

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017227
Article Type:	Protocol
Date Submitted by the Author:	10-Apr-2017
Complete List of Authors:	Feng, Zhenhua; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Li, Xiaobin; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Tang, Qian; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wang, Chenggui; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Zheng, Wenhao ; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Zhang, Hui; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wu, Ai-Min; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Tian, Naifeng; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wu, Yaosen; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Ni, Wenfei
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Ethics
Keywords:	cortical bone trajectory, Transforaminal lumbar interbody fusion, randomized controlled trial, traditional pedicle screw

SCHOLARONE™
Manuscripts

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

3
4 **Authors:** Zhenhua Feng MD, Xiaobin Li MD, Qian Tang MD, Chengui Wang MD,
5 Wenhao Zheng MD, Hui Zhang MD, Aimin Wu MD, Naifeng Tian MD PhD, Yaosen
6 Wu MD PhD, Wenfei Ni * MD PhD;

7 **Affiliated:**

8 Department of Spine Surgery, Orthopaedic Hospital, The Second Affiliated Hospital
9 and Yuying Children's Hospital of the Wenzhou Medical University, The Second
10 Medical School of the Wenzhou Medical University, Zhejiang Spine Center, Wenzhou,
11 China.

12 **Funds and Acknowledgement:** This work is supported by National Natural Science
13 Foundation of China (81501933), Wenzhou Science and Technology Bureau
14 Foundation (Y20160363).The funders had no role in the design, execution, or writing
15 of the study.

16 **Disclosures:** All authours declare that they have no conflict of interest.

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

1
2
3
4 1 **Data sharing statement:** The full data set will be made available when this trial is
5
6 2 completed and published. Application for the data to be released should be made in
7
8
9 3 contact to WFN (principle investigator).

10
11 4 ***Corresponding author:**

12
13
14 5 Weifei Ni E-mail: 739961818@qq.com

15
16 6 Department of Spine Surgery, Orthopaedic Hospital, The Second Affiliated Hospital
17
18 7 and Yuying Children's Hospital of the Wenzhou Medical University, The Second
19
20 8 Medical School of the Wenzhou Medical University, Zhejiang Spine Center, Wenzhou,
21
22 9 China. **Address:** 109# Xueyuan Xi Road, Wenzhou, China, 325027. **Phone:**
23
24 10 8613587676089, **Fax:** 8657788002823.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 1 **Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs.**
5
6 2 **traditional pedicle screws fixation: Study protocol of a randomized controlled**
7
8 3 **trial**
9

10
11
12 4
13 5 **Abstract**

16 6 **Introduction:** Transforaminal lumbar interbody fusion (TLIF) has been widely used
17
18 7 in the treatment of lumbar degenerative disc disorders and shows favorable clinical
19
20 8 results. Recently, cortical bone trajectory (CBT) has become a new trajectory for
21
22 9 screw insertion in the lumbar spine. Several biomechanical studies have demonstrated
23
24 10 that the CBT technique achieves screw purchase and strength greater than the
25
26 11 traditional method. Currently, the available data on the clinical effectiveness of the
27
28 12 two performed surgeries, TLIF with CBT screws (CBT-TLIF) and TLIF with
29
30 13 traditional pedicle screws (PS-TLIF), are insufficient. This is the first randomized
31
32 14 study to compare CBT-TLIF against traditional pedicle screw fixation and will
33
34 15 provide recommendations for treating patients with lumbar degenerative disc
35
36 16 disorders.

37
38 17 **Methods and analysis:** A blinded randomized controlled trial (blinding for the patient
39
40 18 and statistician, rather than for the clinician and researcher) will be conducted. A total
41
42 19 of 125 participants with lumbar disc degenerative disease who are candidates for
43
44 20 TLIF surgery will be randomly allocated to either the CBT-TLIF group or the
45
46 21 PS-TLIF group at a ratio of 1:1. The primary clinical outcome measures are: fusion
47
48 22 rate compared to the PS-TLIF group; the incidence of adjacent cranial facet joint
49
50
51
52
53
54
55
56
57
58
59
60

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

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

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

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

14 **Strengths and limitations of this study:**

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

20

21

22

1 Introduction

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

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

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

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

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

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

1
2
3
4 1 pedicle screw fixation.
5
6

7 2
8

9 **Methods and analysis**

10
11 This study has been reviewed and approved by the Institutional Ethics Review
12 Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou
13 Medical University. All participants will be asked to sign an informed consent form.
14
15
16
17
18
19 The study protocol has been registered at the US National Institutes of Health Clinical
20 Trials Registry: NCT03105167. The protocol was developed by following the
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

12 ***Participants***

13 This study is a parallel group RCT conducted at the Orthopedic Hospital, Second
14 Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University.
15

16 ***Randomization and blinding***

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

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

4 5 ***Inclusion criteria***

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

13 ***Exclusion criteria***

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

1
2
3
4 1 8. Body mass index > 30.

5
6 2 9. Therapy with systemic corticosteroids or immunosuppressants.
7
8

9
10 3

11
12
13 4 ***Interventions***

14
15
16 5 *CBT-TLIF group*

17
18
19 6 After the preventive use of antibiotics, patients were placed under general
20
21 7 anesthesia in the prone position. A small skin incision was made at the fused segment
22
23 8 and an entry point to allow insertion of the CBT screws was drilled in the junction of
24
25 9 the center of the superior articular process and 1 mm inferior to the inferior border of
26
27 10 the transverse process according to Matsukawa et al.[15]. A straight probe was then
28
29 11 used to create a trajectory for the CBT screws from the entry point to the opposite
30
31 12 corner of the pedicle and vertebral body under anteroposterior fluoroscopic guidance.
32
33 13 Screws were placed bilaterally, targeting half of the vertebral body. Unilateral
34
35 14 facetectomy was performed to gain access to the intervertebral disc, followed by
36
37 15 discectomy. The endplate cartilage was prepared to provide a host bed of bleeding
38
39 16 subchondral bone for the placement of the cage. The structure of the interbody cage
40
41 17 was determined by a trial cage and fluoroscopy. The definitive cage was then filled
42
43 18 with autologous bone or allograft and tamped into place and its position was checked
44
45 19 radiologically. After placement of the interbody cage, the remainder of the disc space
46
47 20 was filled with autologous bone obtained from the decompression. A titanium rod
48
49 21 interconnected the screws on either side. The spreader was removed and the wound
50
51
52
53
54
55
56
57
58
59
60

1 thoroughly irrigated and closed in several layers without suction drainage.

2

3 *PS-TLIF group*

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

16

17 ***Outcome measurements***

18 *Primary outcomes:*

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

1
2
3
4 1 3. Screw loosening rate (SLR).
5
6
7 2
8
9 3 *Secondary outcomes:*

10
11 4 1. The intensity of back and lower limb pain during rest and daily activities
12 during follow-up will be assessed by the VAS of back pain and VAS of leg
13 pain[16].
14
15 6

16
17
18 7 2. The ODI will be recorded both preoperatively and postoperatively[17]. The
19 ODI assesses back pain-related disability. It contains 10 questions about daily
20 life, including measures of pain intensity, personal care, lifting, walking,
21 sitting, standing, sleeping, social life, and traveling. Each question is rated on
22 a scale of 0–5, with a higher score indicating a more severe pain-related
23 disability.
24
25 10

26
27
28 11 3. Japanese Orthopedic Association (JOA) scores will be recorded preoperatively,
29 at 3 days, at 3 and 6 months, and at 1 and 2 years postoperatively. Functional
30 improvement is expressed by the rate of recovery of the JOA score[18].
31
32 15

33
34
35 16 4. Operative time, intraoperative blood loss.

