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Title: Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: a study protocol of randomized controlled trial

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Data sharing statement: The full data set will be made available when this trial is completed and published. Application for the data to be released should be made in contact to WFN (principle investigator).

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Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: Study protocol of a randomized controlled trial

Abstract

Introduction: Transforaminal lumbar interbody fusion (TLIF) has been widely used in the treatment of lumbar degenerative disc disorders and shows favorable clinical results. Recently, cortical bone trajectory (CBT) has become a new trajectory for screw insertion in the lumbar spine. Several biomechanical studies have demonstrated that the CBT technique achieves screw purchase and strength greater than the traditional method. Currently, the available data on the clinical effectiveness of the two performed surgeries, TLIF with CBT screws (CBT-TLIF) and TLIF with traditional pedicle screws (PS-TLIF), are insufficient. This is the first randomized study to compare CBT-TLIF against traditional pedicle screw fixation and will provide recommendations for treating patients with lumbar degenerative disc disorders.

Methods and analysis: A blinded randomized controlled trial (blinding for the patient and statistician, rather than for the clinician and researcher) will be conducted. A total of 125 participants with lumbar disc degenerative disease who are candidates for TLIF surgery will be randomly allocated to either the CBT-TLIF group or the PS-TLIF group at a ratio of 1:1. The primary clinical outcome measures are: fusion rate compared to the PS-TLIF group; the incidence of adjacent cranial facet joint

violation; and the screw loosening rate. Secondary clinical outcome measures are: Visual Analog Scale (VAS) of back pain; VAS of leg pain; Oswestry Disability Index; operative time; intraoperative blood loss; and complications. These parameters will be evaluated on Day 3, and then at 3, 6, 12, and 24 months postoperatively.

Ethics and dissemination: This study has been reviewed and approved by the Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (batch: 2017-03). The results will be presented in peer-reviewed journals and an international spine-related meeting after completion of the study.

Trial registration number: This trial was registered with the US National Institutes of Health Clinical Trials Registry: NCT03105167.

Keywords: transforaminal lumbar interbody fusion; randomized controlled trial; cortical bone trajectory; traditional pedicle screws

Strengths and limitations of this study:

- This trial is designed to have a feasible, comparative effectiveness trial design that has similarities to common clinical situations.
- This study is the first randomized controlled trial to compare CBT-TLIF against traditional pedicle screws.
- The size of the study sample limits the power of the observations.

Introduction

With an aging society, the incidence of lumbar disc degenerative diseases is increasing[1, 2]. Lumbar interbody fusion is the accepted method of surgery[3] if conservative treatment, including physiotherapy and adequate pain medication, of lumbar degenerative disease proves ineffective. These days, transforaminal lumbar interbody fusion (TLIF) is widely used in the treatment of lumbar degenerative disc disorders and shows favorable clinical results[4, 5].

In 2009, Santoni et al.[6] introduced a novel method of pedicle screw insertion termed the cortical bone trajectory (CBT) screw, which demonstrated a 30% increase in uniaxial yield pullout load relative to the traditional pedicle screw. In vivo, it was reported that the insertional torque using the CBT technique was about 1.7 times higher than that of the traditional technique[7]. Several other biomechanical studies have demonstrated the non-inferior mechanical properties of the CBT screw in cadaveric studies[8, 9]. Apart from the trajectory of the traditional pedicle screw, the trajectory of the cortical screw follows a caudocephalad path sagittally and a laterally directed path in the axial plane, which may maximize the thread contact with this higher-density bone surface. This pathway not only seeks to minimize the engagement of trabecular bone within the pedicle and allow for greater holding strength, but also minimizes the risk of medial pedicle breach.

CBT screw fixation has evolved as an optional method of spinal instrumentation that may overcome some of the limitations of traditional pedicle screw fixation. Matsukawa et al.[10] demonstrated that the incidence of adjacent cranial facet joint

violation (FJV) caused by CBT screw fixation was lower than that of pedicle screw fixation. FJV was reported to increase facet and intradiscal loading and lead to instability at the affected segment. Additionally, FJV was closely related to symptomatic adjacent segment disease, which may affect the fusion rate (FR) after lumbar interbody fusion surgery.

Single-level minimally invasive posterior lumbar fusion with CBT screws demonstrates a significantly lower rate of screw loosening, reduced loss of correction, and is less invasive compared to that with percutaneous pedicle screw fixation[11]. Kasukawa et al.[12] examined the surgical outcomes of TLIF with CBT screw fixation (CBT-TLIF) compared with TLIF using traditional pedicle screw fixation (PS-TLIF). They showed that CBT-TLIF resulted in reduced blood loss and a shorter operation than PS-TLIF, and showed similar efficacy in the postoperative rates of bone union, maintenance of lordotic angles, and accuracy of pedicle screw positions between the two groups. Chin et al.[13] reported that the Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) scores of patients were significantly improved after lumbar interbody fusion combined with cortical bone trajectory screws. However, the evidence was poor and limited by trials rated as having a high risk of bias and substantial clinical heterogeneity. Therefore, their conclusion could not prove that the efficacy of CBT-TLIF was better than that of PS-TLIF.

To the best of our knowledge, no randomized controlled study of the clinical outcomes of CBT-TLIF vs. PS-TLIF has been performed. In this study, we will conduct a randomized controlled trial (RCT) to compare CBT-TLIF vs. traditional

pedicle screw fixation.

Methods and analysis

This study has been reviewed and approved by the Institutional Ethics Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants will be asked to sign an informed consent form. The study protocol has been registered at the US National Institutes of Health Clinical Trials Registry: NCT03105167. The protocol was developed by following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT)[14]. A chart of the trial design is provided in Figure 1.

Participants

This study is a parallel group RCT conducted at the Orthopedic Hospital, Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University.

Randomization and blinding

Participants will be equally randomized to either the CBT-TLIF group or the PS-TLIF group based on a permuted blocks randomization scheme. Using a block size of 4 in a scheduled computer-generated randomization program, the final group assignments will be sealed in opaque envelops. Patients will be kept blinded for the

allocated treatment until the last questionnaires have been completed. At the end of the follow-up period, the blind can be lifted at the patients' request. In addition, the statistician will also be blinded.

Inclusion criteria

1. Age of at least 18 years.
2. Chronic lower back pain alone or combined with neurological symptoms of the lower extremities after receiving failed conservative treatment for a period of more than 6 months.
3. Indication for monosegmental TLIF due to degenerative disc disease or instability (including spondylolisthesis, foraminal stenosis, spinal stenosis lumbar disc herniation, and painful disc degeneration).

Exclusion criteria

1. Spinal scoliosis with a Cobb angle of more than 10° in the index level.
2. Patients with prior failed fusion at the same level.
3. Pregnancy.
4. Active infection or prior infection at the surgical site.
5. Planned (e)migration abroad within 2 years after inclusion.
6. Metabolic bone disease such as osteomalacia or Paget's disease.
7. Spondylolisthesis according to Meyerding grades III and IV.

8. Body mass index > 30.
9. Therapy with systemic corticosteroids or immunosuppressants.

Interventions

CBT-TLIF group

After the preventive use of antibiotics, patients were placed under general anesthesia in the prone position. A small skin incision was made at the fused segment and an entry point to allow insertion of the CBT screws was drilled in the junction of the center of the superior articular process and 1 mm inferior to the inferior border of the transverse process according to Matsukawa et al.[15]. A straight probe was then used to create a trajectory for the CBT screws from the entry point to the opposite corner of the pedicle and vertebral body under anteroposterior fluoroscopic guidance. Screws were placed bilaterally, targeting half of the vertebral body. Unilateral facetectomy was performed to gain access to the intervertebral disc, followed by discectomy. The endplate cartilage was prepared to provide a host bed of bleeding subchrondral bone for the placement of the cage. The structure of the interbody cage was determined by a trial cage and fluoroscopy. The definitive cage was then filled with autologous bone or allograft and tamped into place and its position was checked radiologically. After placement of the interbody cage, the remainder of the disc space was filled with autologous bone obtained from the decompression. A titanium rod interconnected the screws on either side. The spreader was removed and the wound

thoroughly irrigated and closed in several layers without suction drainage.

PS-TLIF group

A posterior midline incision of about 6 cm was performed at the level of interest under fluoroscopic guidance. Pedicle screws were inserted freehand into the vertebral body, and the inferior and superior articular processes and part of the lamina were removed by an osteotome. The ligamentum flavum was then removed to expose the lateral border of the ipsilateral nerve root. After decompression of the neural structures, a thorough discectomy and endplate preparation were performed followed by transforaminal insertion of an intervertebral tantalum mesh cage packed with autograft materials within the disc space. In both CBT-TLIF and PS-TLIF, prior to cage insertion, the morselized bone graft from the facetectomy and laminectomy was grafted into the prepared disc space. Compression was achieved across the pedicle screws and rod with place screws and optimal placement was confirmed by intraoperative fluoroscopy.

