 Line 17-19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 8 Line 18-21
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ Page 12 Line 1-6, Line 23-24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ Page 12 Line 1-6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ Page 12 Line 1-6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ Page 12 Line 9-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 12 Line 15-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ Page 12 Line 9-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ Page 11 Line 20-24
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ Page 11 Line 20-24
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ Page 11 Line 20-24

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ Page 11 Line 20-24
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Approval obtained
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓Page 6 Line 2-6
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓Page 13 Line 7-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓Page12 Line 1-6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓Page15 Line 16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓Page12 Line 1-6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ Page 12 Line 23-24
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ Page 15 Line 5-9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ Page 6 Line 9-10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ Supplement material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

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Manuscript ID	bmjopen-2020-041129.R2
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Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Sports and exercise medicine, Surgery
Keywords:	Orthopaedic & trauma surgery < SURGERY, SPORTS MEDICINE, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

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Abstract

INTRODUCTION: High tibial osteotomy (HTO) is a treatment of choice for active adult with knee osteoarthritis. With advancement in computed tomographic imaging with 3D model reconstruction, virtual planning and 3D printing, patient specific instrumentation (PSI) in form of cutting jigs are employed to improve surgical accuracy and outcome of HTO. The aim of this randomized controlled trial (RCT) is to explore the surgical outcomes of HTO for the treatment of medial compartment knee osteoarthritis with or without a 3D printed patient specific jig.

METHODS AND ANALYSIS: A double-blind RCT will be conducted with patients and outcome assessors blinded to treatment allocation. This meant that neither the patients nor the outcome assessors would know the actual treatment allocated during the trial. Thirty-six patients with symptomatic medial compartment knee osteoarthritis fulfilling our inclusion criteria will be invited to participate the study. Participants will be randomly allocated to one of two groups (1:1 ratio): operation with 3D printed patient specific jig or operation without jig. Measurements will be taken before surgery (baseline) and at postoperatively (6, 12, and 24 months). The primary outcome includes radiological accuracy of osteotomy. Secondary outcomes include a change in knee function from baseline to postoperatively as measured by 3 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores and Pain Visual Analog Scale (VAS) score.

ETHICS AND DISSEMINATION: Ethical approval has been obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC no. 2019.050), in accordance with the declaration of Helsinki. The results will be presented at international scientific meetings and through publications in peer-reviewed journals.

TRIAL REGISTRATION NUMBER: NCT04000672; Pre-results.

Strengths and limitations of this study

- The first randomized controlled trial designed to study the accuracy and clinical outcome on using 3D-patient specific instrumentation (PSI) on patients with knee osteoarthritis requiring high tibial osteotomy (HTO).

- Data will be collected longitudinally at baseline and during follow-up at 3, 6, 12, and 24 months.

- Valuable evidence will be provided to surgeons and decision-makers by highlighting the efficacy, and benefits of using PSI instrumentation on osteotomy.

- The results are expected to have an immediate substantial impact on clinical practice on the potential of 3D PSI on improving the surgical outcome for patients with knee osteoarthritis.

- A limitation of the study is conducted in a single-center design.

INTRODUCTION

Background

Knee osteoarthritis (OA) is a long-term chronic disease characterized by cartilage degeneration, creating knee pain and impairing movement. It is the single most common cause of disability in older adults according to the World Health Organizations (WHO). In recent *Lancet* review, osteoarthritis is expected to be the fourth leading cause of disability globally by 2020, with knee OA accounts for approximately 85% of the burden of OA worldwide [1]. The medical cost of osteoarthritis has been estimated to be around 1 - 2·5% of the gross domestic product in various high-income countries, with joint replacements representing the major proportion of the cost[1].

Total knee arthroplasty (TKA) is a common and highly effective orthopaedic procedure for treating end-stage knee osteoarthritis with good long-term results when conservative treatment fails. Although TKR has been a successful surgery, up to 20% of patients were unsatisfied with the result[2]. Some of the causes of dissatisfaction have been attributed to the failure of artificial implant to reproduce a normal native knee feeling, and also high functional demand activities after replacement surgery[2]. This has fuelled increasing popularity of joint preserving surgery like high tibial osteotomy (HTO), to preserve the native knee joint and allow better function. Moreover, TKA performed at middle age fails to outlast the patient and is commonly associated with significant bone loss at revision surgery. The functional outcome of revision TKA is worse than TKA after high tibial osteotomy, which has been reported to have excellent long-term survivorship and clinical outcome[3].