36
37
38 17 5. Complications including dural tear, postoperative infection, deep venous
39 thrombosis, hematoma, hardware failure, neurological deficits, and any other
40 direct and indirect surgical complications will be recorded.
41
42 20

43
44
45
46
47
48
49
50
51
52
53
54
55
56 21 *Baseline demographics*
57
58
59
60

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

4 5 ***Follow-up***

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

8 9 ***Monitoring***

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

16 17 ***Sample size calculation***

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

1
2
3
4 1 estimated the sample size on the basis of other similar previous studies[19]. We
5
6 2 assumed a two-tailed α error of 0.05 and a power (1-b) of 0.8. With these assumptions,
7
8
9 3 50 participants in each group are needed for 80% power. We propose to enroll 125
10
11 4 participants (50 randomized to each arm) and allow for a dropout rate of 20% for an
12
13
14 5 effective sample size of 100.
15
16
17
18
19
20
21
22

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

7 ***Statistical analysis***

8 All data will be analyzed using the SPSS 19.0 software. Differences in the
9 operative time and intraoperative blood loss, FR, FJV, and other complications
10 between the CBT-TLIF and PS-TLIF groups will be analyzed by two
11 independent-samples *t*-tests with an α of 0.05. Preoperative VAS and ODI scores, and
12 scores taken immediately post-operation, and at postoperative 3, 6, and 24 months,
13 will be analyzed by a repeated-measures ANOVA. Changes in the data between
14 different follow-up time points and the baseline will also be calculated and the
15 changes in data between the CBT-TLIF and PS-TLIF groups will be assessed by two
16 independent-samples *t*-tests.
17
18
19
20
21

22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

18 **Discussion**

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

1
2
3
4 1 protocol for conducting an RCT in China that will investigate the efficacy of CBT
5
6 2 screws with TLIF in treating lumbar disc degenerative diseases such as lumbar spinal
7
8
9 3 canal stenosis and lumbar disc herniation that require spinal interbody fusion surgery.
10
11 4 In this trial, we designed a PS-TLIF group as a controlled comparison group to
12
13 5 identify the clinical outcomes of TLIF with cortical bone trajectory screw fixation.
14
15
16 6 The demand for spinal interbody fusion surgery has risen steeply over the last ten
17
18 7 years and is expected to increase even further in the near future. It is hypothesized that
19
20
21 8 CBT-TLIF, compared to PS-TLIF, is superior in reducing disability and thus has a
22
23
24 9 better clinical outcome.

25
26 10 This study is the first RCT to compare TLIF with CBT against traditional pedicle
27
28
29 11 screws. An RCT has the advantage of controlling all confounding factors due to
30
31
32 12 random sequence generation, as opposed to observational studies where confounding
33
34 13 factors and bias may be more problematic. High-quality RCTs are generally regarded
35
36
37 14 as the gold standard for studying the effectiveness of an intervention.

38
39 15 Randomized trials that compare surgery with non-surgical treatments have
40
41
42 16 several features that are distinctly different from drug trials and can lead to serious
43
44 17 limitations. Moreover, compared to drug trials, surgery has many irreversible features.

45
46 18 In the case that our hypothesis is confirmed, our results will have a practical value
47
48
49 19 in the planning and development of treatment options in spinal interbody fusion
50
51
52 20 surgery. We anticipate that the results will provide more reliable evidence and clarify
53
54 21 the value of CBT with TLIF as a treatment for patients with lumbar disc degenerative
55
56
57 22 diseases.
58
59
60

1
2
3
4 **Acknowledgement:**
5

6 The English in this document has been checked by at least two professional editors,
7
8 both native speakers of English. For a certificate, please see:
9
10 <http://www.textcheck.com/certificate/tDbZkH>
11
12
13

14
15
16
17 **Ethics and dissemination:**
18

19
20 The study had been reviewed and approved by the ethics committee of the
21
22 Second affiliated hospital of the Wenzhou Medical University, Wenzhou,
23
24 China(batch: 2017-03). The procedure will be performed following the principles
25
26 described in the Declaration of Helsinki. All of participants will be signed the
27
28 informed consent. The protocol has been registered in US National Institutes of
29
30 Health Clinical Trials Registry: NCT03105167. We will share individual patient data
31
32 (IPD) within 2 years after the trial complete, and the original data is collected by
33
34 clinical recording formula (both paper and electronic version). The results will be
35
36 presented in peer-reviewed journals and related website (<https://clinicaltrials.gov/>)
37
38 within 2 years after the last operation.
39
40
41
42
43
44
45
46
47
48

49 **Reference**
50
51
52
53

- 54
55 1. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG *et al*. Guidelines for the
56 performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion
57 for disc herniation and radiculopathy. *Journal of Neurosurgery Spine*2005;2(6):673-78.
58
59
60

- 1 2. Braydabruno M, Tibiletti M, Ito K, Fairbank J, Galbusera F, Zerbi A *et al.* Advances in the diagnosis
2 of degenerated lumbar discs and their possible clinical application. *European Spine*
3 *Journal*2014;23(3):315-23.
- 4 3. Omidikashani F, Hasankhani EG, Ashjazadeh A. Lumbar Spinal Stenosis: Who Should Be Fused?
5 An Updated Review. *Asian Spine Journal*2014;8(4):521.
- 6 4. Harms JG, Jeszenszky D. Die posteriore, lumbale, interkorporelle Fusion in unilateraler
7 transforaminaler Technik. *Operative Orthopädie und Traumatologie*1998;10(2):90-102.
- 8 5. Rouben D, Casnellie M, Ferguson M. Long-term durability of minimal invasive posterior
9 transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. *Clinical Spine*
10 *Surgery*2011;24(5):288-96.
- 11 6. Santoni B, Hynes R, McGilvray K, Rodriguez-Canessa G, Lyons A, Henson M *et al.* Cortical bone
12 trajectory for lumbar pedicle screws. *The Spine Journal*2009;9(5):366-73.
- 13 7. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional
14 torque during pedicle screwing using cortical bone trajectory technique. *Spine*2014;39(4):E240-E45.
- 15 8. Baluch DA, Patel AA, Lullo B, Havey RM, Voronov LI, Nguyen N-L *et al.* Effect of physiological loads
16 on cortical and traditional pedicle screw fixation. *Spine*2014;39(22):E1297-E302.
- 17 9. Perez-Orribo L, Kalb S, Reyes PM, Chang SW, Crawford NR. Biomechanics of lumbar cortical
18 screw-rod fixation versus pedicle screw-rod fixation with and without interbody support.
19 *Spine*2013;38(8):635-41.
- 20 10. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al.* Incidence and Risk Factors
21 of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone
22 Trajectory Technique. *Spine*2016;41(14):E851-E56.
- 23 11. Gonchar I, Kotani Y, Matsumoto Y. Cortical bone trajectory versus percutaneous pedicle screw in
24 minimally invasive posterior lumbar fusion. *The Spine Journal*2014;11(14):S114-S15.
- 25 12. Kasukawa Y, Miyakoshi N, Hongo M, Ishikawa Y, Kudo D, Shimada Y. Short-term results of
26 transforaminal lumbar interbody fusion using pedicle screw with cortical bone trajectory compared
27 with conventional trajectory. *Asian spine journal*2015;9(3):440-48.
- 28 13. Chin KR, Pencil FJ, Coombs AV, Elsharkawy M, Packer CF, Hothem EA *et al.* Clinical Outcomes
29 With Midline Cortical Bone Trajectory Pedicle Screws Versus Traditional Pedicle Screws in Moving
30 Lumbar Fusions From Hospitals to Outpatient Surgery Centers. *Clinical Spine Surgery*2016.
- 31 14. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation
32 and elaboration: guidance for protocols of clinical trials. *Bmj*2013;346:e7586.
- 33 15. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric
34 measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed
35 tomography. *Clinical Spine Surgery*2013;26(6):E248-E53.
- 36 16. Dixon J, Bird H. Reproducibility along a 10 cm vertical visual analogue scale. *Annals of the*
37 *Rheumatic Diseases*1981;40(1):87-89.
- 38 17. Fairbank JC, Pynsent PB. The Oswestry disability index. *Spine*2000;25(22):2940-53.
- 39 18. Okuda S, Miyauchi A, Oda T, Haku T, Yamamoto T, Iwasaki M. Surgical complications of posterior
40 lumbar interbody fusion with total facetectomy in 251 patients. *Journal of Neurosurgery:*
41 *Spine*2006;4(4):304-09.
- 42 19. Sakaura H, Miwa T, Yamashita T, Kuroda Y, Ohwada T. Posterior lumbar interbody fusion with
43 cortical bone trajectory screw fixation versus posterior lumbar interbody fusion using traditional