Outcome measurements

Primary outcomes:

1. FR compared to the PS-TLIF group.
2. The incidence of adjacent cranial FJV.

3. Screw loosening rate (SLR).

Secondary outcomes:

1. The intensity of back and lower limb pain during rest and daily activities during follow-up will be assessed by the VAS of back pain and VAS of leg pain[16].
2. The ODI will be recorded both preoperatively and postoperatively[17]. The ODI assesses back pain-related disability. It contains 10 questions about daily life, including measures of pain intensity, personal care, lifting, walking, sitting, standing, sleeping, social life, and traveling. Each question is rated on a scale of 0–5, with a higher score indicating a more severe pain-related disability.
3. Japanese Orthopedic Association (JOA) scores will be recorded preoperatively, at 3 days, at 3 and 6 months, and at 1 and 2 years postoperatively. Functional improvement is expressed by the rate of recovery of the JOA score[18].
4. Operative time, intraoperative blood loss.
5. Complications including dural tear, postoperative infection, deep venous thrombosis, hematoma, hardware failure, neurological deficits, and any other direct and indirect surgical complications will be recorded.

Baseline demographics

Sex, age, body mass index, smoking habit, diagnosis, level, and occurrence of diabetes will be recorded. Perioperative morbidity will be correlated to the use of antibiotics and duration of surgery.

Follow-up

Follow-up will be conducted at 3 days, and at 3, 6, 12, and 24 months postoperatively.

Monitoring

All investigators who have completed good clinical practice training will independently collect the data and assess the clinical outcomes of the treatments. Data and safety monitoring will be conducted periodically during the study. Only the principal investigator (WFN) will have access to the final trial data set. All paper and electronic versions of the case reports will be stored for 10 years in locked filing cabinets in areas with restricted access.

Sample size calculation

As there has been no previous similar trial that has used our RCT design, we

estimated the sample size on the basis of other similar previous studies[19]. We assumed a two-tailed α error of 0.05 and a power (1-b) of 0.8. With these assumptions, 50 participants in each group are needed for 80% power. We propose to enroll 125 participants (50 randomized to each arm) and allow for a dropout rate of 20% for an effective sample size of 100.

Statistical analysis

All data will be analyzed using the SPSS 19.0 software. Differences in the operative time and intraoperative blood loss, FR, FJV, and other complications between the CBT-TLIF and PS-TLIF groups will be analyzed by two independent-samples *t*-tests with an α of 0.05. Preoperative VAS and ODI scores, and scores taken immediately post-operation, and at postoperative 3, 6, and 24 months, will be analyzed by a repeated-measures ANOVA. Changes in the data between different follow-up time points and the baseline will also be calculated and the changes in data between the CBT-TLIF and PS-TLIF groups will be assessed by two independent-samples *t*-tests.

Discussion

Cortical bone trajectory screw fixation is reported as a minimally invasive technique[20, 21], and biomechanical comparisons with pedicle screw fixation have noted its biomechanical superiority[22, 23]. This paper describes the rationale and

protocol for conducting an RCT in China that will investigate the efficacy of CBT screws with TLIF in treating lumbar disc degenerative diseases such as lumbar spinal canal stenosis and lumbar disc herniation that require spinal interbody fusion surgery. In this trial, we designed a PS-TLIF group as a controlled comparison group to identify the clinical outcomes of TLIF with cortical bone trajectory screw fixation. The demand for spinal interbody fusion surgery has risen steeply over the last ten years and is expected to increase even further in the near future. It is hypothesized that CBT-TLIF, compared to PS-TLIF, is superior in reducing disability and thus has a better clinical outcome.

This study is the first RCT to compare TLIF with CBT against traditional pedicle screws. An RCT has the advantage of controlling all confounding factors due to random sequence generation, as opposed to observational studies where confounding factors and bias may be more problematic. High-quality RCTs are generally regarded as the gold standard for studying the effectiveness of an intervention.

Randomized trials that compare surgery with non-surgical treatments have several features that are distinctly different from drug trials and can lead to serious limitations. Moreover, compared to drug trials, surgery has many irreversible features.

In the case that our hypothesis is confirmed, our results will have a practical value in the planning and development of treatment options in spinal interbody fusion surgery. We anticipate that the results will provide more reliable evidence and clarify the value of CBT with TLIF as a treatment for patients with lumbar disc degenerative diseases.

Acknowledgement:

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/tDbZkH

Ethics and dissemination:

The study had been reviewed and approved by the ethics committee of the Second affiliated hospital of the Wenzhou Medical University, Wenzhou, China(batch：2017-03). The procedure will be performed following the principles described in the Declaration of Helsinki. All of participants will be signed the informed consent. The protocol has been registered in US National Institutes of Health Clinical Trials Registry: NCT03105167. We will share individual patient data (IPD) within 2 years after the trial complete, and the original data is collected by clinical recording formula (both paper and electronic version). The results will be presented in peer-reviewed journals and related website (https://clinicaltrials.gov/) within 2 years after the last operation.

Reference

1. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG *et al.* Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy. Journal of Neurosurgery Spine2005;2(6):673-78.

2. Braydabruno M, Tibiletti M, Ito K, Fairbank J, Galbusera F, Zerbi A *et al.* Advances in the diagnosis of degenerated lumbar discs and their possible clinical application. European Spine Journal2014;23(3):315-23.

3. Omidikashani F, Hasankhani EG, Ashjazadeh A. Lumbar Spinal Stenosis: Who Should Be Fused? An Updated Review. Asian Spine Journal2014;8(4):521.

4. Harms JG, Jeszenszky D. Die posteriore, lumbale, interkorporelle Fusion in unilateraler transforaminaler Technik. Operative Orthopädie und Traumatologie1998;10(2):90-102.

5. Rouben D, Casnellie M, Ferguson M. Long-term durability of minimal invasive posterior transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. Clinical Spine Surgery2011;24(5):288-96.

6. Santoni B, Hynes R, McGilvray K, Rodriguez-Canessa G, Lyons A, Henson M *et al.* Cortical bone trajectory for lumbar pedicle screws. The Spine Journal2009;9(5):366-73.

7. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. Spine2014;39(4):E240-E45.

8. Baluch DA, Patel AA, Lullo B, Havey RM, Voronov LI, Nguyen N-L *et al.* Effect of physiological loads on cortical and traditional pedicle screw fixation. Spine2014;39(22):E1297-E302.

9. Perez-Orribo L, Kalb S, Reyes PM, Chang SW, Crawford NR. Biomechanics of lumbar cortical screw–rod fixation versus pedicle screw–rod fixation with and without interbody support. Spine2013;38(8):635-41.

10. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al.* Incidence and Risk Factors of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone Trajectory Technique. Spine2016;41(14):E851-E56.

11. Gonchar I, Kotani Y, Matsumoto Y. Cortical bone trajectory versus percutaneous pedicle screw in minimally invasive posterior lumbar fusion. The Spine Journal2014;11(14):S114-S15.

12. Kasukawa Y, Miyakoshi N, Hongo M, Ishikawa Y, Kudo D, Shimada Y. Short-term results of transforaminal lumbar interbody fusion using pedicle screw with cortical bone trajectory compared with conventional trajectory. Asian spine journal2015;9(3):440-48.

13. Chin KR, Pencle FJ, Coombs AV, Elsharkawy M, Packer CF, Hothem EA *et al.* Clinical Outcomes With Midline Cortical Bone Trajectory Pedicle Screws Versus Traditional Pedicle Screws in Moving Lumbar Fusions From Hospitals to Outpatient Surgery Centers. Clinical Spine Surgery2016.

14. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj2013;346:e7586.

15. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed tomography. Clinical Spine Surgery2013;26(6):E248-E53.

16. Dixon J, Bird H. Reproducibility along a 10 cm vertical visual analogue scale. Annals of the Rheumatic Diseases1981;40(1):87-89.

17. Fairbank JC, Pynsent PB. The Oswestry disability index. Spine2000;25(22):2940-53.

18. Okuda S, Miyauchi A, Oda T, Haku T, Yamamoto T, Iwasaki M. Surgical complications of posterior lumbar interbody fusion with total facetectomy in 251 patients. Journal of Neurosurgery: Spine2006;4(4):304-09.

19. Sakaura H, Miwa T, Yamashita T, Kuroda Y, Ohwada T. Posterior lumbar interbody fusion with cortical bone trajectory screw fixation versus posterior lumbar interbody fusion using traditional

pedicle screw fixation for degenerative lumbar spondylolisthesis: a comparative study. Journal of Neurosurgery Spine2016:1.

20. Xuan J, Zhang D, Jin HM, Chen JX, Xu DL, Xu HM *et al.* Minimally invasive cortical bone trajectory screws placement via pedicle or pedicle rib unit in the lower thoracic spine: a cadaveric and radiographic study. European Spine Journal2016:1-9.

21. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed tomography. Journal of Spinal Disorders & Techniques2013;26(6):E248.

22. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. Spine2014;39(4):240-5.

23. Matsukawa K, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite element study. Journal of neurosurgery Spine2015;23(4):471.

Table 1: Time of data collection.