HTO can relieve the symptoms and slow down structural damage by unloading the medial knee compartment. It redistributes mechanical load in the knee, hence extending the longevity of native knee joint in this group of moderate OA patients with high daily activity demand. It is also a well-established surgical procedure for medial compartment knee OA with the probability of survival between 85.4% to 91.6% at ten years[4]. In Asia, HTO is increasingly popular as treatment for knee OA with rising number of HTO performed in conjunction with the fell in number of TKA performed. For example, the annual number of HTO in Korea increased from 2649 cases in 2009 to 8207 cases in 2013, and the annual number of HTO

in Japan increased from 261 cases in 2007 to 2152 cases in 2014[5 6]. Recently with the advancement of technology, we started employing patient specific instrumentation (PSI) on HTO. PSI is a surgical advancement made possible by the advancement in computed tomographic imaging with 3D model reconstruction, virtual planning and 3D printing. By virtue of close approximation of PSI onto patient's bony surface, PSI HTO cutting jigs are designed to improve surgical accuracy and outcome of HTO. Several groups have reported their results of using PSI jigs on HTO in small case series without a control group. However, without a well-designed randomized trial type of study design, whether there exists scientific significant difference in accuracy and clinical outcome by using PSI on HTO is not known.

Objectives

This trial will explore the surgical outcomes of HTO for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific jig (PSI jig). The primary outcomes will be the radiological differences reflecting difference in surgical accuracy with or without PSI jig and the secondary outcomes will be the postoperative change in knee function from baseline using 4 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores, Lysholm Knee Scoring Scale and Pain Visual Analog Scale (VAS) score[7-10].

Trial design

The study is a randomized, double-blind controlled study to compare the surgical outcomes for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific jig, in terms of radiological outcomes, knee scores, range of motion and pain score with a 24-month follow-up.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in online supplemental files). The underlying protocol also follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see CONSORT checklist in online supplemental files. The trial was registered on clinicaltrials.gov). (NCT04000672).

Participants, interventions and outcomes

Participants and setting

Participants will be primarily recruited from the outpatient clinic of the Department of Orthopaedics and Traumatology at the Alice Ho Miu Ling Nethersole Hospital. Additionally, the Prince of Wales Hospital (affiliated with the Chinese University of Hong Kong) in the same New Territories East Cluster, will also help to refer suitable patients for the trial. Figure 1 shows the overall flowchart of the study.

Eligibility criteria

To be enrolled in this trial, the following eligibility criteria, assessed at screening, will be met:

Inclusion criteria

The inclusion criteria are as follows:

1. Age ≥ 18 years and ≤ 70 years
2. Symptomatic patient with medial compartment knee OA
3. Clinical diagnosis of knee OA (American College of Rheumatology criteria) with radiographic changes (Kellgren-Lawrence [KL] grades 2 or 3)
4. Body mass index (BMI) ≤ 35 kg/m^2.
5. Informed consent obtained

Exclusion criteria

The exclusion criteria are as follows:

1. Lateral compartment OA
2. Symptomatic patellofemoral compartment OA
3. Inflammatory arthritis
4. Significant loss of knee joint range in flexion (less than 100°) or in extension (less than − 10°)
5. Ligamentous instability
6. Obesity with BMI > 35 kg/m^2
7. Significant psychological disorder
8. Inability to communicate in Chinese or English language

Recruitment

Eligible patients will be recruited from the outpatient clinic with written consent in the Alice Ho Miu Ling Nethersole Hospital, based on the inclusion and exclusion criteria. Basic patient demographics, including age, gender, ethnicity, occupation, body mass index and smoking and drinking habits, will be recorded. Medical history will also be confirmed and recorded from the Clinical Management System (CMS), Hospital Authority, which is the central electronic database for public hospitals in Hong Kong. Before signing the consent form, each patient will be explained the objectives, benefits and risks of the study and their rights and responsibilities, as well as privacy and confidentiality information. An information sheet will be distributed, and all patients are asked for their understanding of the trial and encouraged to ask questions at any time.

Sample size calculation

Radiological assessment of accuracy will serve as the study primary outcome. Specifically the average osteotomy cut from joint line will be used as a determinant outcome of this study. As no previous reports guide the expected results, our preliminary pilot data has guided our calculations. Based on our

previous cases of high tibial osteotomy, we noted the average osteotomy plane entry point deviation from planning with PSI jig is 0 cm ± 0.3 cm and without PSI jig is 0.76 cm ± 1.2 cm. Therefore, a sample size of 15 per group can achieve an 95% power to detect the difference between the two groups, with an alpha level of 0.05 and effect size of 0.95 using a two-sided two sample t-test. To account for attrition we have increased our sample by 20%. Our sample size of 18 participants per treatment arm (total $n = 36$) will be sufficient to address our primary objective. Our secondary objectives will be considered hypothesis generating information to guide future work. The sample size was calculated using G*Power 3.0 software.

Randomization and allocation concealment

Randomization will be accomplished by computer-generated randomization sequence using serially numbered opaque, sealed envelopes with patients assigned either to intervention or control groups. All investigators, research staff, and patients will be blinded to the group assignment of the subjects, nor will they be aware of the allocation during the study and evaluation periods. However, blinding the surgeon performing the HTO is not feasible because they shall perform surgery either with or without using the jig, but the subsequent assessment and analysis shall be done by blinded research staffs and investigators. A randomization code will be allocated to each included subject to maintain blindness. Randomization code will be broken only after the database had been locked. Patient rehabilitation, post-operative assessment and data analysis are conducted by personnel blinded to the patients' randomization assignment.