- 1
2
3 1 pedicle screw fixation for degenerative lumbar spondylolisthesis: a comparative study. *Journal of*
4 2 *Neurosurgery Spine*2016:1.
5 3 20. Xuan J, Zhang D, Jin HM, Chen JX, Xu DL, Xu HM *et al*. Minimally invasive cortical bone trajectory
6 4 screws placement via pedicle or pedicle rib unit in the lower thoracic spine: a cadaveric and
7 5 radiographic study. *European Spine Journal*2016:1-9.
8 6 21. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric
9 7 measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed
10 8 tomography. *Journal of Spinal Disorders & Techniques*2013;26(6):E248.
11 9 22. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional
12 10 torque during pedicle screwing using cortical bone trajectory technique. *Spine*2014;39(4):240-5.
13 11 23. Matsukawa K, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical
14 12 evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite
15 13 element study. *Journal of neurosurgery Spine*2015;23(4):471.
16 14
17 15
18 16
19 17
20 18
21 19
22 20
23 21
24 22
25 23
26 24
27 25
28 26
29 27
30 28
31
32
33
34
35
36
37
38
39

Table 1:Time of data collection.

Measures	Baseline	Operation		Follow-up			
	Periope ration	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							✓

1						
2						
3	FJV		✓			
4	SLR			✓	✓	✓
5	VAS of back pain	✓	✓	✓	✓	✓
6	VAS of leg pain	✓	✓	✓	✓	✓
7	ODI	✓	✓	✓	✓	✓
8	JOA	✓	✓	✓	✓	✓
9						
10						
11						

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.

1

2

3

4

5

6

7

8

9

10

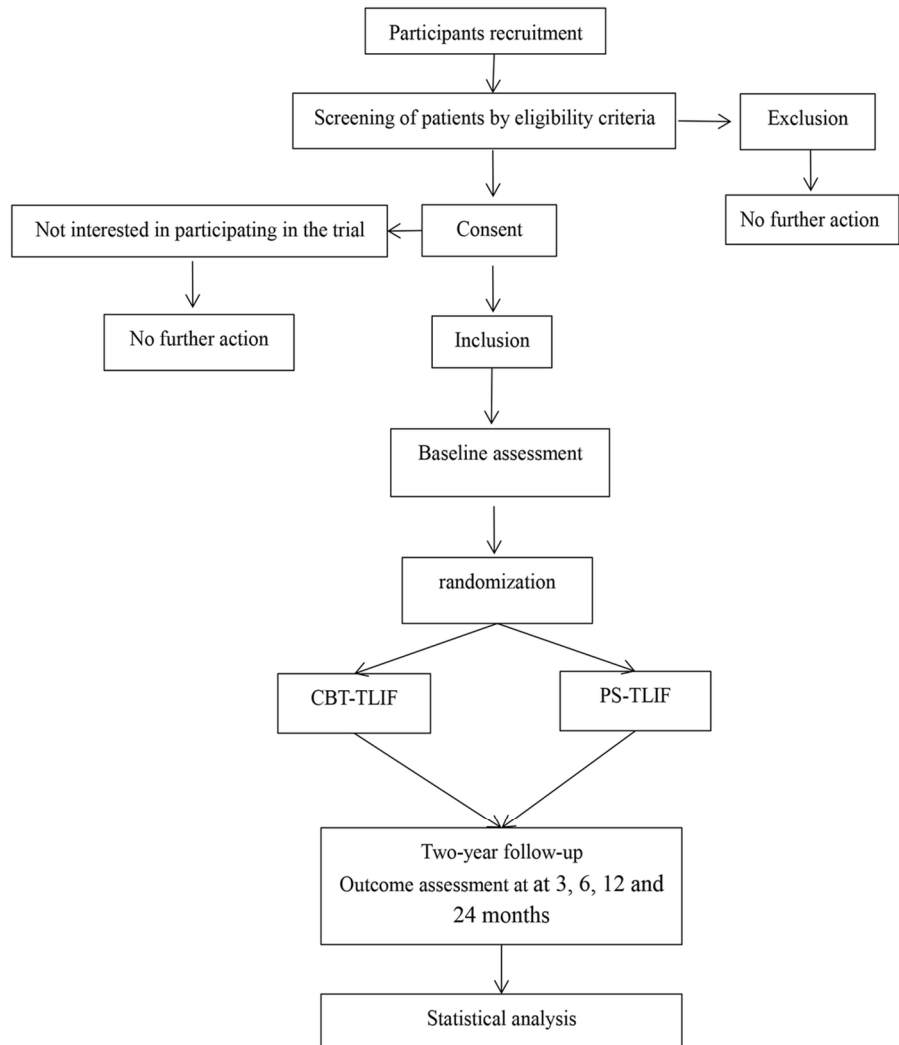
11

12 Figure Legend

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

15

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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

106x134mm (300 x 300 DPI)



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__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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___

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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 ___



1				
2				
3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___15___
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___15___
7				
8				
9	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___15___
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___1___
13				
14				
15	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___
16				
17				
18	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___
19				
20				
21	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___
22				
23				
24				
25				
26		31b	Authorship eligibility guidelines and any intended use of professional writers	___15___
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___15___
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___NA___
33				
34				
35	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___
36				
37				

38 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 39 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 40 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
 41

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017227.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Aug-2017
Complete List of Authors:	Feng, Zhenhua; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Li, Xiaobin; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Tang, Qian; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wang, Chenggui; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Zheng, Wenhao ; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Zhang, Hui; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wu, Ai-Min; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Tian, Naifeng; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wu, Yaosen; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Ni, Wenfei
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Ethics
Keywords:	cortical bone trajectory, Transforaminal lumbar interbody fusion, randomized controlled trial, traditional pedicle screw

SCHOLARONE™
Manuscripts

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

3
4 **Authors:** Zhenhua Feng MD, Xiaobin Li MD, Qian Tang MD, Chengui Wang MD,
5 Wenhao Zheng MD, Hui Zhang MD, Aimin Wu MD, Naifeng Tian MD PhD, Yaosen
6 Wu MD PhD, Wenfei Ni * MD PhD;

7 **Affiliated:**

8 Department of Spine Surgery, Orthopaedic Hospital, The Second Affiliated Hospital
9 and Yuying Children's Hospital of the Wenzhou Medical University, The Second
10 Medical School of the Wenzhou Medical University, Zhejiang Spine Center, Wenzhou,
11 China.

12 **Funds and Acknowledgement:** This work is supported by National Natural Science
13 Foundation of China (81501933), Wenzhou Science and Technology Bureau
14 Foundation (Y20160363).The funders had no role in the design, execution, or writing
15 of the study.

16 **Disclosures:** All authours declare that they have no conflict of interest.