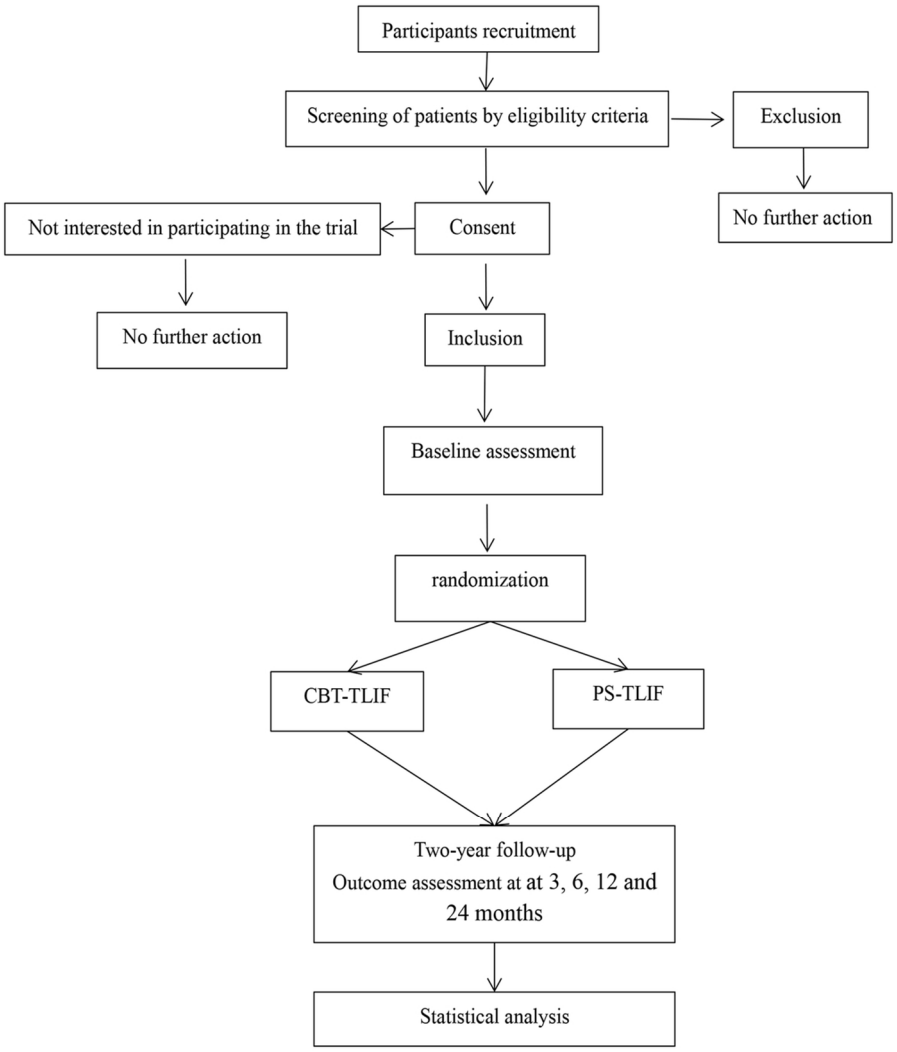
	Baseline	Operation	Follow-up				
Measures	Preoperation	duration	3 days	3 months	6 months	12 months	24 months
Screening for inclusion/exclusion criteria	√						
Informed consent	√						
Assignment to two group	√						
Baseline demographics	√						
operative time		√					
Blood loss		√					
Complications		√	√	√	√	√	√
FR							√

FJV		√				
SLR			√	√	√	√
VAS of back pain	√	√	√	√	√	√
VAS of leg pain	√	√	√	√	√	√
ODI	√	√	√	√	√	√
JOA	√	√	√	√	√	√

Note: FR: fusion rate; FJV: adjacent cranial facet joint violation; SLR: screw loosening rate; VAS of back pain: Visual Analog Scale of back pain; VAS of leg pain: Visual Analog Scale of leg pain; ODI: Oswestry Disability Index;JOA: Japanese Orthopedic Association.

Figure Legend

Figure 1 Flow chart showing the steps in participant recruitment, treatment and analysis.



Flow chart showing the steps in participant recruitment, treatment and analysis.

106x134mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___3_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___4_____
	2b	All items from the World Health Organization Trial Registration Data Set	___7_____
Protocol version	3	Date and version identifier	___2-3_____
Funding	4	Sources and types of financial, material, and other support	___1_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1_____
	5b	Name and contact information for the trial sponsor	___1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___1_____
	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)	___1_____

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	___5_____
	6b	Explanation for choice of comparators	__ 6_____
Objectives	7	Specific objectives or hypotheses	__6_____
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)	__7_____
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	__7_____
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)	_8-9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-10 and Figure 1
	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)	__9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__8、12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__10_____
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	__11_____
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)	__12 and table 1_

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__13_____
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	___8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__8_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__8_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__7 _____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__10-11_____

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	____11_____
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	____13-14_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____NA_____
	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)	___ NA _____
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	___12_____
	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	____12_____
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	____12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____12_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____15_____
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)	__15_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____15_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___15_____
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	___15_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___1_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____NA_____
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	____NA_____
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	__15_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____15_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____NA_____
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	_____NA____

*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

Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: a study protocol of randomized controlled trial

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Title: Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: a study protocol of randomized controlled trial

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Author contributors: ZHF helped to conceive and design the trial and wrote the manuscript. XBL helped to conceive of and design the trial. QT helped to conceive the trial and revised the manuscript. CGW and WHZ will recruit the patients and conduct the trial. HZ planned the statistical analysis. AMW and NFT will supervise the trial. YSW and WFN helped to conceive and design the study and critically revised the manuscript. All authors read and approved the final manuscript.

Data sharing statement: The full data set will be made available when this trial is completed and published. Application for the data to be released should be made in contact to WFN (principle investigator).

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Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: Study protocol of a randomized controlled trial

Abstract

Introduction: Transforaminal lumbar interbody fusion (TLIF) has been widely used in the treatment of lumbar degenerative disc disorders and shows favorable clinical results. Recently, cortical bone trajectory (CBT) has become a new trajectory for screw insertion in the lumbar spine. Several biomechanical studies have demonstrated that the CBT technique achieves screw purchase and strength greater than the traditional method. Currently, the available data on the clinical effectiveness of the two performed surgeries, TLIF with CBT screws (CBT-TLIF) and TLIF with traditional pedicle screws (PS-TLIF), are insufficient. This is the first randomized study to compare CBT-TLIF against traditional pedicle screw fixation and will provide recommendations for treating patients with lumbar degenerative disc disorders.

Methods and analysis: A blinded randomized controlled trial (blinding for the patient and statistician, rather than for the clinician and researcher) will be conducted. A total of 254 participants with lumbar disc degenerative disease who are candidates for TLIF surgery will be randomly allocated to either the CBT-TLIF group or the PS-TLIF group at a ratio of 1:1. The primary clinical outcome measures are: the incidence of adjacent cranial facet joint violation; fusion rate; and the screw loosening

rate. Secondary clinical outcome measures are: Visual Analog Scale (VAS) of back pain; VAS of leg pain; Oswestry Disability Index; operative time; intraoperative blood loss; and complications. These parameters will be evaluated on Day 3, and then at 1, 3, 6, 12, and 24 months postoperatively.

Ethics and dissemination: This study has been reviewed and approved by the Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (batch: 2017-03). The results will be presented in peer-reviewed journals and an international spine-related meeting after completion of the study.

Trial registration number: This trial was registered with the US National Institutes of Health Clinical Trials Registry: NCT03105167.

Keywords: transforaminal lumbar interbody fusion; randomized controlled trial; cortical bone trajectory; traditional pedicle screws

Strengths and limitations of this study:

- This trial is designed to have a feasible, comparative effectiveness trial design that has similarities to common clinical situations.
- This study is the first randomized controlled trial to compare CBT-TLIF against traditional pedicle screws.
- The size of the study sample limits the power of the observations.

Introduction

With an aging society, the incidence of lumbar disc degenerative diseases is increasing[1, 2]. Lumbar interbody fusion is the accepted method of surgery[3] if conservative treatment, including physiotherapy and adequate pain medication, of lumbar degenerative disease proves ineffective. These days, transforaminal lumbar interbody fusion (TLIF) is widely used in the treatment of lumbar degenerative disc disorders and shows favorable clinical results[4, 5].

In 2009, Santoni et al.[6] introduced a novel method of pedicle screw insertion termed the cortical bone trajectory (CBT) screw, which demonstrated a 30% increase in uniaxial yield pullout load relative to the traditional pedicle screw. In vivo, it was reported that the insertional torque using the CBT technique was about 1.7 times higher than that of the traditional technique[7]. Several other biomechanical studies have demonstrated the non-inferior mechanical properties of the CBT screw in cadaveric studies[8, 9]. Apart from the trajectory of the traditional pedicle screw, the trajectory of the cortical screw follows a caudocephalad path sagittally and a laterally directed path in the axial plane, which may maximize the thread contact with this higher-density bone surface. This pathway not only seeks to minimize the engagement of trabecular bone within the pedicle and allow for greater holding strength, but also minimizes the risk of medial pedicle breach.

CBT screw fixation has evolved as an optional method of spinal instrumentation that may overcome some of the limitations of traditional pedicle screw fixation. Matsukawa et al.[10] demonstrated that the incidence of adjacent cranial facet joint

violation (FJV) caused by CBT screw fixation was lower than that of pedicle screw fixation. FJV was reported to increase facet and intradiscal loading and lead to instability at the affected segment. Additionally, FJV was closely related to symptomatic adjacent segment disease, which may affect the fusion rate (FR) after lumbar interbody fusion surgery.

