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SUcceSS: Surgery for Spinal Stenosis – protocol of a randomised, placebo-controlled trial

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Title: SUcCeSS: Surgery for Spinal Stenosis – protocol of a randomised, placebo-controlled trial

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Abstract

Introduction: Central lumbar spinal canal stenosis (LSS) is a common cause of pain and reduced function and quality of life in older adults. Current management of LSS includes surgery to decompress the spinal canal and alleviate symptoms. However, evidence supporting surgical decompression derives from unblinded randomised trials with high cross-over rates or cohort studies showing modest benefits. This protocol describes the design of SUcceSS (SUrgery for Spinal Stenosis) - the first randomised placebo-controlled trial of decompressive surgery for symptomatic LSS.

Methods and analysis: SUcceSS will be a prospectively registered, randomised placebo-controlled trial of decompressive spinal surgery. 160 eligible participants (80 participants/group) with symptomatic LSS will be randomised to either surgical spine decompression or placebo surgical intervention. The placebo surgical group is identical in all other ways with the exception of removal of any bone or ligament. All participants and assessors will be blinded to treatment allocation. Outcomes will be assessed at baseline and at 3, 6, 12, and 24 months. The co-primary outcomes will be function measured with the Oswestry Disability Index (ODI) and the proportion of participants who have meaningfully improved their walking capacity at 3 months post-randomisation. Secondary outcomes include back pain intensity, lower limb pain intensity, disability, quality of life, anxiety and depression, neurogenic claudication score, perceived recovery, treatment satisfaction, adverse events, reoperation rate, and rehospitalisation rate. Those who decline to be randomised will be invited to participate in a parallel observational cohort. Data analysis will be blinded and by intention-to-treat. A trial-based cost-effectiveness analysis will determine the potential incremental cost per quality adjusted life year gained.

Ethics and dissemination: Ethics approval has been granted by the NSW Health (reference:17/247/POWH/601) and the Monash University (reference: 12371) Human Research Ethics Committees. Dissemination of results will be via journal articles and presentations at national and international conferences.

Trial registration number ACTRN12617000884303p (registered on 16/06/2017).

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Key words: randomised controlled trial, placebo controlled trial, surgery, lumbar spinal stenosis

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Article Summary

- This will be the first randomised placebo-controlled trial of surgery for symptomatic LSS.
- Participants and study assessors will be blinded to treatment allocation.
- The placebo intervention will resemble surgical decompression, but exclude removal of the bone and ligament (i.e. to increase the diameter of the spinal canal)
- The findings of this study will provide Level 1 evidence for the treatment efficacy, safety and cost-effectiveness of decompression for LSS.

Introduction

Lumbar spinal stenosis (LSS) is a common source of pain and reduced function in those over the age of 50.¹ The condition is attributed to a reduction in the diameter of the lumbar spinal canal from age-related degenerative changes of the surrounding structures, including the intervertebral discs, facet joints and ligaments.²⁻⁴ Symptoms typically include neurogenic claudication, which is defined as pain, paraesthesia, and/or fatigue in the gluteal area and/or legs that is aggravated by walking, and relieved by bending forward or sitting.⁵

In the Japanese population, approximately three quarters of those over 40 years of age have MRI signs of moderate central canal stenosis (i.e. narrowing by one third of the canal area).³ Thirty percent have severe stenosis (narrowing by two thirds), but only around one fifth of those report clinical symptoms.³ A case-multiple control study from the USA and including 126 individuals (50 with a clinical diagnosis of lumbar stenosis, 44 with back pain and no diagnosis of stenosis and 32 with no pain) found no correlation between imaging findings and clinical diagnosis of stenosis, with approximately 50% (n=13/32) of the asymptomatic participants being diagnosed with stenosis by blinded assessors.⁶ The diagnosis of LSS therefore, requires both the presence of clinical symptoms (i.e. neurogenic claudication) and evidence of stenosis on diagnostic imaging (e.g. Magnetic Resonance Imaging (MRI)).³ Current guidelines recommend symptomatic LSS be managed initially with non-operative treatment⁷, including oral medication (i.e. non-steroidal anti-inflammatory drugs and analgesics) and physical therapies (e.g. exercise therapy or manual therapy).⁸ If patients with symptomatic LSS fail to improve with non-operative treatment, referral for surgical assessment is recommended.^{7,9}