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

1
2
3
4 1 **Data sharing statement:** The full data set will be made available when this trial is
5
6 2 completed and published. Application for the data to be released should be made in
7
8
9 3 contact to WFN (principle investigator).

10
11 4 ***Corresponding author:**

12
13
14 5 Weifei Ni E-mail: 739961818@qq.com

15
16 6 Department of Spine Surgery, Orthopaedic Hospital, The Second Affiliated Hospital
17
18 7 and Yuying Children's Hospital of the Wenzhou Medical University, The Second
19
20 8 Medical School of the Wenzhou Medical University, Zhejiang Spine Center, Wenzhou,
21
22 9 China. **Address:** 109# Xueyuan Xi Road, Wenzhou, China, 325027. **Phone:**
23
24 10 8613587676089, **Fax:** 8657788002823.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 1 **Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs.**
5
6 2 **traditional pedicle screws fixation: Study protocol of a randomized controlled**
7
8 3 **trial**
9

10
11
12 4
13 5 **Abstract**

16 6 **Introduction:** Transforaminal lumbar interbody fusion (TLIF) has been widely used
17
18 7 in the treatment of lumbar degenerative disc disorders and shows favorable clinical
19
20 8 results. Recently, cortical bone trajectory (CBT) has become a new trajectory for
21
22 9 screw insertion in the lumbar spine. Several biomechanical studies have demonstrated
23
24 10 that the CBT technique achieves screw purchase and strength greater than the
25
26 11 traditional method. Currently, the available data on the clinical effectiveness of the
27
28 12 two performed surgeries, TLIF with CBT screws (CBT-TLIF) and TLIF with
29
30 13 traditional pedicle screws (PS-TLIF), are insufficient. This is the first randomized
31
32 14 study to compare CBT-TLIF against traditional pedicle screw fixation and will
33
34 15 provide recommendations for treating patients with lumbar degenerative disc
35
36 16 disorders.

37
38 17 **Methods and analysis:** A blinded randomized controlled trial (blinding for the patient
39
40 18 and statistician, rather than for the clinician and researcher) will be conducted. A total
41
42 19 of 254 participants with lumbar disc degenerative disease who are candidates for
43
44 20 TLIF surgery will be randomly allocated to either the CBT-TLIF group or the
45
46 21 PS-TLIF group at a ratio of 1:1. The primary clinical outcome measures are: the
47
48 22 incidence of adjacent cranial facet joint violation; fusion rate; and the screw loosening
49
50
51
52
53
54
55
56
57
58
59
60

1 rate. Secondary clinical outcome measures are: Visual Analog Scale (VAS) of back
2 pain; VAS of leg pain; Oswestry Disability Index; operative time; intraoperative blood
3 loss; and complications. These parameters will be evaluated on Day 3, and then at 1, 3,
4 6, 12, and 24 months postoperatively.

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

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

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

14 **Strengths and limitations of this study:**

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

1 Introduction

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

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

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

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

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

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

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

6 7 **Methods and analysis**

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

15 16 ***Participants***

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

19 20 ***Randomization and blinding***

1
2
3
4 1 Participants will be equally randomized to either the CBT-TLIF group or the
5
6 2 PS-TLIF group based on a permuted blocks randomization scheme. Using a block
7
8 3 size of 4 in a scheduled computer-generated randomization program, the final group
9
10 4 assignments will be sealed in opaque envelopes. In order to ensure the proper
11
12 5 management of the randomisation procedure, the sequence numbers will be marked
13
14 6 on the opaque envelope, and the group assignment will be sealed inside. All envelopes
15
16 7 will be numbered sequentially. The envelopes will be delivered according to the
17
18 8 patients' sequence numbers, and the surgeon will be informed of the random numbers
19
20 9 and group assignments by either telephone or email. Patients will be kept blinded for
21
22 10 the allocated treatment until the last questionnaires have been completed. At the end
23
24 11 of the follow-up period, the blind can be lifted at the patients' request. In addition, the
25
26 12 statistician will also be blinded.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

14 ***Inclusion criteria***

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

1
2
3
4 **1 Exclusion criteria**
5
6

- 7 1. Spinal scoliosis with a Cobb angle of more than 10° in the index level.
8
9
10 2. Patients with prior failed fusion at the same level.
11
12 3. Pregnancy.
13
14 4. Active infection or prior infection at the surgical site.
15
16 5. Planned (e)migration abroad within 2 years after inclusion.
17
18 6. Metabolic bone disease such as osteomalacia or Paget's disease.
19
20 7. Spondylolisthesis according to Meyerding grades III and IV.
21
22 8. Therapy with systemic corticosteroids or immunosuppressants.
23
24
25
26
27
28
29
30
31

32 **11 Interventions**
33
34

35 **12 CBT-TLIF group**
36

37
38 After the preventive use of antibiotics, patients were placed under general
39
40 anesthesia in the prone position. A small skin incision was made at the fused segment
41
42 and an entry point to allow insertion of the CBT screws was drilled in the junction of
43
44 the center of the superior articular process and 1 mm inferior to the inferior border of
45
46 the transverse process according to Matsukawa et al.[15]. A straight probe was then
47
48 used to create a trajectory for the CBT screws from the entry point to the opposite
49
50 corner of the pedicle and vertebral body under anteroposterior fluoroscopic guidance.
51
52
53
54
55
56
57
58
59
60
60 Screws were placed bilaterally, targeting half of the vertebral body. Unilateral

1
2
3
4 1 facetectomy was performed to gain access to the intervertebral disc, followed by
5
6 2 discectomy. The endplate cartilage was prepared to provide a host bed of bleeding
7
8
9 3 subchondral bone for the placement of the cage. The structure of the interbody cage
10
11 4 was determined by a trial cage and fluoroscopy. The definitive cage was then filled
12
13 5 with autologous bone or allograft and tamped into place and its position was checked
14
15 6 radiologically. After placement of the interbody cage, the remainder of the disc space
16
17 7 was filled with autologous bone obtained from the decompression. A titanium rod
18
19 8 interconnected the screws on either side. The spreader was removed and the wound
20
21 9 thoroughly irrigated and closed in several layers without suction drainage.
22
23
24
25
26
27
28
29
30

31 *PS-TLIF group*
32
33

34 12 After the preventive use of antibiotics, patients were placed under general
35
36 13 anesthesia in the prone position. A posterior midline incision of about 6 cm was
37
38 14 performed at the level of interest under fluoroscopic guidance. Pedicle screws were
39
40 15 inserted freehand into the vertebral body, and the inferior and superior articular
41
42 16 processes and part of the lamina were removed by an osteotome. The ligamentum
43
44 17 flavum was then removed to expose the lateral border of the ipsilateral nerve root.
45
46 18 After decompression of the neural structures, a thorough discectomy and endplate
47
48 19 preparation were performed followed by transforaminal insertion of an intervertebral
49
50 20 tantalum mesh cage packed with autograft materials within the disc space. In both
51
52 21 CBT-TLIF and PS-TLIF, prior to cage insertion, the morselized bone graft from the
53
54
55
56
57
58
59
60

1
2
3
4 1 facetectomy and laminectomy was grafted into the prepared disc space. Compression
5
6 2 was achieved across the pedicle screws and rod with place screws and optimal
7
8
9 3 placement was confirmed by intraoperative fluoroscopy.
10
11
12
13
14

15 ***Outcome measurements***

16 *Primary outcomes:*

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

25 *Secondary outcomes:*

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

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

19 Table 1 presents the data collection times.

20 ***Baseline demographics***

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

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

3

4 ***Follow-up***

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

7

8 ***Monitoring***

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

15

16 ***Sample size calculation***

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

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

7 ***Statistical analysis***

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

18 **Discussion**

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

1
2
3
4 1 protocol for conducting an RCT in China that will investigate the efficacy of CBT
5
6 2 screws with TLIF in treating lumbar disc degenerative diseases such as lumbar spinal
7
8
9 3 canal stenosis and lumbar disc herniation that require spinal interbody fusion surgery.
10
11 4 In this trial, we designed a PS-TLIF group as a controlled comparison group to
12
13 5 identify the clinical outcomes of TLIF with cortical bone trajectory screw fixation.
14
15
16 6 The demand for spinal interbody fusion surgery has risen steeply over the last ten
17
18 7 years and is expected to increase even further in the near future. It is hypothesized that
19
20
21 8 CBT-TLIF, compared to PS-TLIF, is superior in reducing disability and thus has a
22
23 9 better clinical outcome.