Single-level minimally invasive posterior lumbar fusion with CBT screws demonstrates a significantly lower rate of screw loosening, reduced loss of correction, and is less invasive compared to that with percutaneous pedicle screw fixation[11]. Kasukawa et al.[12] examined the surgical outcomes of TLIF with CBT screw fixation (CBT-TLIF) compared with TLIF using traditional pedicle screw fixation (PS-TLIF). They showed that CBT-TLIF resulted in reduced blood loss and a shorter operation than PS-TLIF, and showed similar efficacy in the postoperative rates of bone union, maintenance of lordotic angles, and accuracy of pedicle screw positions between the two groups. Chin et al.[13] reported that the Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) scores of patients were significantly improved after lumbar interbody fusion combined with cortical bone trajectory screws. However, the evidence was poor and limited by trials rated as having a high risk of bias and substantial clinical heterogeneity in controlled clinical trials (CCTs). Therefore, their conclusion could not prove that the efficacy of CBT-TLIF was better than that of PS-TLIF.

Compared with CCTs, randomized controlled trials (RCTs) have the advantage of controlling all possible variables because of the random sequence generation, in

which confounding and bias may be more problematic. High-quality RCTs are generally considered to be the gold standard for studying the effectiveness of an intervention. To the best of our knowledge, no randomized controlled study of the clinical outcomes of CBT-TLIF vs. PS-TLIF has been performed. In this study, we will conduct a RCT to compare CBT-TLIF vs. traditional pedicle screw fixation.

Methods and analysis

This study has been reviewed and approved by the Institutional Ethics Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants will be asked to sign an informed consent form. The study protocol has been registered at the US National Institutes of Health Clinical Trials Registry: NCT03105167. The protocol was developed by following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT)[14]. A chart of the trial design is provided in Figure 1.

Participants

This study is a parallel group RCT conducted at the Orthopedic Hospital, Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University.

Randomization and blinding

Participants will be equally randomized to either the CBT-TLIF group or the PS-TLIF group based on a permuted blocks randomization scheme. Using a block size of 4 in a scheduled computer-generated randomization program, the final group assignments will be sealed in opaque envelops. In order to ensure the proper management of the randomisation procedure, the sequence numbers will be marked on the opaque envelope, and the group assignment will be sealed inside. All envelopes will be numbered sequentially. The envelops will be delivered according to the patients' sequence numbers, and the surgeon will be informed of the random numbers and group assignments by either telephone or email. Patients will be kept blinded for the allocated treatment until the last questionnaires have been completed. At the end of the follow-up period, the blind can be lifted at the patients' request. In addition, the statistician will also be blinded.

Inclusion criteria

1. Age of at least 18 years.
2. Chronic lower back pain alone or combined with neurological symptoms of the lower extremities after receiving failed conservative treatment for a period of more than 3 months.
3. Indication for monosegmental TLIF due to degenerative disc disease or instability (including spondylolisthesis, foraminal stenosis, spinal stenosis lumbar disc herniation, and painful disc degeneration).

Exclusion criteria

1. Spinal scoliosis with a Cobb angle of more than 10° in the index level.
2. Patients with prior failed fusion at the same level.
3. Pregnancy.
4. Active infection or prior infection at the surgical site.
5. Planned (e)migration abroad within 2 years after inclusion.
6. Metabolic bone disease such as osteomalacia or Paget's disease.
7. Spondylolisthesis according to Meyerding grades III and IV.
8. Therapy with systemic corticosteroids or immunosuppressants.

Interventions

CBT-TLIF group

After the preventive use of antibiotics, patients were placed under general anesthesia in the prone position. A small skin incision was made at the fused segment and an entry point to allow insertion of the CBT screws was drilled in the junction of the center of the superior articular process and 1 mm inferior to the inferior border of the transverse process according to Matsukawa et al.[15]. A straight probe was then used to create a trajectory for the CBT screws from the entry point to the opposite corner of the pedicle and vertebral body under anteroposterior fluoroscopic guidance. Screws were placed bilaterally, targeting half of the vertebral body. Unilateral

facetectomy was performed to gain access to the intervertebral disc, followed by discectomy. The endplate cartilage was prepared to provide a host bed of bleeding subchrondral bone for the placement of the cage. The structure of the interbody cage was determined by a trial cage and fluoroscopy. The definitive cage was then filled with autologous bone or allograft and tamped into place and its position was checked radiologically. After placement of the interbody cage, the remainder of the disc space was filled with autologous bone obtained from the decompression. A titanium rod interconnected the screws on either side. The spreader was removed and the wound thoroughly irrigated and closed in several layers without suction drainage.

PS-TLIF group

After the preventive use of antibiotics, patients were placed under general anesthesia in the prone position. A posterior midline incision of about 6 cm was performed at the level of interest under fluoroscopic guidance. Pedicle screws were inserted freehand into the vertebral body, and the inferior and superior articular processes and part of the lamina were removed by an osteotome. The ligamentum flavum was then removed to expose the lateral border of the ipsilateral nerve root. After decompression of the neural structures, a thorough discectomy and endplate preparation were performed followed by transforaminal insertion of an intervertebral tantalum mesh cage packed with autograft materials within the disc space. In both CBT-TLIF and PS-TLIF, prior to cage insertion, the morselized bone graft from the

facetectomy and laminectomy was grafted into the prepared disc space. Compression was achieved across the pedicle screws and rod with place screws and optimal placement was confirmed by intraoperative fluoroscopy.

Outcome measurements

Primary outcomes:

1. The incidence of adjacent cranial FJV. FJV will be evaluated by using two-dimensional computed Tomographic reconstruction at 3 days, and 6 months, and at 1 and 2 years postoperatively.
2. Fusion rate (FR). FR will be evaluated by using two-dimensional computed Tomographic reconstruction at 6 months postoperatively. If not fused, it will be evaluated at 1 year postoperatively once again.
3. Screw loosening rate (SLR). SLR will be evaluated at 3 and 6 months, and at 1 and 2 years postoperatively.

Secondary outcomes:

1. The intensity of back and lower limb pain during rest and daily activities during follow-up will be assessed by the VAS of back pain and VAS of leg pain[16]. The scores of VAS of back pain and VAS of leg pain will be recorded preoperatively, at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively.

2. The ODI will be recorded both preoperatively and postoperatively[17]. The ODI scores will be recorded preoperatively, at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively. The ODI assesses back pain-related disability. It contains 10 questions about daily life, including measures of pain intensity, personal care, lifting, walking, sitting, standing, sleeping, social life, and traveling. Each question is rated on a scale of 0–5, with a higher score indicating a more severe pain-related disability.
3. Japanese Orthopedic Association (JOA) scores will be recorded preoperatively, at 3 days, at1, 3 and 6 months, and at 1 and 2 years postoperatively. Functional improvement is expressed by the rate of recovery of the JOA score[18].
4. The parameters of intervertebral height (including anterior and posterior height of intervertebral), intervertebral foramen height, and Kyphosis anlge will be measured in X-ray fluorescence preoperatively, at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively.
5. Operative time, intraoperative blood loss.
6. Complications including dural tear, postoperative infection, deep venous thrombosis, hematoma, hardware failure, neurological deficits, and any other direct and indirect surgical complications will be recorded.

Table 1 presents the data collection times.

Baseline demographics

Sex, age, body mass index, smoking habit, diagnosis, level, and occurrence of

diabetes will be recorded. Perioperative morbidity will be correlated to the use of antibiotics and duration of surgery.

Follow-up

Follow-up will be conducted at 3 days, and at 1, 3, 6, 12, and 24 months postoperatively.

Monitoring

All investigators who have completed good clinical practice training will independently collect the data and assess the clinical outcomes of the treatments. Data and safety monitoring will be conducted periodically during the study. Only the principal investigator (WFN) will have access to the final trial data set. All paper and electronic versions of the case reports will be stored for 10 years in locked filing cabinets in areas with restricted access.

Sample size calculation

As there has been no previous similar trial that has used our RCT design, we performed a power analysis to assess the required sample size to show safety with a

power (1-b) of 0.8 and α error of 0.05. Based on the related literature[19], the proportion of the control group was 11.8%, and the proportion of intervention group was 27%. We performed a two independent proportions power analysis on PASS (Power Analysis and Sample Size), and the results was 106. We propose to enroll 254 participants (127 randomized to each arm) and allow for a dropout rate of 20% for an effective sample size of 212.

Statistical analysis

All data will be analyzed using the SPSS 19.0 software. Differences in the operative time and intraoperative blood loss, FR, FJV, and other complications between the CBT-TLIF and PS-TLIF groups will be analyzed by two independent-samples *t*-tests with an α of 0.05. Preoperative VAS and ODI scores, and scores taken immediately post-operation, and at postoperative 3, 6, and 24 months, will be analyzed by a repeated-measures ANOVA. Changes in the data between different follow-up time points and the baseline will also be calculated and the changes in data between the CBT-TLIF and PS-TLIF groups will be assessed by two independent-samples *t*-tests.