Surgical management of LSS involves decompression of the spinal canal via laminectomy or laminotomy.¹⁰⁻¹² The procedure is the most common form of spinal surgery in adults over the age of 65.¹³ Recent data from the USA estimates an adjusted rate of lumbar stenosis surgery of 135.5 per 100,000 Medicare beneficiaries, with a resulting aggregated hospital bill

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3 of \$1.65 billion per year. The evidence supporting this practice is however, inconclusive. The
4 latest Cochrane review assessing the efficacy of surgery compared to non-surgical care for
5 this population included five randomised controlled trials (643 participants) and concluded
6 there is low quality evidence that surgery provides little benefit after two years follow up
7 compared to non-surgical treatment (a difference in the Oswestry Disability Index of 4.43,
8 which is less than the accepted minimally clinically important difference of 15).¹⁴ This is in
9 part attributed to the methodological limitations of existing trials, including lack of participant
10 and assessor blinding, imprecise results due to small samples and high treatment
11 crossovers.¹⁵⁻¹⁹ For example, the Spine Patient Outcome Research Trial (SPORT trial)
12 published in 2008, evaluated the effects of surgery for spinal canal stenosis²⁰ in an open
13 randomised parallel group design. Over one third of participants assigned to surgery did not
14 undergo surgery, and almost half (43%) of those assigned to non-operative management
15 underwent surgery. Given patients' often have strong preferences for one treatment over the
16 other, treatment cross-overs are common in pragmatic open trials of surgical interventions.²⁰
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²¹ The results of the as-treated analysis in the SPORT trial favoured surgery in reducing pain and disability, but these results were not confirmed in the intention-to-treat analyses. A more recent trial by Delitto et al (2015) that randomised 169 patients to either decompressive surgery or physical therapy²¹ also failed to find any clinically important differences in pain improvement or physical function between treatment groups. Given the lack of robust evidence confirming the superiority of surgery compared to non-surgical care; the benefits of surgery observed in clinical practice might be attributable to non-specific effects, including regression to the mean and the placebo effects associated with invasive procedures.²² These findings highlight the need for a placebo-controlled trial of surgical decompression in this population.

The importance of a placebo surgical intervention is that it is indistinguishable (i.e. to the participant) from the traditional surgical procedure in many aspects. These include pre-operative and anaesthetic management; incision length and surgical dissection; and post-

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3 operative discomfort and management. By design and intention, the observable differences
4 between participants receiving placebo surgical intervention and those receiving the
5 traditional surgical procedure are more reliably due to the procedure itself and not the events
6 surrounding the procedure. In the case of lumbar surgical decompression, this means that
7 the placebo surgical intervention must include muscle dissection down to the bone of the
8 lumbar lamina, but no removal of bone or ligamentum flavum. Placebo interventions also
9 differ from sham in that a sham intervention might only involve a skin incision; falling short of
10 replicating the experience of the traditional surgical procedure, including absence of post-
11 surgical pain from muscle dissection, or any potential benefits from denervation effects of
12 surgical dissection.
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24 Placebo-controlled trials of surgical interventions are not new. In the late 1950s two
25 landmark randomised trials for patients with severe angina pectoris compared the common
26 practice of internal mammary artery ligation to placebo intervention.^{23 24} The observation that
27 the placebo intervention resulted in similar and sustained symptom relief as true ligation
28 surgery disproved the rationale of the procedure to increase coronary artery blood flow. A
29 recent systematic review identified a total of 53 randomised placebo-controlled trials of
30 surgery published between 1946 and 2013, with about half showing the index procedure
31 was superior to a placebo comparator, while the other half showed no superiority of the
32 surgical procedure.²⁵ The review also found that placebo trials can be safe, and that placebo
33 interventions are, in general, associated with less frequent and less severe adverse events
34 than the experimental group.
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48 Given the growing rates of surgical management of symptomatic LSS and the inconclusive
49 evidence supporting its efficacy, we have designed and will conduct the first placebo-
50 controlled trial of surgical decompression for this population. The aim of the SUcceSS trial is
51 to evaluate the efficacy, safety and cost-effectiveness of decompressive surgery for people
52 with severe LSS who have failed to respond to non-operative care. We will evaluate relevant
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3 participant outcomes related to LSS, including disability, walking capacity, pain, quality of
4 life, serious adverse events and reoperation rates. Our study hypothesis is that
5 decompression surgery is more effective, more cost-effective and safer than placebo
6 intervention in improving pain and function in patients with LSS. The study will also include a
7 parallel observational study of eligible participants who decline to be randomised to the
8 placebo-controlled trial to test for any selection bias.
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17 **Methods**