24
25
26 10 This study is the first RCT to compare TLIF with CBT against traditional pedicle
27
28 11 screws. An RCT has the advantage of controlling all confounding factors due to
29
30 12 random sequence generation, as opposed to observational studies where confounding
31
32 13 factors and bias may be more problematic. High-quality RCTs are generally regarded
33
34 14 as the gold standard for studying the effectiveness of an intervention.

35
36
37
38
39 15 Randomized trials that compare surgery with non-surgical treatments have
40
41 16 several features that are distinctly different from drug trials and can lead to serious
42
43 17 limitations. Moreover, compared to drug trials, surgery has many irreversible features.

44
45
46 18 In the case that our hypothesis is confirmed, our results will have a practical value
47
48 19 in the planning and development of treatment options in spinal interbody fusion
49
50 20 surgery. We anticipate that the results will provide more reliable evidence and clarify
51
52 21 the value of CBT with TLIF as a treatment for patients with lumbar disc degenerative
53
54 22 diseases.
55
56
57
58
59
60

1
2
3
4 **Acknowledgement:**
5

6 The English in this document has been checked by at least two professional editors,
7
8 both native speakers of English. For a certificate, please see:
9
10 <http://www.textcheck.com/certificate/tDbZkH>
11
12
13

14
15
16
17 **Ethics and dissemination:**
18

19
20 The study had been reviewed and approved by the ethics committee of the
21
22 Second affiliated hospital of the Wenzhou Medical University, Wenzhou,
23
24 China(batch: 2017-03). The procedure will be performed following the principles
25
26 described in the Declaration of Helsinki. All of participants will be signed the
27
28 informed consent. The protocol has been registered in US National Institutes of
29
30 Health Clinical Trials Registry: NCT03105167. We will share individual patient data
31
32 (IPD) within 2 years after the trial complete, and the original data is collected by
33
34 clinical recording formula (both paper and electronic version). The results will be
35
36 presented in peer-reviewed journals and related website (<https://clinicaltrials.gov/>)
37
38 within 2 years after the last operation.
39
40
41
42
43
44
45
46
47
48

49 **Reference**
50
51
52
53

- 54
55 1. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG *et al*. Guidelines for the
56 performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion
57 for disc herniation and radiculopathy. *Journal of Neurosurgery Spine*2005;2(6):673-78.
58
59
60

- 1 2. Braydabruno M, Tibiletti M, Ito K, Fairbank J, Galbusera F, Zerbi A *et al*. Advances in the diagnosis
2 of degenerated lumbar discs and their possible clinical application. *European Spine*
3 *Journal*2014;23(3):315-23.
- 4 3. Omidikashani F, Hasankhani EG, Ashjazadeh A. Lumbar Spinal Stenosis: Who Should Be Fused?
5 An Updated Review. *Asian Spine Journal*2014;8(4):521.
- 6 4. Harms JG, Jeszenszky D. Die posteriore, lumbale, interkorporelle Fusion in unilateraler
7 transforaminaler Technik. *Operative Orthopädie und Traumatologie*1998;10(2):90-102.
- 8 5. Rouben D, Casnellie M, Ferguson M. Long-term durability of minimal invasive posterior
9 transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. *Clinical Spine*
10 *Surgery*2011;24(5):288-96.
- 11 6. Santoni B, Hynes R, McGilvray K, Rodriguez-Canessa G, Lyons A, Henson M *et al*. Cortical bone
12 trajectory for lumbar pedicle screws. *The Spine Journal*2009;9(5):366-73.
- 13 7. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional
14 torque during pedicle screwing using cortical bone trajectory technique. *Spine*2014;39(4):E240-E45.
- 15 8. Baluch DA, Patel AA, Lullo B, Havey RM, Voronov LI, Nguyen N-L *et al*. Effect of physiological loads
16 on cortical and traditional pedicle screw fixation. *Spine*2014;39(22):E1297-E302.
- 17 9. Perez-Orribo L, Kalb S, Reyes PM, Chang SW, Crawford NR. Biomechanics of lumbar cortical
18 screw-rod fixation versus pedicle screw-rod fixation with and without interbody support.
19 *Spine*2013;38(8):635-41.
- 20 10. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al*. Incidence and Risk Factors
21 of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone
22 Trajectory Technique. *Spine*2016;41(14):E851-E56.
- 23 11. Gonchar I, Kotani Y, Matsumoto Y. Cortical bone trajectory versus percutaneous pedicle screw in
24 minimally invasive posterior lumbar fusion. *The Spine Journal*2014;11(14):S114-S15.
- 25 12. Kasukawa Y, Miyakoshi N, Hongo M, Ishikawa Y, Kudo D, Shimada Y. Short-term results of
26 transforaminal lumbar interbody fusion using pedicle screw with cortical bone trajectory compared
27 with conventional trajectory. *Asian spine journal*2015;9(3):440-48.
- 28 13. Chin KR, Pencle FJ, Coombs AV, Elsharkawy M, Packer CF, Hothem EA *et al*. Clinical Outcomes
29 With Midline Cortical Bone Trajectory Pedicle Screws Versus Traditional Pedicle Screws in Moving
30 Lumbar Fusions From Hospitals to Outpatient Surgery Centers. *Clinical Spine Surgery*2016.
- 31 14. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al*. SPIRIT 2013 explanation
32 and elaboration: guidance for protocols of clinical trials. *Bmj*2013;346:e7586.
- 33 15. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric
34 measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed
35 tomography. *Clinical Spine Surgery*2013;26(6):E248-E53.
- 36 16. Dixon J, Bird H. Reproducibility along a 10 cm vertical visual analogue scale. *Annals of the*
37 *Rheumatic Diseases*1981;40(1):87-89.
- 38 17. Fairbank JC, Pynsent PB. The Oswestry disability index. *Spine*2000;25(22):2940-53.
- 39 18. Okuda S, Miyauchi A, Oda T, Haku T, Yamamoto T, Iwasaki M. Surgical complications of posterior
40 lumbar interbody fusion with total facetectomy in 251 patients. *Journal of Neurosurgery:*
41 *Spine*2006;4(4):304-09.
- 42 19. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al*. Incidence and Risk Factors
43 of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone
44 Trajectory Technique. *Spine*2016;41(14):E851.

1 20. Xuan J, Zhang D, Jin HM, Chen JX, Xu DL, Xu HM *et al*. Minimally invasive cortical bone trajectory
 2 screws placement via pedicle or pedicle rib unit in the lower thoracic spine: a cadaveric and
 3 radiographic study. *European Spine Journal*2016;1-9.
 4 21. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric
 5 measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed
 6 tomography. *Journal of Spinal Disorders & Techniques*2013;26(6):E248.
 7 22. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional
 8 torque during pedicle screwing using cortical bone trajectory technique. *Spine*2014;39(4):240-5.
 9 23. Matsukawa K, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical
 10 evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite
 11 element study. *Journal of neurosurgery Spine*2015;23(4):471.

12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36

Table 1:Time of data collection.