Study interventions

Current Standard Practice (Routine HTO surgery)

The controlled arm would be standard medial open-wedge high tibial osteotomy using current standard practice. In brief, an incision is made in the midway between posteromedial border of the tibia and medial aspect of the tibial tuberosity. Sartorius fascia is cut and retracted medially to expose the medial collateral ligament (MCL). Two to three 2.5mm K-wires are placed 4 cm below the medial joint line toward the proximal tibiofibular joint over lateral tibial cortex under fluoroscopy and osteotomy is done below and

parallel to the k-wires using an oscillating saw (blade thickness 0.9mm) leaving the lateral 5 mm intact. Thin osteotomes are used to gradually open the osteotomy and finally the desired correction is achieved with the use of computer navigation (Orthomap ASM, Stryker, Michigan) checking overall lower limb alignment.

Intervention group:

3D printed patient specific jigs (PSI jig) (figure 2) are created based on the pre-operative CT image. Before operation, lower limb from hip to ankle center were scanned by CT with slice thickness ≤1 mm covering the proximal tibia and knee joint. CT image data were made available in Digital Imaging and Communications in Medicine (DICOM) format and transferred to a standard desktop computer and loaded to Mimics software (Materialise, Louvain, Belgium) for segmentation. Virtual planning of osteotomy plane and the associated jig was performed on Materialise 3-matic 13.0 (Materialise, Leuven, Belgium) according to TomoFix™ plate (Synthes Medical, Oberdorf, Switzerland) surgical technique manual. PSI jigs were printed in stainless steel by 3D metal printing machine (LUMEX Avance-25, Matsuura, Japan). Standard medial open wedge osteotomy similar as described previously is performed with modification. Incision is made in the midway between posteromedial border of the tibia and medial aspect of the tibial tuberosity. Sartorius fascia is cut and retracted medially to expose the medial collateral ligament (MCL). Then the PSI jig is positioned onto the tibia. Due to the patient specific design (individually based on each patient's CT image), it can fit closely to the proximal tibia. The slot opening on the PSI jig corresponds to 4 cm below the medial joint line and the slot design allow the sawblade (blade thickness 0.9mm) cut direction toward proximal tibiofibular joint over lateral tibial cortex under fluoroscopy. The PSI jig is removed after the bone cut completed and would not retain in patient's body. Thin osteotomes are used to gradually open the osteotomy. A 3D printed wedge that corresponds to opening gap size of osteotomy is used to achieve the desired correction, and supersede the computer navigation (set-up also as part of blinding) values for

alignment in case of discrepancy. The rehabilitation and follow-up of the intervention group is the same as the routine patients (Control group) undergoing MOWHTO for knee osteoarthritis.

Outcomes and outcome assessments

Outcome assessments of the patients will be performed at baseline (0 month), immediately before discharge, at 3 months, 6 months, 12 months, and 24-months timepoints. Table 1 shows the overall assessments needed for each timepoint.

Primary Outcome

Radiographic assessment on surgical outcome

The primary outcome is obtained by post-operative radiological assessment of radiographs and computer tomography (CT) images to compare the accuracy of PSI jig with freehand bone cut in achieving pre-operative planned bone cut. The planned bone cut is from 4 cm below the medial joint line towards proximal tibiofibular joint (PTFJ) near the lateral tibial cortex. Accuracy is measured by comparing the planned versus final position of: the blade entrance point (proximal/distal translation on CT images), osteotomy plane (towards PTFJ) angulation and osteotomy gap opening angle (2D angles in coronal and sagittal plane on CT images) It also includes comparison with navigation on overall alignment correction. Anteroposterior full-length lower-limb radiographs are taken with patients in the standing position to assess postoperative lower-limb alignment correction, which is compared with the preoperative planning, based on Miniaci method calculation to achieve target alignment passing through the Fujisawa point[11 12].

Secondary Outcome

Knee Function and Pain Score

Secondary outcomes include the clinical outcome on knee score and knee function. The quality of knee function and pain will be assessed by the previously reported and validated Knee Society Knee Score and Function Score. The Knee Society Score (KSS) was designed to provide a simple and objective scoring

system to rate the knee and patient's functional abilities before and after total knee arthroplasty and also employed to assess high tibial osteotomy as well[13 14]. The KSS has a Knee Score section and a Functional Score section, covering on pain, symptom, and activities of daily living. Both sections are scored from 0 to 100 with lower scores being indicative of worse knee conditions and higher scores being indicative of better knee conditions.