18 *Study Design*

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20 This paper describes a research protocol for the SUcceSS (SUrgery for Spinal Stenosis)
21 trial, a prospectively registered, randomised placebo-controlled trial of decompressive spinal
22 surgery for LSS. The participants, investigators other than the surgical team performing the
23 procedure, and outcome assessors will be blinded to treatment allocation. The protocol was
24 developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for
25 Interventional Trials), and TIDieR (Template for Intervention Description and Replication)
26 statements.^{26 27} The study design appears in Figure 1.
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37 *Participants and Recruitment*

38 Consecutive patients who present to one of the study surgeons in New South Wales or
39 Victoria, Australia will be assessed for eligibility and invited to participate. All study surgeons
40 will be qualified Orthopaedic Spine Surgeons or Neurosurgeons, and are required to have
41 current registration to perform spinal decompression surgery in Australia.
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48 *Inclusion criteria*

49 Participants will need to meet all the following inclusion criteria:

- 50 - Be 50 years of age or older;
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- Present with complaints of neurogenic claudication for at least three months. Neurogenic claudication is defined as pain, numbness and/or fatigue below the gluteal line with or without back pain (if back pain is present, leg pain is greater than back pain) that is precipitated by walking and alleviated by sitting or other posture of lumbar flexion.
- Have grades C or D stenosis as defined by Schizas et al²⁸ indicating occlusion (absent cerebrospinal fluid signal) of the central lumbar spinal canal at one or two levels on T2 weighted MRI or CT-Myelogram;
- Be considered by a study surgeon to be in need of single or dual-level decompressive surgery;
- Have not improved with non-surgical treatment (e.g. physiotherapy, medication).

Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

- Are pregnant;
- Are under a worker's compensation claim;
- Have been diagnosed with serious spinal pathology including: cancer, infection, cauda equina syndrome, spinal fracture;
- Present with active Paget's disease of the spine;
- Have a diagnosis of lumbar instability defined as more than 4mm translation or 10 degrees of angular motion between flexion and extension on upright lateral radiographs (to exclude participants who might need to undergo concurrent surgical fusion);
- Have had previous lumbar spine surgery at the same levels;
- Inadequate English to complete outcome measures;
- Motor deficit related to lumbar compression (Medical Research Council (MRC) grades 0-4) and the motor deficit interferes with walking ability;
- Presence of significant scoliosis (Cobb angle >25°) or other spinal deformities;

- Presence of known or demonstrated peripheral vascular disease causing vascular claudication i.e. claudication accompanied by absent foot pulse or vascular insufficiency detected with Doppler Ultrasound or CT angiography;
- Meyerding Classification grade 2 or greater spondylolisthesis;
- Symptomatic hip disease with symptoms reproduced with external or internal rotation of the hip joint; and
- Cognitive impairment interfering with participant's ability to give full and informed consent or complete the baseline or follow-up assessments.

If a study surgeon determines the participant has met the trial eligibility criteria, the participant will be provided with information about the trial and asked if they consent for a study researcher to contact them. As part of consent, participants will be informed they could be allocated on a 50:50 basis to receive either conventional decompression surgery or placebo intervention (no decompression). A researcher will then contact them, provide detailed trial information, obtain written informed consent, and collect all baseline assessments. A subject/participant identification (ID) number will then be allocated and the participant booked for surgery at the earliest available date. When surgery cannot be scheduled within six weeks from baseline, baseline assessments will be repeated to ensure a maximum of six weeks from baseline assessment to randomisation. Eligible patients who do not consent to participate in the randomised trial will be invited to participate in a parallel observational cohort. Participants who consent to participate in the observational cohort will be followed up for the duration of the trial and the same outcome measures will be collected at all time points.