Discussion

Cortical bone trajectory screw fixation is reported as a minimally invasive technique[20, 21], and biomechanical comparisons with pedicle screw fixation have noted its biomechanical superiority[22, 23]. This paper describes the rationale and

protocol for conducting an RCT in China that will investigate the efficacy of CBT screws with TLIF in treating lumbar disc degenerative diseases such as lumbar spinal canal stenosis and lumbar disc herniation that require spinal interbody fusion surgery. In this trial, we designed a PS-TLIF group as a controlled comparison group to identify the clinical outcomes of TLIF with cortical bone trajectory screw fixation. The demand for spinal interbody fusion surgery has risen steeply over the last ten years and is expected to increase even further in the near future. It is hypothesized that CBT-TLIF, compared to PS-TLIF, is superior in reducing disability and thus has a better clinical outcome.

This study is the first RCT to compare TLIF with CBT against traditional pedicle screws. An RCT has the advantage of controlling all confounding factors due to random sequence generation, as opposed to observational studies where confounding factors and bias may be more problematic. High-quality RCTs are generally regarded as the gold standard for studying the effectiveness of an intervention.

Randomized trials that compare surgery with non-surgical treatments have several features that are distinctly different from drug trials and can lead to serious limitations. Moreover, compared to drug trials, surgery has many irreversible features.

In the case that our hypothesis is confirmed, our results will have a practical value in the planning and development of treatment options in spinal interbody fusion surgery. We anticipate that the results will provide more reliable evidence and clarify the value of CBT with TLIF as a treatment for patients with lumbar disc degenerative diseases.

Acknowledgement:

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/tDbZkH

Ethics and dissemination:

The study had been reviewed and approved by the ethics committee of the Second affiliated hospital of the Wenzhou Medical University, Wenzhou, China(batch：2017-03). The procedure will be performed following the principles described in the Declaration of Helsinki. All of participants will be signed the informed consent. The protocol has been registered in US National Institutes of Health Clinical Trials Registry: NCT03105167. We will share individual patient data (IPD) within 2 years after the trial complete, and the original data is collected by clinical recording formula (both paper and electronic version). The results will be presented in peer-reviewed journals and related website (https://clinicaltrials.gov/) within 2 years after the last operation.

Reference

1. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG *et al.* Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy. Journal of Neurosurgery Spine2005;2(6):673-78.

2. Braydabruno M, Tibiletti M, Ito K, Fairbank J, Galbusera F, Zerbi A *et al.* Advances in the diagnosis of degenerated lumbar discs and their possible clinical application. European Spine Journal2014;23(3):315-23.

3. Omidikashani F, Hasankhani EG, Ashjazadeh A. Lumbar Spinal Stenosis: Who Should Be Fused? An Updated Review. Asian Spine Journal2014;8(4):521.

4. Harms JG, Jeszenszky D. Die posteriore, lumbale, interkorporelle Fusion in unilateraler transforaminaler Technik. Operative Orthopädie und Traumatologie1998;10(2):90-102.

5. Rouben D, Casnellie M, Ferguson M. Long-term durability of minimal invasive posterior transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. Clinical Spine Surgery2011;24(5):288-96.

6. Santoni B, Hynes R, McGilvray K, Rodriguez-Canessa G, Lyons A, Henson M *et al.* Cortical bone trajectory for lumbar pedicle screws. The Spine Journal2009;9(5):366-73.

7. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. Spine2014;39(4):E240-E45.

8. Baluch DA, Patel AA, Lullo B, Havey RM, Voronov LI, Nguyen N-L *et al.* Effect of physiological loads on cortical and traditional pedicle screw fixation. Spine2014;39(22):E1297-E302.

9. Perez-Orribo L, Kalb S, Reyes PM, Chang SW, Crawford NR. Biomechanics of lumbar cortical screw–rod fixation versus pedicle screw–rod fixation with and without interbody support. Spine2013;38(8):635-41.

10. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al.* Incidence and Risk Factors of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone Trajectory Technique. Spine2016;41(14):E851-E56.

11. Gonchar I, Kotani Y, Matsumoto Y. Cortical bone trajectory versus percutaneous pedicle screw in minimally invasive posterior lumbar fusion. The Spine Journal2014;11(14):S114-S15.

12. Kasukawa Y, Miyakoshi N, Hongo M, Ishikawa Y, Kudo D, Shimada Y. Short-term results of transforaminal lumbar interbody fusion using pedicle screw with cortical bone trajectory compared with conventional trajectory. Asian spine journal2015;9(3):440-48.

13. Chin KR, Pencle FJ, Coombs AV, Elsharkawy M, Packer CF, Hothem EA *et al.* Clinical Outcomes With Midline Cortical Bone Trajectory Pedicle Screws Versus Traditional Pedicle Screws in Moving Lumbar Fusions From Hospitals to Outpatient Surgery Centers. Clinical Spine Surgery2016.

14. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj2013;346:e7586.

15. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed tomography. Clinical Spine Surgery2013;26(6):E248-E53.

16. Dixon J, Bird H. Reproducibility along a 10 cm vertical visual analogue scale. Annals of the Rheumatic Diseases1981;40(1):87-89.

17. Fairbank JC, Pynsent PB. The Oswestry disability index. Spine2000;25(22):2940-53.

18. Okuda S, Miyauchi A, Oda T, Haku T, Yamamoto T, Iwasaki M. Surgical complications of posterior lumbar interbody fusion with total facetectomy in 251 patients. Journal of Neurosurgery: Spine2006;4(4):304-09.

19. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al.* Incidence and Risk Factors of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone Trajectory Technique. Spine2016;41(14):E851.

20. Xuan J, Zhang D, Jin HM, Chen JX, Xu DL, Xu HM *et al.* Minimally invasive cortical bone trajectory screws placement via pedicle or pedicle rib unit in the lower thoracic spine: a cadaveric and radiographic study. European Spine Journal2016:1-9.

21. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed tomography. Journal of Spinal Disorders & Techniques2013;26(6):E248.

22. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. Spine2014;39(4):240-5.

23. Matsukawa K, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite element study. Journal of neurosurgery Spine2015;23(4):471.

Table 1: Time of data collection.

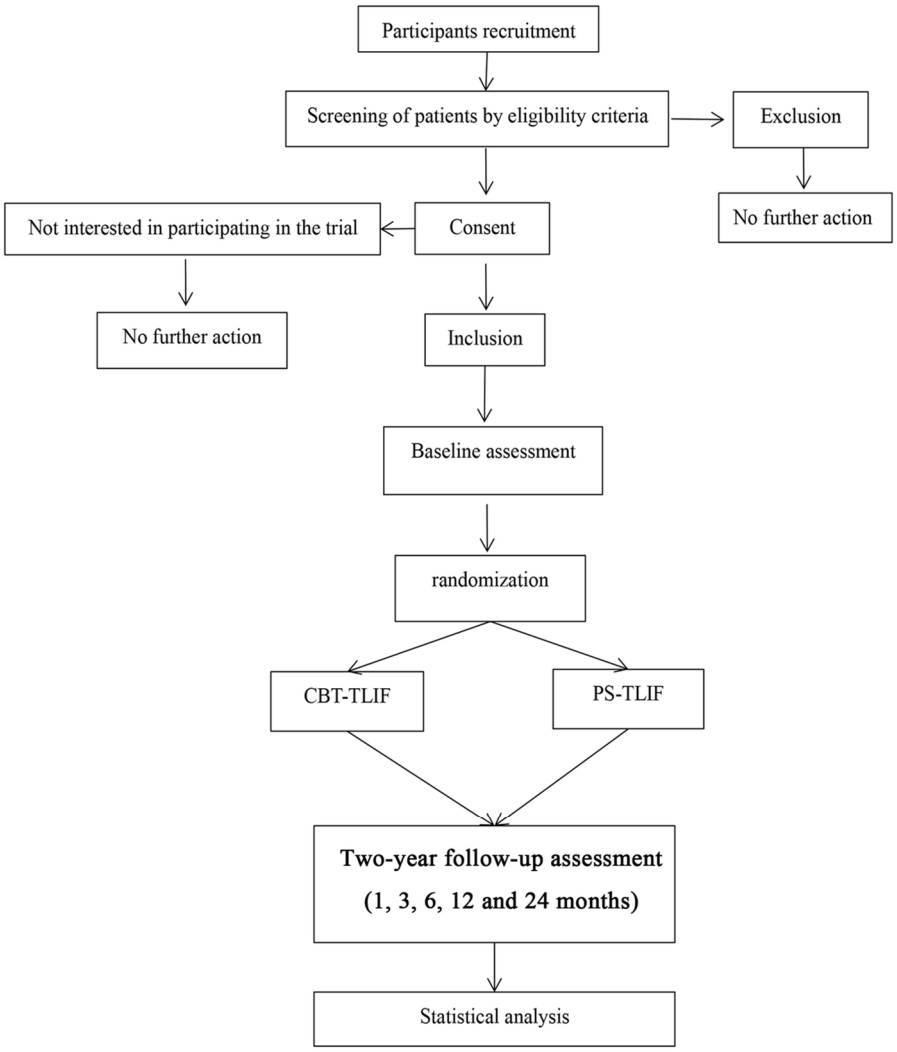
	Baseline	Operation	Follow-up					
Measures	Preoperation	duration	3 days	1 months	3 months	6 months	12 months	24 months
Screening for inclusion/exclusion criteria	√							
Informed consent	√							
Assignment to two group	√							
Baseline demographics	√							
operative time		√						
Blood loss		√						
Complications		√	√	√	√	√	√	√
FR						√	X or √	

FJV		√			√	√	√
SLR			√	√	√	√	√
VAS of back pain	√	√	√	√	√	√	√
VAS of leg pain	√	√	√	√	√	√	√
ODI	√	√	√	√	√	√	√
JOA	√	√	√	√	√	√	√
X-ray	√	√	√	√	√	√	√

Note: FR: fusion rate; FJV: adjacent cranial facet joint violation; SLR: screw loosening rate; VAS of back pain: Visual Analog Scale of back pain; VAS of leg pain: Visual Analog Scale of leg pain; ODI: Oswestry Disability Index;JOA: Japanese Orthopedic Association.