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1							
2							
3	FJV		✓			✓	✓
4	SLR			✓	✓	✓	✓
5	VAS of back pain	✓	✓	✓	✓	✓	✓
6	VAS of leg pain	✓	✓	✓	✓	✓	✓
7	ODI	✓	✓	✓	✓	✓	✓
8	JOA	✓	✓	✓	✓	✓	✓
9	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.

18 1

19 2

20 3

21 4

22 5

23 6

24 7

25 8

26 9

27 10

28 11

29 12

30 13

31 14

32 15

33 16

34 17

35 18

36 19

37 20

38 21

39 22

40 23

41 24

42 25

43 26

44 27

45 28

46 29

47 30

48 31

49 32

50 33

51 34

52 35

53 36

54 37

55 38

56 39

57 40

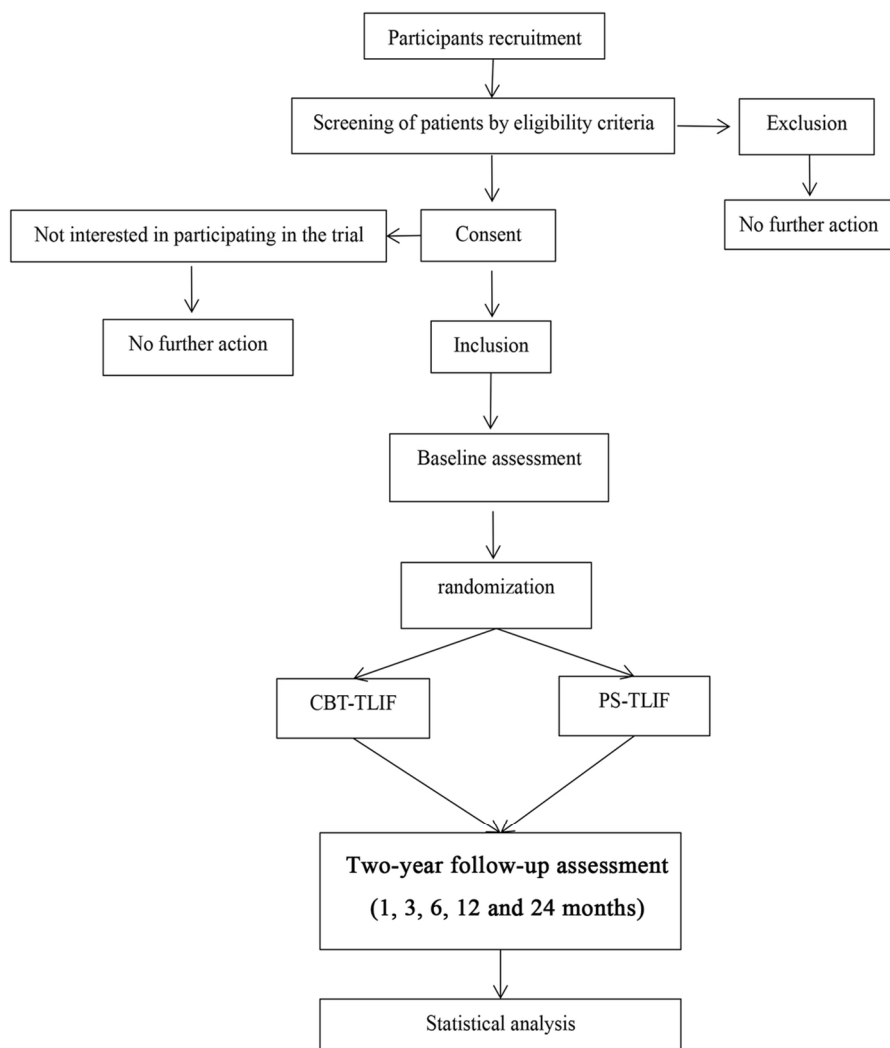
58 41

59 42

60 43

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)



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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___

1				
2				
3	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 ___
4				
5				
6				
7	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 ___
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ NA ___
11				
12		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 ___
13				
14				
15				

Methods: Monitoring

16				
17				
18	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 ___
19				
20				
21				
22				
23		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 ___
24				
25				
26	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 ___
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 12 ___
30				
31				
32				

Ethics and dissemination

33				
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 15 ___
36				
37				
38	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 ___
39				
40				
41				
42				
43				
44				
45				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017227.R2
Article Type:	Protocol
Date Submitted by the Author:	24-Aug-2017
Complete List of Authors:	Feng, Zhenhua; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Li, Xiaobin; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Tang, Qian; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wang, Chenggui; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Zheng, Wenhao ; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Zhang, Hui; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wu, Ai-Min; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Tian, Naifeng; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Wu, Yaosen; The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Ni, Wenfei
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Ethics
Keywords:	cortical bone trajectory, Transforaminal lumbar interbody fusion, randomized controlled trial, traditional pedicle screw

SCHOLARONE™
Manuscripts

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

3
4 **Authors:** Zhenhua Feng MD, Xiaobin Li MD, Qian Tang MD, Chengui Wang MD,
5 Wenhao Zheng MD, Hui Zhang MD, Aimin Wu MD, Naifeng Tian MD PhD, Yaosen
6 Wu MD PhD, Wenfei Ni * MD PhD;

7 **Affiliated:**

8 Department of Spine Surgery, Orthopaedic Hospital, The Second Affiliated Hospital
9 and Yuying Children's Hospital of the Wenzhou Medical University, The Second
10 Medical School of the Wenzhou Medical University, Zhejiang Spine Center, Wenzhou,
11 China.

12 **Funds and Acknowledgement:** This work is supported by National Natural Science
13 Foundation of China (81501933), Wenzhou Science and Technology Bureau
14 Foundation (Y20160363).The funders had no role in the design, execution, or writing
15 of the study.

16 **Disclosures:** All authours declare that they have no conflict of interest.

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

1
2
3
4 1 **Data sharing statement:** The full data set will be made available when this trial is
5
6 2 completed and published. Application for the data to be released should be made in
7
8
9 3 contact to WFN (principle investigator).

10
11 4 ***Corresponding author:**

12
13
14 5 Weifei Ni E-mail: 739961818@qq.com

15
16 6 Department of Spine Surgery, Orthopaedic Hospital, The Second Affiliated Hospital
17
18 7 and Yuying Children's Hospital of the Wenzhou Medical University, The Second
19
20
21 8 Medical School of the Wenzhou Medical University, Zhejiang Spine Center, Wenzhou,
22
23
24 9 China. **Address:** 109# Xueyuan Xi Road, Wenzhou, China, 325027. **Phone:**
25
26 10 8613587676089, **Fax:** 8657788002823.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 1 **Transforaminal lumbar interbody fusion with cortical bone trajectory screws vs.**
5
6 2 **traditional pedicle screws fixation: Study protocol of a randomized controlled**
7
8 3 **trial**
9

10
11
12 4
13 5 **Abstract**

16 6 **Introduction:** Transforaminal lumbar interbody fusion (TLIF) has been widely used
17
18 7 in the treatment of lumbar degenerative disc disorders and shows favorable clinical
19
20 8 results. Recently, cortical bone trajectory (CBT) has become a new trajectory for
21
22 9 screw insertion in the lumbar spine. Several biomechanical studies have demonstrated
23
24 10 that the CBT technique achieves screw purchase and strength greater than the
25
26 11 traditional method. Currently, the available data on the clinical effectiveness of the
27
28 12 two performed surgeries, TLIF with CBT screws (CBT-TLIF) and TLIF with
29
30 13 traditional pedicle screws (PS-TLIF), are insufficient. This is the first randomized
31
32 14 study to compare CBT-TLIF against traditional pedicle screw fixation and will
33
34 15 provide recommendations for treating patients with lumbar degenerative disc
35
36 16 disorders.