Whereas, the Oxford Knee Score (OKS) is a 12-item patient-reported outcome measures (PROMs) originally designed and developed to measure subjective outcome after total knee arthroplasty but later have also been used to assess outcome of high tibial osteotomy[8 15 16]. Each question is scored from 0 to 4 (0 being the worst outcome and 4 being the best). The overall score is the sum of all items and can range from 0 to 48, with higher scores corresponding to better outcomes. The Lysholm Knee Scoring Scale is a patient-reported instrument that consists of subscales for pain, instability, locking, swelling, limp, stair climbing, squatting, and the need for support. Scores range from 0 (worse disability) to 100 (less disability)[10].

The pain visual analog scale (VAS) is an unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with degenerative knee diseases.

Adverse Events, safety and compliance assessment

Any postoperative pain, complications and other complaints from the participants will be monitored and taken care of by medical officers. Any adverse event or problems arise during the study will be reported directly to the ethnic committee in the institution. In addition, participants are allowed to quit the study at any time for any reason; if so, they will be asked whether they wish to be followed up according to the trial schedule.

Data management and confidentiality

A research assistant will be trained to ensure accuracy of outcome assessments and data collection. The ethics committee will oversee any issues disturbing quality of research, and corresponding measures will be taken if necessary. Patients are free to withdraw from the study at any time without giving any

reasons, and their medical care or legal rights will not be affected. The study will comply with the good clinical practice guideline according to the International Council for Harmonisation. Each patient will be assigned an identification code. The patient identification code list and database will be safeguarded.

Data statement

Data and resources will be shared with other eligible investigators through academically established means. The protocol and datasets used and/or analysed in this study will be available from the corresponding author on reasonable request.

Statistical analysis

Data in this study will be analyzed according to the intention-to-treat principle. Only full analysis set and per-protocol set will be used for primary analysis. Any missing data will not be input for calculation. Quantitative variables will be expressed as mean ± standard deviation. Normality tests will be performed to determine whether the data is normally distributed. Analysis of variance tests with Bonferroni correction are used for multiple testing of continuous variables. Whereas, Chi-square test will be used to compare proportions of categorical variables and to calculate the differences in the count data. Mixed effects models will be used to analyze the trend of changes in the scores with two factors of groups and time. In addition, a survival analysis on the surgical approach will be shown as a Kaplan-Meier curve. The statistical analysis will be performed using a commercialized statistical software (SPSS, version 25, IBM). All statistical significance is defined as $P < 0.05$.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethics and dissemination

Ethics approval and consent to participate have been obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC no. 2019.050), in accordance with the declaration of Helsinki. The results will be presented at international scientific meetings and through publications in peer-reviewed journals

Protocol version

This study protocol was approved on 13 March 2019 as detailed in this manuscript.

Study participant consent (See supplementary file)

1. Surgeon consent: the PI and co-investigators met with potential surgeons (with ≥ 5 year of experience in performing HTO) individually or as part of faculty meetings to discuss the study and to answer any questions. The surgeons were given a copy of the proposal detailing the assessments to review. Surgeons provided verbal and email consent to the PI to indicate their willingness to participate.
2. Patient consent: Informed written consents for participation into this PROTECTED HTO trial will be obtained from every patient before their operation. Detailed risks and benefits will be explained when obtaining the consent from the patients.

DISCUSSION

As previously shown, HTO is a proven effective method to treat relative young and active adults with knee osteoarthritis[17]. In conventional method, HTO is performed using intraoperative fluoroscopy to judge the site and direction of osteotomy, degree of alignment correction and change of posterior slope. However, surgical accuracy with the conventional method is reported to be limited and hence computer navigation has been introduced to improve accuracy in performing HTO. In a recent publication on comparing between computer navigated HTO and conventional HTO, it reported that the risk of outlier in alignment was lower in computer navigated HTO than conventional method[18]. In addition, the tibial slope

maintenance was comparable, if not better, in navigated HTO than conventional HTO[18]. Moreover, navigated HTO did not show a discrepancy with conventional HTO on the functional scores[18].

PSI is a development in orthopedic field made possible by the advancement in in computed tomographic imaging with 3D model reconstruction, virtual planning and 3D printing technology, in which an instrument that can couple closely to the targeting bony surface is virtually planned and later produced by 3D printing. The putative benefits of these PSI include increased surgical accuracy, decreased operation time, and elimination of the need for extra devices or reference trackers[19 20]. The application of PSI on HTO as a cutting jig is reported achieving precise osteotomy and accurate realignment of lower limb in case series[19]. However, evidence in form of randomized controlled trial evaluating outcome of HTO performed with PSI is lacking. The current study described in this protocol can fill this gap in knowledge regarding the advantages of PSI use on HTO. A head-to-head comparison with computer navigated HTO was designed in this protocol given previously reported superiority of computer navigated HTO over conventional HTO[18]. Radiological outcome, in terms of discrepancy to planned osteotomy and realignment, and clinical outcome, in terms of functioning score assessment, were reported. Various patient-reported outcome measures (PROMs) or clinical scoring system have been used to gauge the surgical outcome of HTO[21]. And in this study, Knee Society Score (Knee Score and Function Score) and Oxford Knee Score (OKS) will be used. These are also the commonest PROMs and clinical scoring system for unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA), with the former being a common alternative treatment for isolated medial compartment OA and the latter being the choice of conversion when HTO fails. Moreover, by using the same sets of PROMs and clinical scoring system as in other reports, this would allow seamless and meaningful comparison between different treatment modalities for the same clinical problem.[21]