Figure Legend

Figure 1 Flow chart showing the steps in participant recruitment, treatment and analysis.



Flow chart showing the steps in participant recruitment, treatment and analysis.

106x134mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___3_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___4_____
	2b	All items from the World Health Organization Trial Registration Data Set	___7_____
Protocol version	3	Date and version identifier	___2-3_____
Funding	4	Sources and types of financial, material, and other support	___1_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1_____
	5b	Name and contact information for the trial sponsor	___1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___1_____
	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)	___1_____

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	___5_____
	6b	Explanation for choice of comparators	__ 6_____
Objectives	7	Specific objectives or hypotheses	__6_____
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)	__7_____

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	__7_____
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)	_8-9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-10 and Figure 1
	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)	__9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__8、12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__10_____
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	__11_____
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)	__12 and table 1_

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__13_____
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	___8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__8_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__8_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__7 _____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__10-11_____

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	____11_____
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	____13-14_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____NA_____
	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)	___ NA _____
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	___12_____
	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	____12_____
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	____12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____12_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____15_____
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)	__15_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____15_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___15_____
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	___15_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___1_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____NA_____
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	____NA_____
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	__15_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____15_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____NA_____
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	_____NA____

*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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Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: a study protocol of randomized controlled trial

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Title: Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: a study protocol of randomized controlled trial

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Author contributors: ZHF helped to conceive and design the trial and wrote the manuscript. XBL helped to conceive of and design the trial. QT helped to conceive the trial and revised the manuscript. CGW and WHZ will recruit the patients and conduct the trial. HZ planned the statistical analysis. AMW and NFT will supervise the trial. YSW and WFN helped to conceive and design the study and critically revised the manuscript. All authors read and approved the final manuscript.

Data sharing statement: The full data set will be made available when this trial is completed and published. Application for the data to be released should be made in contact to WFN (principle investigator).

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Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs. traditional pedicle screws fixation: Study protocol of a randomized controlled trial

Abstract

Introduction: Transforaminal lumbar interbody fusion (TLIF) has been widely used in the treatment of lumbar degenerative disc disorders and shows favorable clinical results. Recently, cortical bone trajectory (CBT) has become a new trajectory for screw insertion in the lumbar spine. Several biomechanical studies have demonstrated that the CBT technique achieves screw purchase and strength greater than the traditional method. Currently, the available data on the clinical effectiveness of the two performed surgeries, TLIF with CBT screws (CBT-TLIF) and TLIF with traditional pedicle screws (PS-TLIF), are insufficient. This is the first randomized study to compare CBT-TLIF against traditional pedicle screw fixation and will provide recommendations for treating patients with lumbar degenerative disc disorders.

Methods and analysis: A blinded randomized controlled trial (blinding for the patient and statistician, rather than for the clinician and researcher) will be conducted. A total of 254 participants with lumbar disc degenerative disease who are candidates for TLIF surgery will be randomly allocated to either the CBT-TLIF group or the PS-TLIF group at a ratio of 1:1. The primary clinical outcome measures are: the incidence of adjacent cranial facet joint violation; fusion rate; and the screw loosening

rate. Secondary clinical outcome measures are: Visual Analog Scale (VAS) of back pain; VAS of leg pain; Oswestry Disability Index; operative time; intraoperative blood loss; and complications. These parameters will be evaluated on Day 3, and then at 1, 3, 6, 12, and 24 months postoperatively.

Ethics and dissemination: This study has been reviewed and approved by the Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (batch: 2017-03). The results will be presented in peer-reviewed journals and an international spine-related meeting after completion of the study.

Trial registration number: This trial was registered with the US National Institutes of Health Clinical Trials Registry: NCT03105167.

Keywords: transforaminal lumbar interbody fusion; randomized controlled trial; cortical bone trajectory; traditional pedicle screws

Strengths and limitations of this study:

- This trial is designed to have a feasible, comparative effectiveness trial design that has similarities to common clinical situations.
- This study is the first randomized controlled trial to compare CBT-TLIF against traditional pedicle screws.
- The size of the study sample limits the power of the observations.

Introduction

With an aging society, the incidence of lumbar disc degenerative diseases is increasing[1, 2]. Lumbar interbody fusion is the accepted method of surgery[3] if conservative treatment, including physiotherapy and adequate pain medication, of lumbar degenerative disease proves ineffective. These days, transforaminal lumbar interbody fusion (TLIF) is widely used in the treatment of lumbar degenerative disc disorders and shows favorable clinical results[4, 5].

In 2009, Santoni et al.[6] introduced a novel method of pedicle screw insertion termed the cortical bone trajectory (CBT) screw, which demonstrated a 30% increase in uniaxial yield pullout load relative to the traditional pedicle screw. In vivo, it was reported that the insertional torque using the CBT technique was about 1.7 times higher than that of the traditional technique[7]. Several other biomechanical studies have demonstrated the non-inferior mechanical properties of the CBT screw in cadaveric studies[8, 9]. Apart from the trajectory of the traditional pedicle screw, the trajectory of the cortical screw follows a caudocephalad path sagittally and a laterally directed path in the axial plane, which may maximize the thread contact with this higher-density bone surface. This pathway not only seeks to minimize the engagement of trabecular bone within the pedicle and allow for greater holding strength, but also minimizes the risk of medial pedicle breach.

CBT screw fixation has evolved as an optional method of spinal instrumentation that may overcome some of the limitations of traditional pedicle screw fixation. Matsukawa et al.[10] demonstrated that the incidence of adjacent cranial facet joint

violation (FJV) caused by CBT screw fixation was lower than that of pedicle screw fixation. FJV was reported to increase facet and intradiscal loading and lead to instability at the affected segment. Additionally, FJV was closely related to symptomatic adjacent segment disease, which may affect the fusion rate (FR) after lumbar interbody fusion surgery.

Single-level minimally invasive posterior lumbar fusion with CBT screws demonstrates a significantly lower rate of screw loosening, reduced loss of correction, and is less invasive compared to that with percutaneous pedicle screw fixation[11]. Kasukawa et al.[12] examined the surgical outcomes of TLIF with CBT screw fixation (CBT-TLIF) compared with TLIF using traditional pedicle screw fixation (PS-TLIF). They showed that CBT-TLIF resulted in reduced blood loss and a shorter operation than PS-TLIF, and showed similar efficacy in the postoperative rates of bone union, maintenance of lordotic angles, and accuracy of pedicle screw positions between the two groups. Chin et al.[13] reported that the Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) scores of patients were significantly improved after lumbar interbody fusion combined with cortical bone trajectory screws. However, the evidence was poor and limited by trials rated as having a high risk of bias and substantial clinical heterogeneity in controlled clinical trials (CCTs). Therefore, their conclusion could not prove that the efficacy of CBT-TLIF was better than that of PS-TLIF.

Compared with CCTs, randomized controlled trials (RCTs) have the advantage of controlling all possible variables because of the random sequence generation, in

which confounding and bias may be more problematic. High-quality RCTs are generally considered to be the gold standard for studying the effectiveness of an intervention. To the best of our knowledge, no randomized controlled study of the clinical outcomes of CBT-TLIF vs. PS-TLIF has been performed. In this study, we will conduct a RCT to compare CBT-TLIF vs. traditional pedicle screw fixation.

Methods and analysis

This study has been reviewed and approved by the Institutional Ethics Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants will be asked to sign an informed consent form. The study protocol has been registered at the US National Institutes of Health Clinical Trials Registry: NCT03105167. The protocol was developed by following the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT)[14]. A chart of the trial design is provided in Figure 1.

Participants

This study is a parallel group RCT conducted at the Orthopedic Hospital, Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University.

Randomization and blinding

Participants will be equally randomized to either the CBT-TLIF group or the PS-TLIF group based on a permuted blocks randomization scheme. Using a block size of 4 in a scheduled computer-generated randomization program, the final group assignments will be sealed in opaque envelops. In order to ensure the proper management of the randomisation procedure, the sequence numbers will be marked on the opaque envelope, and the group assignment will be sealed inside. All envelopes will be numbered sequentially. The envelops will be delivered according to the patients' sequence numbers, and the surgeon will be informed of the random numbers and group assignments by either telephone or email. Patients will be kept blinded for the allocated treatment until the last questionnaires have been completed. At the end of the follow-up period, the blind can be lifted at the patients' request. In addition, the statistician will also be blinded.