37
38 17 **Methods and analysis:** A blinded randomized controlled trial (blinding for the patient
39
40 18 and statistician, rather than for the clinician and researcher) will be conducted. A total
41
42 19 of 254 participants with lumbar disc degenerative disease who are candidates for
43
44 20 TLIF surgery will be randomly allocated to either the CBT-TLIF group or the
45
46 21 PS-TLIF group at a ratio of 1:1. The primary clinical outcome measures are: the
47
48 22 incidence of adjacent cranial facet joint violation; fusion rate; and the screw loosening
49
50
51
52
53
54
55
56
57
58
59
60

1 rate. Secondary clinical outcome measures are: Visual Analog Scale (VAS) of back
2 pain; VAS of leg pain; Oswestry Disability Index; operative time; intraoperative blood
3 loss; and complications. These parameters will be evaluated on Day 3, and then at 1, 3,
4 6, 12, and 24 months postoperatively.

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

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

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

14 **Strengths and limitations of this study:**

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

1 Introduction

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

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

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

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

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

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

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

6 7 **Methods and analysis**

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

15 16 ***Participants***

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

19 20 ***Randomization and blinding***

1
2
3
4 1 Participants will be equally randomized to either the CBT-TLIF group or the
5
6 2 PS-TLIF group based on a permuted blocks randomization scheme. Using a block
7
8 3 size of 4 in a scheduled computer-generated randomization program, the final group
9
10 4 assignments will be sealed in opaque envelopes. In order to ensure the proper
11
12 5 management of the randomisation procedure, the sequence numbers will be marked
13
14 6 on the opaque envelope, and the group assignment will be sealed inside. All envelopes
15
16 7 will be numbered sequentially. The envelopes will be delivered according to the
17
18 8 patients' sequence numbers, and the surgeon will be informed of the random numbers
19
20 9 and group assignments by either telephone or email. Patients will be kept blinded for
21
22 10 the allocated treatment until the last questionnaires have been completed. At the end
23
24 11 of the follow-up period, the blind can be lifted at the patients' request. In addition, the
25
26 12 statistician will also be blinded.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

14 ***Inclusion criteria***

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

1
2
3
4 **1 Exclusion criteria**
5
6

- 7 1. Spinal scoliosis with a Cobb angle of more than 10° in the index level.
8
9
10 2. Patients with prior failed fusion at the same level.
11
12 3. Pregnancy.
13
14 4. Active infection or prior infection at the surgical site.
15
16 5. Planned (e)migration abroad within 2 years after inclusion.
17
18 6. Metabolic bone disease such as osteomalacia or Paget's disease.
19
20 7. Spondylolisthesis according to Meyerding grades III and IV.
21
22 8. Therapy with systemic corticosteroids or immunosuppressants.
23
24
25
26
27
28
29
30
31

32 **11 Interventions**
33
34

35 **12 CBT-TLIF group**
36

37
38 After the preventive use of antibiotics, patients were placed under general
39
40 anesthesia in the prone position. A small skin incision was made at the fused segment
41
42 and an entry point to allow insertion of the CBT screws was drilled in the junction of
43
44 the center of the superior articular process and 1 mm inferior to the inferior border of
45
46 the transverse process according to Matsukawa et al.[15]. A straight probe was then
47
48 used to create a trajectory for the CBT screws from the entry point to the opposite
49
50 corner of the pedicle and vertebral body under anteroposterior fluoroscopic guidance.
51
52
53
54
55
56
57
58
59
60
60 Screws were placed bilaterally, targeting half of the vertebral body. Unilateral

1
2
3
4 1 facetectomy was performed to gain access to the intervertebral disc, followed by
5
6 2 discectomy. The endplate cartilage was prepared to provide a host bed of bleeding
7
8
9 3 subchondral bone for the placement of the cage. The structure of the interbody cage
10
11 4 was determined by a trial cage and fluoroscopy. The definitive cage was then filled
12
13 5 with autologous bone or allograft and tamped into place and its position was checked
14
15 6 radiologically. After placement of the interbody cage, the remainder of the disc space
16
17 7 was filled with autologous bone obtained from the decompression. A titanium rod
18
19 8 interconnected the screws on either side. The spreader was removed and the wound
20
21 9 thoroughly irrigated and closed in several layers without suction drainage.
22
23
24
25
26
27
28
29
30

31 *PS-TLIF group*
32
33

34 12 After the preventive use of antibiotics, patients were placed under general
35
36 13 anesthesia in the prone position. A posterior midline incision of about 6 cm was
37
38 14 performed at the level of interest under fluoroscopic guidance. Pedicle screws were
39
40 15 inserted freehand into the vertebral body, and the inferior and superior articular
41
42 16 processes and part of the lamina were removed by an osteotome. The ligamentum
43
44 17 flavum was then removed to expose the lateral border of the ipsilateral nerve root.
45
46 18 After decompression of the neural structures, a thorough discectomy and endplate
47
48 19 preparation were performed followed by transforaminal insertion of an intervertebral
49
50 20 tantalum mesh cage packed with autograft materials within the disc space. In both
51
52 21 CBT-TLIF and PS-TLIF, prior to cage insertion, the morselized bone graft from the
53
54
55
56
57
58
59
60

1
2
3
4 1 facetectomy and laminectomy was grafted into the prepared disc space. Compression
5
6 2 was achieved across the pedicle screws and rod with place screws and optimal
7
8
9 3 placement was confirmed by intraoperative fluoroscopy.
10
11
12
13
14

15 ***Outcome measurements***

16 *Primary outcomes:*

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

25 *Secondary outcomes:*

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

- 1
2
3
4 1 2. The ODI will be recorded both preoperatively and postoperatively[17]. The
5
6 2 ODI scores will be recorded preoperatively, at 3 days, at 1, 3 and 6 months,
7
8 3 and at 1 and 2 years postoperatively. The ODI assesses back pain-related
9
10 4 disability. It contains 10 questions about daily life, including measures of pain
11
12 5 intensity, personal care, lifting, walking, sitting, standing, sleeping, social life,
13
14 6 and traveling. Each question is rated on a scale of 0–5, with a higher score
15
16 7 indicating a more severe pain-related disability.
17
18 8
19 3. Japanese Orthopedic Association (JOA) scores will be recorded preoperatively,
20
21 9 at 3 days, at 1, 3 and 6 months, and at 1 and 2 years postoperatively. Functional
22
23 10 improvement is expressed by the rate of recovery of the JOA score[18].
24
25 11
26 4. The parameters of intervertebral height (including anterior and posterior
27
28 12 height of intervertebral), intervertebral foramen height, and Kyphosis angle
29
30 13 will be measured in X-ray fluorescence preoperatively, at 3 days, at 1, 3 and 6
31
32 14 months, and at 1 and 2 years postoperatively.
33
34 15
35 5. Operative time, intraoperative blood loss.
36
37 16
38 6. Complications including dural tear, postoperative infection, deep venous
39
40 17 thrombosis, hematoma, hardware failure, neurological deficits, and any other
41
42 18 direct and indirect surgical complications will be recorded.
43
44
45
46
47
48
49

50 Table 1 presents the data collection times.
51
52

53 ***Baseline demographics*** 54

55
56
57 21 Sex, age, body mass index, smoking habit, diagnosis, level, and occurrence of
58
59
60

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

3

4 ***Follow-up***

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

7

8 ***Monitoring***

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

15

16 ***Sample size calculation***

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

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

7 ***Statistical analysis***

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

18 **Discussion**

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

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

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

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

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

1
2
3
4 **Acknowledgement:**
5

6 The English in this document has been checked by at least two professional editors,
7
8 both native speakers of English. For a certificate, please see:
9
10 <http://www.textcheck.com/certificate/tDbZkH>
11
12
13