Enrolment of this trial have commenced on late 2019, and completion is expected to take 36 months. The results from this trial may help to change the current clinical practice, as this will be the first randomized study to evaluate whether patient specific jigs can improve the surgical accuracy and clinical outcome for

those requiring HTO. Importantly, we speculate that positive results would allow the incorporation of PSI into multiple orthopedics surgeries to help to improve healthcare for our patients in the future.

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None.

Authors' contributions:

LCML and ECSC planned the study. LCML and GCWM planned the statistical analysis methods. LCML, YWH and ECSC designed the jig. All authors contributed to the design and development of the trial (LCML, JCHF, GCWM, YWH, KKWH, ECSC, KYC, SYCW, JWWC, PSHY and MB). LCML and GCWM drafted the manuscript. LCML, KYC, PSHY and MB contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests statement:

None declared.

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Figure and Table Legends

Figure 1. The study flow diagram, including participants' recruitment, eligibility, screening, randomization, allocation concealment and outcome assessments.

Figure 2. Image of PSI jig.

Table 1. Study Timeline of Assessment

Table 1. Study Timeline of Assessment

	Enrollment	Assessment period				
	Pre-op	Immediate before discharge	3 months	6 months	12 months	24 months
Enrollment						
Informed consent	✓					
Assessment of eligibility	✓					
Randomization	✓					
Assessments						
Anatomical						
CT Scan	✓	✓	✓			
Scanogram	✓		✓			
Knee radiographs	✓	✓	✓	✓	✓	✓
Functional						
Knee Society knee score	✓			✓	✓	✓
Knee Society function score	✓			✓	✓	✓
Oxford Knee Score	✓			✓	✓	✓
Lysholm Knee Scoring Scale	✓			✓	✓	✓

ROM	✓	✓	✓	✓	✓	✓
VAS score	✓	✓	✓	✓	✓	✓
Others						
Additional use of analgesics		✓				
Postoperative complications and adverse events		✓	✓	✓	✓	✓

PSI, patient specific instrumentation; CT, computed tomography; ROM, range of motion; VAS, visual analog scale