Inclusion criteria

1. Age of at least 18 years.
2. Chronic lower back pain alone or combined with neurological symptoms of the lower extremities after receiving failed conservative treatment for a period of more than 3 months.
3. Indication for monosegmental TLIF due to degenerative disc disease or instability (including spondylolisthesis, foraminal stenosis, spinal stenosis lumbar disc herniation, and painful disc degeneration).

Exclusion criteria

1. Spinal scoliosis with a Cobb angle of more than 10° in the index level.
2. Patients with prior failed fusion at the same level.
3. Pregnancy.
4. Active infection or prior infection at the surgical site.
5. Planned (e)migration abroad within 2 years after inclusion.
6. Metabolic bone disease such as osteomalacia or Paget's disease.
7. Spondylolisthesis according to Meyerding grades III and IV.
8. Therapy with systemic corticosteroids or immunosuppressants.

Interventions

CBT-TLIF group

After the preventive use of antibiotics, patients were placed under general anesthesia in the prone position. A small skin incision was made at the fused segment and an entry point to allow insertion of the CBT screws was drilled in the junction of the center of the superior articular process and 1 mm inferior to the inferior border of the transverse process according to Matsukawa et al.[15]. A straight probe was then used to create a trajectory for the CBT screws from the entry point to the opposite corner of the pedicle and vertebral body under anteroposterior fluoroscopic guidance. Screws were placed bilaterally, targeting half of the vertebral body. Unilateral

facetectomy was performed to gain access to the intervertebral disc, followed by discectomy. The endplate cartilage was prepared to provide a host bed of bleeding subchrondral bone for the placement of the cage. The structure of the interbody cage was determined by a trial cage and fluoroscopy. The definitive cage was then filled with autologous bone or allograft and tamped into place and its position was checked radiologically. After placement of the interbody cage, the remainder of the disc space was filled with autologous bone obtained from the decompression. A titanium rod interconnected the screws on either side. The spreader was removed and the wound thoroughly irrigated and closed in several layers without suction drainage.

PS-TLIF group

After the preventive use of antibiotics, patients were placed under general anesthesia in the prone position. A posterior midline incision of about 6 cm was performed at the level of interest under fluoroscopic guidance. Pedicle screws were inserted freehand into the vertebral body, and the inferior and superior articular processes and part of the lamina were removed by an osteotome. The ligamentum flavum was then removed to expose the lateral border of the ipsilateral nerve root. After decompression of the neural structures, a thorough discectomy and endplate preparation were performed followed by transforaminal insertion of an intervertebral tantalum mesh cage packed with autograft materials within the disc space. In both CBT-TLIF and PS-TLIF, prior to cage insertion, the morselized bone graft from the

facetectomy and laminectomy was grafted into the prepared disc space. Compression was achieved across the pedicle screws and rod with place screws and optimal placement was confirmed by intraoperative fluoroscopy.

Outcome measurements

Primary outcomes:

1. The incidence of adjacent cranial FJV. FJV will be evaluated by using two-dimensional computed Tomographic reconstruction at 3 days, and 6 months, and at 1 and 2 years postoperatively.
2. Fusion rate (FR). FR will be evaluated by using two-dimensional computed Tomographic reconstruction at 6 months postoperatively. If not fused, it will be evaluated at 1 year postoperatively once again.
3. Screw loosening rate (SLR). SLR will be evaluated at 3 and 6 months, and at 1 and 2 years postoperatively.

Secondary outcomes:

1. The intensity of back and lower limb pain during rest and daily activities during follow-up will be assessed by the VAS of back pain and VAS of leg pain[16]. The scores of VAS of back pain and VAS of leg pain will be recorded preoperatively, at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively.

2. The ODI will be recorded both preoperatively and postoperatively[17]. The ODI scores will be recorded preoperatively, at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively. The ODI assesses back pain-related disability. It contains 10 questions about daily life, including measures of pain intensity, personal care, lifting, walking, sitting, standing, sleeping, social life, and traveling. Each question is rated on a scale of 0–5, with a higher score indicating a more severe pain-related disability.
3. Japanese Orthopedic Association (JOA) scores will be recorded preoperatively, at 3 days, at1, 3 and 6 months, and at 1 and 2 years postoperatively. Functional improvement is expressed by the rate of recovery of the JOA score[18].
4. The parameters of intervertebral height (including anterior and posterior height of intervertebral), intervertebral foramen height, and Kyphosis anlge will be measured in X-ray fluorescence preoperatively, at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively.
5. Operative time, intraoperative blood loss.
6. Complications including dural tear, postoperative infection, deep venous thrombosis, hematoma, hardware failure, neurological deficits, and any other direct and indirect surgical complications will be recorded.

Table 1 presents the data collection times.

Baseline demographics

Sex, age, body mass index, smoking habit, diagnosis, level, and occurrence of

diabetes will be recorded. Perioperative morbidity will be correlated to the use of antibiotics and duration of surgery.

Follow-up

Follow-up will be conducted at 3 days, and at 1, 3, 6, 12, and 24 months postoperatively.

Monitoring

All investigators who have completed good clinical practice training will independently collect the data and assess the clinical outcomes of the treatments. Data and safety monitoring will be conducted periodically during the study. Only the principal investigator (WFN) will have access to the final trial data set. All paper and electronic versions of the case reports will be stored for 10 years in locked filing cabinets in areas with restricted access.

Sample size calculation

As there has been no previous similar trial that has used our RCT design, we performed a power analysis to assess the required sample size to show safety with a

power (1-b) of 0.8 and α error of 0.05. Based on the related literature[19], the proportion of the control group was 11.8%, and the proportion of intervention group was 27%. We performed a two independent proportions power analysis on PASS (Power Analysis and Sample Size), and the results was 106. We propose to enroll 254 participants (127 randomized to each arm) and allow for a dropout rate of 20% for an effective sample size of 212.

Statistical analysis

All data will be analyzed using the SPSS 19.0 software. Differences in the operative time and intraoperative blood loss, FR, FJV, and other complications between the CBT-TLIF and PS-TLIF groups will be analyzed by two independent-samples *t*-tests with an α of 0.05. Preoperative VAS and ODI scores, and scores taken immediately post-operation, and at postoperative 1, 3, 6, and 24 months, will be analyzed by a repeated-measures ANOVA. Changes in the data between different follow-up time points and the baseline will also be calculated and the changes in data between the CBT-TLIF and PS-TLIF groups will be assessed by two independent-samples *t*-tests.

Discussion

Cortical bone trajectory screw fixation is reported as a minimally invasive technique[20, 21], and biomechanical comparisons with pedicle screw fixation have noted its biomechanical superiority[22, 23]. This paper describes the rationale and

protocol for conducting an RCT in China that will investigate the efficacy of CBT screws with TLIF in treating lumbar disc degenerative diseases such as lumbar spinal canal stenosis and lumbar disc herniation that require spinal interbody fusion surgery. In this trial, we designed a PS-TLIF group as a controlled comparison group to identify the clinical outcomes of TLIF with cortical bone trajectory screw fixation. The demand for spinal interbody fusion surgery has risen steeply over the last ten years and is expected to increase even further in the near future. It is hypothesized that CBT-TLIF, compared to PS-TLIF, is superior in reducing disability and thus has a better clinical outcome.

This study is the first RCT to compare TLIF with CBT against traditional pedicle screws. An RCT has the advantage of controlling all confounding factors due to random sequence generation, as opposed to observational studies where confounding factors and bias may be more problematic. High-quality RCTs are generally regarded as the gold standard for studying the effectiveness of an intervention.

Randomized trials that compare surgery with non-surgical treatments have several features that are distinctly different from drug trials and can lead to serious limitations. Moreover, compared to drug trials, surgery has many irreversible features.

In the case that our hypothesis is confirmed, our results will have a practical value in the planning and development of treatment options in spinal interbody fusion surgery. We anticipate that the results will provide more reliable evidence and clarify the value of CBT with TLIF as a treatment for patients with lumbar disc degenerative diseases.

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The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/tDbZkH

Ethics and dissemination:

The study had been reviewed and approved by the ethics committee of the Second affiliated hospital of the Wenzhou Medical University, Wenzhou, China(batch：2017-03). The procedure will be performed following the principles described in the Declaration of Helsinki. All of participants or their authorised surrogates will be signed the informed consent. Participants' questions will be answered by researchers. Researchers will obtain the informed consent form from potential trial participants or authorised surrogates. The protocol has been registered in US National Institutes of Health Clinical Trials Registry: NCT03105167. We will share individual patient data (IPD) within 2 years after the trial complete, and the original data is collected by clinical recording formula (both paper and electronic version). The results will be presented in peer-reviewed journals and related website (https://clinicaltrials.gov/) within 2 years after the last operation.