Study Treatment

On the scheduled day of surgery, each participant will be admitted to the hospital of the recruiting study surgeon and follow the hospital's routine admission protocol. Participants will receive general anaesthesia, venous thromboembolism prophylaxis and prophylactic

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3 antibiotics. Based upon each individual surgeon's standard surgical practice, local
4 anaesthetic may be infiltrated into the subcutaneous tissues, with a single midline or dual
5 paramedian longitudinal skin incision made through skin and adipose layers. The posterior
6 spinal muscles will then be dissected in a subperiosteal fashion to expose lumbar laminae,
7 and self-retaining retractors placed. Participants will be randomised to treatment groups
8 following muscle dissection. If the patient is randomised to placebo, the surgeon will
9 progress no further and close the wound. In this case, the lumbar spinal canal will not be
10 entered or the dural sac decompressed. If the patient is randomised to receive surgery
11 involving decompression, the surgeon will proceed to remove bone from the lamina, and
12 underlying ligamentum flavum in order to enter the lumbar spinal canal and decompress the
13 dural sac. Following the decompression or placebo intervention, routine post-operative care
14 will follow as per the standard of care from the operating hospital (e.g. mobility advice,
15 wound care).

30 *Randomisation*

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32 Central randomisation will be utilised to ensure concealment of treatment allocation. An
33 interactive voice response will be used for automatic, 24 hours/day, 7 days/week allocation
34 of participants and delivered to participating surgeons at the time of surgery. The
35 randomisation will be obtained by a study trained theatre nurse who will contact the central
36 randomisation service following muscle dissection, but prior to decompression.
37 Randomisation will be by random permuted blocks of 4 and 6 and stratified by surgeon.

46 *Blinding*

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48 Participants, assessors and investigators other than the treating surgical team will be blinded
49 to treatment allocation. Randomisation will occur in the surgical theatre to eliminate
50 treatment bias by any of the surgical team prior to the procedure. Members of the surgical
51 team will not be involved in patient care after the procedure. Arrangements will be made for
52 surgical colleagues who are unaware of the treatment given to provide post-operative care

Data Collection

Blinded research staff will collect all baseline data including demographic data (e.g. work status, socioeconomic status, symptom duration etc), and outcome data, serious adverse events, and hospital admissions and medications. Outcomes will be collected at baseline and at 3, 6, 12 and 24 months (with adverse events and hospital admissions additionally collected at 9, 15, 18 and 21 months). All research staff will be trained to ensure data accuracy, consistency and completeness.

Primary Outcomes

The co-primary outcomes will be the function measured with the Oswestry Disability Index (ODI) score²⁹; and the proportion of participants who have meaningfully improved their walking capacity.³⁰ Meaningful improvement will be defined as a score of 6 or 7 on the walking capacity change scale: 'How would you say your walking capacity is today compared to immediately before surgery?', where 1 is 'a great deal worse' and 7 is 'a great deal better'.³¹ Co-primary outcomes will be measured at baseline (ODI only), 3, 6, 12, and 24 months. The primary outcome timepoint will be 3 months because the beneficial effects of definitive surgical decompression are likely to be apparent by then, and patients with poor clinical response are more likely to undergo further spinal imaging to assess adequacy of decompression, resulting in unblinding.

Secondary Outcomes

Secondary outcomes include:

1. Walking ability, using the walking section of the ODI³¹ will be measured at baseline, 3, 6, 12 and 24 months;
2. Assessment of Neurogenic Claudication: claudication will be measured using the Swiss Spinal Stenosis Questionnaire³² and will be measured at baseline, 3, 6, 12 and 24 months;