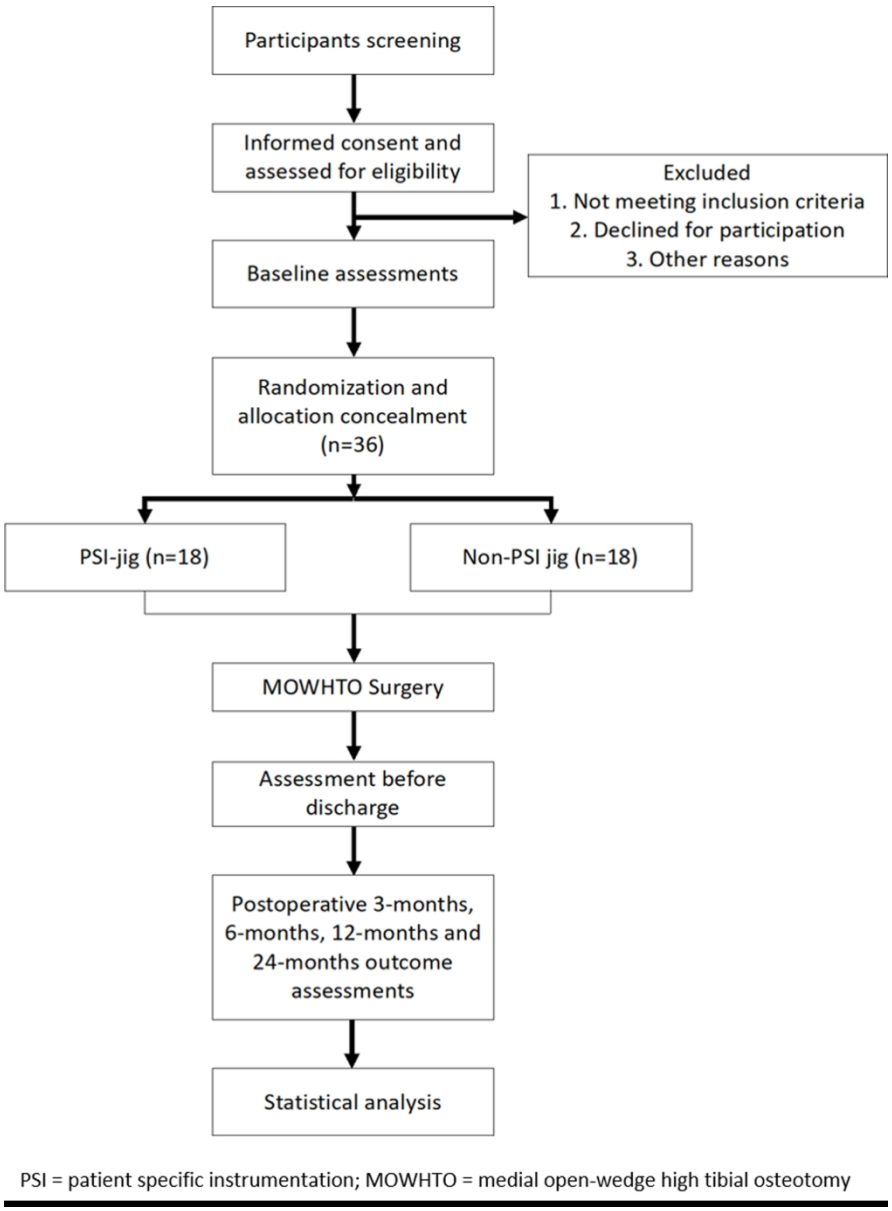


Figure 1. The study flow diagram, including participants' recruitment, eligibility, screening, randomization, allocation concealment and outcome assessments.

141x191mm (300 x 300 DPI)

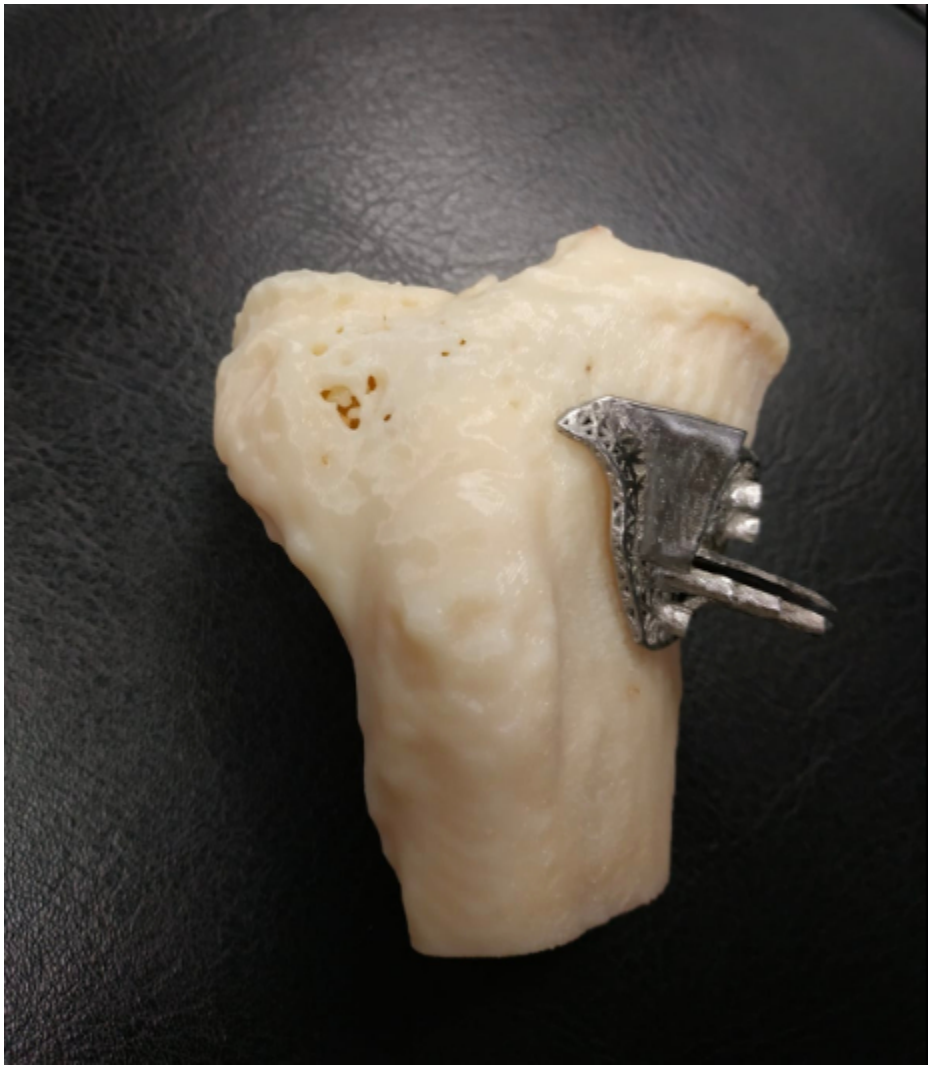
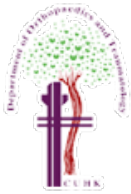


Figure 2. Image of PSI jig



Department of Orthopaedics & Traumatology
The Chinese University of Hong Kong
香港中文大學 矯形外科及創傷學系

Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

Informed consent - Information Sheet

The Department of Orthopedics and Traumatology, Alice Ho Miu Ling Nethersole Hospital and The Department of Orthopedics and Traumatology, The Chinese University of Hong Kong are organizing a randomized control trial (RCT) to explore the surgical outcomes of medial open wedge high tibial osteotomy (MOWHTO) for the treatment of medial compartment knee osteoarthritis with or without the use of 3D printed patient specific metal jig (PSI jig).