Reference

1. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG *et al.* Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy. Journal of Neurosurgery Spine2005;2(6):673-78.
2. Braydabruno M, Tibiletti M, Ito K, Fairbank J, Galbusera F, Zerbi A *et al.* Advances in the diagnosis of degenerated lumbar discs and their possible clinical application. European Spine Journal2014;23(3):315-23.
3. Omidikashani F, Hasankhani EG, Ashjazadeh A. Lumbar Spinal Stenosis: Who Should Be Fused? An Updated Review. Asian Spine Journal2014;8(4):521.
4. Harms JG, Jeszenszky D. Die posteriore, lumbale, interkorporelle Fusion in unilateraler transforaminaler Technik. Operative Orthopädie und Traumatologie1998;10(2):90-102.
5. Rouben D, Casnellie M, Ferguson M. Long-term durability of minimal invasive posterior transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. Clinical Spine Surgery2011;24(5):288-96.
6. Santoni B, Hynes R, McGilvray K, Rodriguez-Canessa G, Lyons A, Henson M *et al.* Cortical bone trajectory for lumbar pedicle screws. The Spine Journal2009;9(5):366-73.
7. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. Spine2014;39(4):E240-E45.
8. Baluch DA, Patel AA, Lullo B, Havey RM, Voronov LI, Nguyen N-L *et al.* Effect of physiological loads on cortical and traditional pedicle screw fixation. Spine2014;39(22):E1297-E302.
9. Perez-Orribo L, Kalb S, Reyes PM, Chang SW, Crawford NR. Biomechanics of lumbar cortical screw–rod fixation versus pedicle screw–rod fixation with and without interbody support. Spine2013;38(8):635-41.
10. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al.* Incidence and Risk Factors of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone Trajectory Technique. Spine2016;41(14):E851-E56.
11. Gonchar I, Kotani Y, Matsumoto Y. Cortical bone trajectory versus percutaneous pedicle screw in minimally invasive posterior lumbar fusion. The Spine Journal2014;11(14):S114-S15.
12. Kasukawa Y, Miyakoshi N, Hongo M, Ishikawa Y, Kudo D, Shimada Y. Short-term results of transforaminal lumbar interbody fusion using pedicle screw with cortical bone trajectory compared with conventional trajectory. Asian spine journal2015;9(3):440-48.
13. Chin KR, Pencle FJ, Coombs AV, Elsharkawy M, Packer CF, Hothem EA *et al.* Clinical Outcomes With Midline Cortical Bone Trajectory Pedicle Screws Versus Traditional Pedicle Screws in Moving Lumbar Fusions From Hospitals to Outpatient Surgery Centers. Clinical Spine Surgery2016.
14. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj2013;346:e7586.
15. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed tomography. Clinical Spine Surgery2013;26(6):E248-E53.
16. Dixon J, Bird H. Reproducibility along a 10 cm vertical visual analogue scale. Annals of the Rheumatic Diseases1981;40(1):87-89.
17. Fairbank JC, Pynsent PB. The Oswestry disability index. Spine2000;25(22):2940-53.
18. Okuda S, Miyauchi A, Oda T, Haku T, Yamamoto T, Iwasaki M. Surgical complications of posterior lumbar interbody fusion with total facetectomy in 251 patients. Journal of Neurosurgery: Spine2006;4(4):304-09.

19. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al.* Incidence and Risk Factors of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone Trajectory Technique. Spine2016;41(14):E851.

20. Xuan J, Zhang D, Jin HM, Chen JX, Xu DL, Xu HM *et al.* Minimally invasive cortical bone trajectory screws placement via pedicle or pedicle rib unit in the lower thoracic spine: a cadaveric and radiographic study. European Spine Journal2016:1-9.

21. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed tomography. Journal of Spinal Disorders & Techniques2013;26(6):E248.

22. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional torque during pedicle screwing using cortical bone trajectory technique. Spine2014;39(4):240-5.

23. Matsukawa K, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite element study. Journal of neurosurgery Spine2015;23(4):471.

Table 1: Time of data collection.

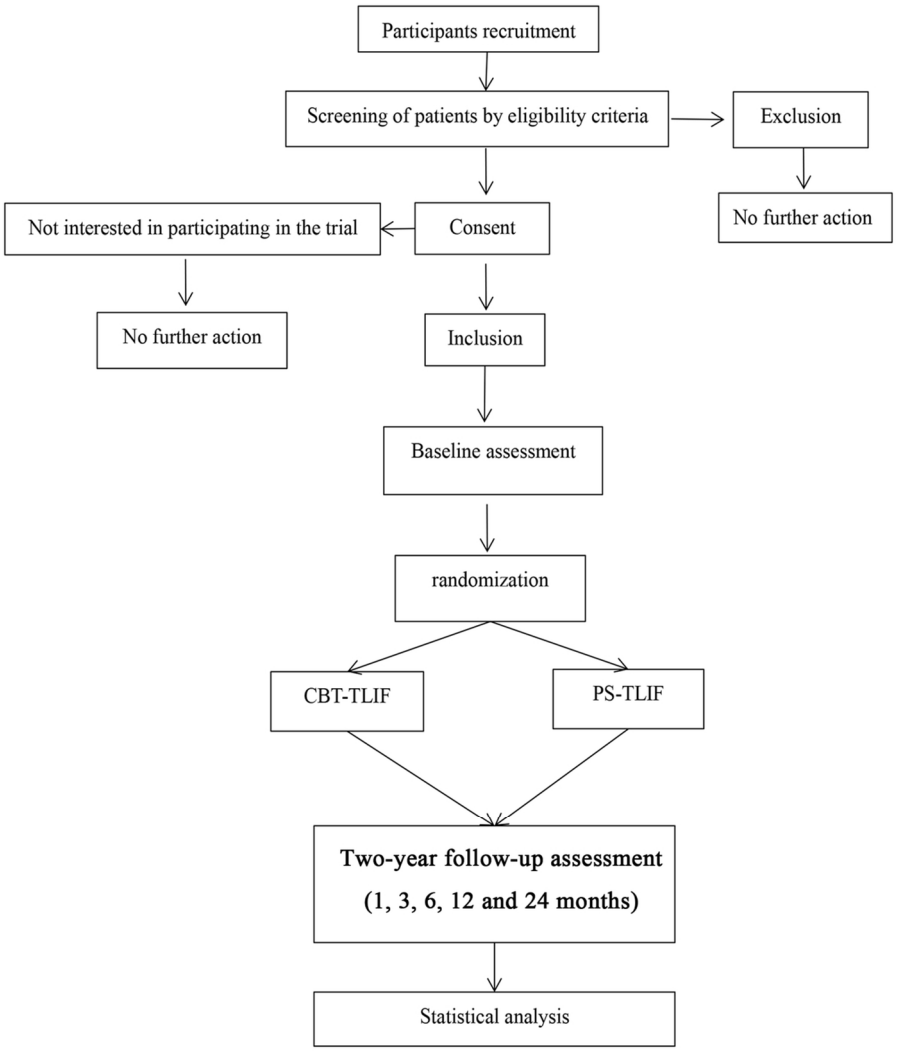
	Baseline	Operation	Follow-up					
Measures	Preoperation	duration	3 days	1 months	3 months	6 months	12 months	24 months
Screening for inclusion/exclusion criteria	√							
Informed consent	√							
Assignment to two group	√							
Baseline demographics	√							
operative time		√						

Blood loss		√						
Complications		√	√	√	√	√	√	√
FR						√	X or √	
FJV			√			√	√	√
SLR				√	√	√	√	√
VAS of back pain	√		√	√	√	√	√	√
VAS of leg pain	√		√	√	√	√	√	√
ODI	√		√	√	√	√	√	√
JOA	√		√	√	√	√	√	√
X-ray	√		√	√	√	√	√	√

Note: FR: fusion rate; FJV: adjacent cranial facet joint violation; SLR: screw loosening rate; VAS of back pain: Visual Analog Scale of back pain; VAS of leg pain: Visual Analog Scale of leg pain; ODI: Oswestry Disability Index;JOA: Japanese Orthopedic Association.

Figure Legend

Figure 1 Flow chart showing the steps in participant recruitment, treatment and analysis.



Flow chart showing the steps in participant recruitment, treatment and analysis.

106x134mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___3_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___4_____
	2b	All items from the World Health Organization Trial Registration Data Set	___7_____
Protocol version	3	Date and version identifier	___2_____
Funding	4	Sources and types of financial, material, and other support	___1_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1_____
	5b	Name and contact information for the trial sponsor	___1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___1_____
	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)	___1_____

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	___5_____
	6b	Explanation for choice of comparators	__ 5-6_____
Objectives	7	Specific objectives or hypotheses	__6-7_____
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)	__7_____

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	__7_____
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)	_8-9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__9-11 and Figure 1
	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)	__8_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__8、13_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__13_____
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	__11-12_____
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)	__13 and table 1_

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13-14_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__14_____
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	___8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__8_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__8_____
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	__12-13 _____
	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	___12-13_____

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	____13_____
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	____14_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____NA_____
	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)	___ NA _____
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	___13_____
	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	____13_____
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	____13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____13_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____16_____
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)	__16_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____16_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___16_____
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	___16_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___1_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____NA_____
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	____NA_____
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	__16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___16_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____16_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary file
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	_____NA____

*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.