14
15
16
17 **Ethics and dissemination:**
18

19
20 The study had been reviewed and approved by the ethics committee of the
21
22 Second affiliated hospital of the Wenzhou Medical University, Wenzhou,
23
24 China(batch: 2017-03). The procedure will be performed following the principles
25
26 described in the Declaration of Helsinki. All of participants or their authorised
27
28 surrogates will be signed the informed consent. Participants' questions will be
29
30 answered by researchers. Researchers will obtain the informed consent form from
31
32 potential trial participants or authorised surrogates. The protocol has been registered
33
34 in US National Institutes of Health Clinical Trials Registry: NCT03105167. We will
35
36 share individual patient data (IPD) within 2 years after the trial complete, and the
37
38 original data is collected by clinical recording formula (both paper and electronic
39
40 version). The results will be presented in peer-reviewed journals and related website
41
42 (https://clinicaltrials.gov/) within 2 years after the last operation.
43
44
45
46
47
48
49

50
51

52
53
54 **Reference**
55

56
57
58
59
60

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 Spine*2005;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 Journal*2014;23(3):315-23.
3. Omidikashani F, Hasankhani EG, Ashjazadeh A. Lumbar Spinal Stenosis: Who Should Be Fused? An Updated Review. *Asian Spine Journal*2014;8(4):521.
4. Harms JG, Joeszszky D. Die posteriore, lumbale, interkorporelle Fusion in unilateraler transforaminaler Technik. *Operative Orthopädie und Traumatologie*1998;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 Surgery*2011;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 Journal*2009;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. *Spine*2014;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. *Spine*2014;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. *Spine*2013;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. *Spine*2016;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 Journal*2014;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 journal*2015;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 Surgery*2016.
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. *Bmj*2013;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 Surgery*2013;26(6):E248-E53.
16. Dixon J, Bird H. Reproducibility along a 10 cm vertical visual analogue scale. *Annals of the Rheumatic Diseases*1981;40(1):87-89.
17. Fairbank JC, Pynsent PB. The Oswestry disability index. *Spine*2000;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: Spine*2006;4(4):304-09.

- 1
2
3 19. Matsukawa K, Kato T, Yato Y, Sasao H, Imabayashi H, Hosogane N *et al*. Incidence and Risk Factors
4 of Adjacent Cranial Facet Joint Violation Following Pedicle Screw Insertion Using Cortical Bone
5 Trajectory Technique. *Spine*2016;41(14):E851.
6
7 20. Xuan J, Zhang D, Jin HM, Chen JX, Xu DL, Xu HM *et al*. Minimally invasive cortical bone trajectory
8 screws placement via pedicle or pedicle rib unit in the lower thoracic spine: a cadaveric and
9 radiographic study. *European Spine Journal*2016:1-9.
10
11 21. Matsukawa K, Yato Y, Nemoto O, Imabayashi H, Asazuma T, Nemoto K. Morphometric
12 measurement of cortical bone trajectory for lumbar pedicle screw insertion using computed
13 tomography. *Journal of Spinal Disorders & Techniques*2013;26(6):E248.
14
15 22. Matsukawa K, Yato Y, Kato T, Imabayashi H, Asazuma T, Nemoto K. In vivo analysis of insertional
16 torque during pedicle screwing using cortical bone trajectory technique. *Spine*2014;39(4):240-5.
17
18 23. Matsukawa K, Yato Y, Imabayashi H, Hosogane N, Asazuma T, Nemoto K. Biomechanical
19 evaluation of the fixation strength of lumbar pedicle screws using cortical bone trajectory: a finite
20 element study. *Journal of neurosurgery Spine*2015;23(4):471.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Table 1:Time of data collection.

Measures	Baseline	Operation	Follow-up					
			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		✓						

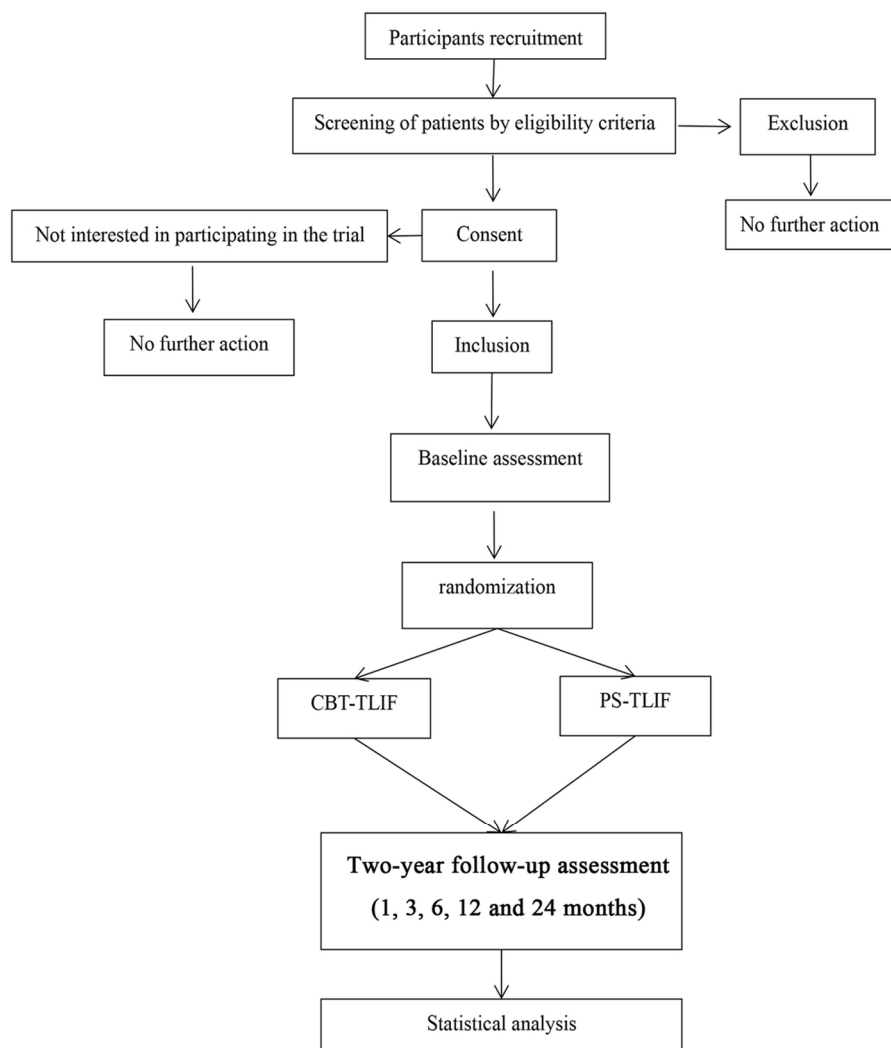
Blood loss	✓						
Complications	✓	✓	✓	✓	✓	✓	✓
FR					✓	X or ✓	
FJV		✓			✓	✓	✓
SLR			✓	✓	✓	✓	✓
VAS of back pain	✓	✓	✓	✓	✓	✓	✓
VAS of leg pain	✓	✓	✓	✓	✓	✓	✓
ODI	✓	✓	✓	✓	✓	✓	✓
JOA	✓	✓	✓	✓	✓	✓	✓
X-ray	✓	✓	✓	✓	✓	✓	✓

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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___

1				
2				
3	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___
4				
5				
6				
7	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___
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___NA___
11				
12		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___
13				
14				
15				
16	Methods: Monitoring			
17				
18	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___
19				
20				
21				
22				
23		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___
24				
25				
26	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___
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___13___
30				
31				
32				
33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___16___
36				
37				
38	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___
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.