Medial open wedge high tibial osteotomy is a surgery performed to treat knee osteoarthritis in young patients. Currently we perform high tibial osteotomy under the guidance of computer navigation to achieve the required alignment and the bone cut (osteotomy) is done by free hand cutting. During the bone cut, there are risks of cutting into the posterior proximal tibia compartment and transecting the neurovascular bundles which is a surgical disaster and may then lead to loss of limb. An inaccuracy bone cut would also increase the chance of lateral hinge fracture. This accuracy of free hand cutting is limited by experience of surgeons. Although in our high tibial osteotomy operation transection of neurovascular bundles has never happened given our meticulous surgical technique, further protection and guidance are seeked to improve surgical accuracy and safety to benefit our patients. Recently with the advancement of technology in our department, we performed computed tomography for the patient's lower limb and 3D reconstruct the image. Based on the 3D reconstructed image, we planned our planned bone cut on computer software Materialize 3-matic and we then 3D printed a metal jig that has a slot to produce the osteotomy and also protected the neurovascular bundles. Therefore these metal jigs are specific to each patients (PSI). We have performed a few cases of HTO under this extra metal jig protection and guidance and noted it has improved accuracy and safety clinically. However, whether it has scientific significance difference in accuracy is not known.

We would like to invite your participation in this study. It is purely voluntary. It is a randomized control (RCT) study. Total 36 patients will be recruited in this study.

If you are candidate for high tibial osteotomy surgery, you would be invited to participate into this study.

All the pre-operative and post-operative clinical assessment and radiological assessment would be the same as our current practice for high tibial osteotomy.

The only difference for the study participants in this study is then they would be randomly allocated to the control and intervention group. The control group would have the high tibial osteotomy done by free hand bone cutting during osteotomy as our current practice and the intervention group wound have the 3D metal jig (Patient specific) guided bone cutting during osteotomy.

So the difference in the intervention group is that they have an additional metal jig to guide bone cutting and protect neurovascular bundles.

If you agree to join the study, baseline assessments and post-operation follow-ups will be arranged, data related to you functional and physical performance will be collected.

Details of assessments and follow-up are listed and summarized in the following table:

Timeline of Assessment and follow-up

	Before surgery	Immediate before discharge	3 months post-op	6 months post-op	1 year post-op	2 year post-op
Knee Society knee score	✓			✓	✓	✓
Knee Society function score	✓			✓	✓	✓
Oxford Knee Score	✓			✓	✓	✓
Lysholm Knee Scoring Scale	✓			✓	✓	✓
Range of motion	✓	✓	✓	✓	✓	✓
Pain Visual Analog Scale (VAS) score	✓	✓	✓	✓	✓	✓
Computed tomography	✓	✓	✓			

scanogram	✓		✓			
Knee X-Rays	✓	✓	✓	✓	✓	✓

Potential complications and/or risks of interventions

- The 3D printed patient specific metal jig (PSI jig)

  The 3D printed patient specific metal jig (PSI jig) is based on the patient's individual CT image and theoretically and in our experience is more accurate than free hand bone cut. However, whether it is truly more accurate or inaccurate is unknown in scientific literature.

  Patient may have allergy to the metal used in the metal jig. But as the jig is just for temporary use and not retaining in the body and metal allergy itself is rare, the chance of allergic reaction is considered rare.

- High tibial osteotomy

  The high tibial osteotomy is performed in control and intervention group as in our current standard practice. The risks described below is intrinsic to high tibial osteotomy but not related to the PSI jig (intervention in this study): bleeding, infection, damage surrounding structure, bone malunion, nonunion, implant failure, pain, fracture, malalignment, progression of osteoarthritis

- X-ray and scanogram and plain computed tomography

  X-ray and scanogram and plain computed tomography are common medical imaging tests which use electromagnetic radiation with a very short wavelength to produce the image. The radiation dosage in diagnostic procedures is considered safe for adults and far below the dosage that will cause damage. These imaging are also required as in current standard practice of high tibial osteotomy for three-dimensional

  planning of bone cut and also for follow-up to look for complications like iatrogenic fractures, malpositioning of implants, etc.

Rights, confidentiality and Insurance

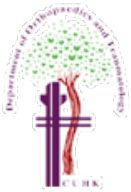
We would like to invite your participation in this study. Your participation into the study is purely voluntary. You have the right to terminate or withdraw from the study at any time, without having to explain your decision and with no consequences to your medical care. Your participation or not will not affect the service being provided to you in this hospital at all. Should new information arise which is deemed to be relevant as to the consent of the patients to the clinical investigation, such information will immediately be reported to you.

Treatment procedures in this study have been recorded in a protocol which has been approved by the Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (the CUHK-NTEC CREC). All the information collected will be coded and analyzed for this research study. Your personal information will remain strictly confidential. You must be aware that the results of this clinical study may be published without revealing the identity of the individuals involved. Information could only be accessed by related research staff, regulatory authorities and ethics committee.

Clinical trial indemnity and insurance will be purchased for you via the Faculty and Planning office, Faculty of Medicine, the Chinese University of Hong Kong. You are requested to report any unexpected or unusual symptom to the physician who is responsible for the study.

Contacts

This research study is to explore the surgical outcomes of medial open wedge high tibial osteotomy (MOWHTO) for the treatment of medial compartment knee osteoarthritis with or without the 3D printed patient specific metal jig (PSI jig). We sincerely hope that you can support this. Any clarification regarding the clinical study can be directed to the principal investigator of the study, Dr. Lau Chun Man Lawrence at 35052211, or the CUHK-NTEC CREC at 35053935. If there's any trial-related injury, please telephone the principal investigator, Dr. Lau Chun Man Lawrence at 35052211, appropriate follow ups and medical care will be arranged.



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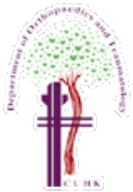
Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

1. Through this declaration, I accept to participate to the trial "PROTECTED HTO trial" study according to the modalities described in the protocol.
2. I was given an information sheet and I received explanations regarding the nature, the duration and possible side effects that could result from the study and I was told what I will be asked to do.
3. I was given the information of alternative treatment for my orthopaedic condition and it is my will to choose this clinical trial as my choice of treatment.
4. I declare that I have understood the explanations that were given to me as well as the aims, risks and limitations of the treatment proposed.

   In particular, I declare that I have understood and accepted the possible risks connected with the implantation of the 3D printed patient specific metal jig (PSI jig) which were explained to me by the physician who is responsible for the study, the most frequent of which are: bleeding, infection, damage surrounding structure, bone malunion, nonunion, implant failure, pain, fracture, malalignment, progression of osteoarthritis, radiation, inaccuracy jig, allergy.
5. I accept to collaborate with the physician responsible for the study and report to him any unexpected or unusual symptom I may have.
6. I have been informed that this study is covered by the university insurance policy.
7. I have been informed that this study has been submitted to the Joint CUHK-NTEC CREC for approval.
8. I have been informed that my refusal to participate to the study will not incur any penalty and I declare to accept to participate in the study voluntarily.
9. I am free to withdraw from the study at any time, without having to motivate my decision and without my decision causing any harm to the continuation of my therapy.
10. I accept that the study results may be disclosed to the competent authorities. My name and address will remain confidential.
11. By signing this document, I accept that my clinical report be examined by anyone duly appointed by them.



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Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)

Informed consent – consent form

(Patient's name)	*(Patient's HKID number)*
(Patient's signature)	*(Date)*
(Physician's name - Print name of person obtaining consent)	*(Physician's code)*
*(*Physician's signature - Signature of person obtaining consent*)*	*(Date)*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4, 5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	6, 7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8, 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9, 10, 11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11, 12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11, 12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

Section/item	ItemNo	Description	line/page numbers
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ Page 1 Line 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ Page 2 Line 25
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	✓ Page 13 Line 1
Funding	4	Sources and types of financial, material, and other support	✓Page 15 Line 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ Page 1 Line 5-7
	5b	Name and contact information for the trial sponsor	No sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No sponsor

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	✓ Page 11 Line 20-24
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ Page 4-5
	6b	Explanation for choice of comparators	✓ Page 9 Line 1-26
Objectives	7	Specific objectives or hypotheses	✓ Page 5 Line 11-16
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ Page 5 Line 19-21
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ Page 6 Line 14-17
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ Page 6 Line 22-25 and Page 7 Line 1-15
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓Page 91-26 and Page 7 1-5

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not relevant. Surgery done
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not relevant. Surgery done
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A. Unrestricted
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ Page 10 Line 7-26, Page 11 Line 1-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ Page 10 Line 7-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ Page 8 Line 2-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ Page 8 Line 8-12

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ Page 8 Line 15-23
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ Page 8 Line 15-22
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ Page 8 Line 15-16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 8 Line 17-19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 8 Line 18-21
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ Page 12 Line 1-6, Line 23-24
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ Page 12 Line 1-6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ Page 12 Line 1-6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ Page 12 Line 9-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 12 Line 15-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ Page 12 Line 9-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ Page 11 Line 20-24
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ Page 11 Line 20-24
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ Page 11 Line 20-24

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ Page 11 Line 20-24
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Approval obtained
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓Page 6 Line 2-6
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓Page 13 Line 7-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓Page12 Line 1-6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓Page15 Line 16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓Page12 Line 1-6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ Page 12 Line 23-24
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ Page 15 Line 5-9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ Page 6 Line 9-10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ Supplement material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.