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- 3 **3.** Average lower limb pain in the past week will be measured using the 11-point
- 4 Numerical Rating Scale (NRS), where 0 is 'no pain' and 10 is 'worst possible pain',³³
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- 6 ³⁴ at baseline, 3, 6, 12 and 24 months;
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- 9 **4.** Average low back pain in the past week will be measured using the 11-point NRS
- 10 scale, where 0 is 'no pain' and 10 is 'worst possible pain',^{33 34} at baseline, 3, 6, 12
- 11 and 24 months;
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- 14 **5.** Quality of life: the Assessment of Quality of Life questionnaire will be used to assess
- 15 quality of life and to estimate quality-adjusted-life-years (QALYS) for the cost-
- 16 effectiveness analyses.^{35 36} It will be measured at baseline, 3, 6, 12 and 24 months;
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- 18 **6.** Self-reported perceived recovery: will be measured using a seven-point Likert scale
- 19 where 1 is 'worse than ever', and 7 is 'completely recovered'³⁷ will be measured at 3,
- 20 6, 12, and 24 months;
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- 23 **7.** Satisfaction with surgery: measured using section XIII of the Swiss Spinal Stenosis
- 24 Questionnaire, which asks "how satisfied are you with the overall result of your back
- 25 operation" where 1 is very satisfied and 4 is very dissatisfied³² will be measured at 3
- 26 months only;
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- 28 **8.** Re-operation and re-hospitalisation rates: data on hospital and/or privately funded
- 29 healthcare visits will be collected over the phone via the use of a diary which the
- 30 participant will keep and complete at all listed time-points. This data will be measured
- 31 at 3, 6, 9, 12, 15, 18, 21 and 24 months³⁸;
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- 33 **9.** Healthcare utilisation will be collected from participant diaries for the cost
- 34 effectiveness analysis at 3, 6, 9, 12, 15, 18, 21 and 24 months;
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- 36 **10.** Adverse events will be collected from participant diaries at screening, baseline, 3, 6,
- 37 9, 12, 15, 18, 21 and 24 months following treatment;
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- 40 **11.** Surgical decompression and placebo intervention fidelity: an MRI scan will be
- 41 performed on a random 20% selection of the decompression and placebo
- 42 intervention groups to assess fidelity of the surgical decompression and placebo
- 43 surgeries. This will be completed at the 24 month follow-up only.
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Other Data Collected

Demographic information, clinical data and expectation of treatment outcome will be collected at baseline. These measures include expectation of satisfaction with treatment outcome in terms of pain and walking capacity measured as: “How much pain relief would you expect from treatment?” and “How much improvement in your walking capacity would you expect from treatment?”. Participants will be asked to rate their expectation of change in walking capacity and expected pain relief using a seven-point Likert scale where 1 is ‘no improvement expected’ and 7 is ‘full recovery expected’.³⁹ Anxiety and Depression will be measured at baseline via the Hospital Anxiety and Depression Scale.⁴⁰ Blinding fidelity will be assessed by asking the patient “which study group do you think you were in?” (decompression surgery, placebo intervention, don’t know) and will be measured at hospital discharge following surgery; and at 3 months.

Adverse events

A Standard Operating Procedure (SOP) for clinical trial safety will be used to guide the data collection of adverse events, serious adverse events, suspected and unexpected serious adverse reactions in this study. This SOP will describe in detail the actions to be taken should adverse events occur and the relevant timelines. Serious Adverse events (SAE) are defined as any event that is life threatening, results in death, hospitalisation, or significant disability.³⁸ Any SAE will be immediately reported to the Data Monitoring committee by a notified study member. The Steering Committee will investigate the nature of the adverse event and whether unblinding of treatment allocation is necessary. The ethics committee will also be informed of all serious adverse events.

Treatment Fidelity

All staff involved in the delivery of the study will be required to undertake research training. This will include study surgeons, anaesthetists and nurses involved in the care of

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3 participants. Regular research meetings will be conducted with study staff, and site visits of
4 participating hospitals completed. Study patients will be provided with a study pamphlet that
5 can be shown to their other treating health care professionals (eg, physiotherapists, GPs
6 etc). The pamphlet explains the trial and their participation in it.
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10 11 12 *Unblinding*

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14 Unblinding will be carried out in the case of serious adverse events where knowledge of the
15 participant's treatment allocation is necessary for further medical management of the
16 participant, or in cases where the participant requests to be unblinded due to his/her
17 withdrawal from the study. Following unblinding the following information must be provided:
18 the reason for unblinding, details of the clinician, the date and time the decision was made,
19 and any supporting documentation. Regardless of unblinding, a follow-up schedule for data
20 collection will be attempted, to enable full analysis of all participant data on an intention-to-
21 treat basis.
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31 32 *Data Integrity*

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34 A Data Monitoring Committee has been convened and will overview data collection and
35 integrity. Data collected by the trained research staff will be directly entered into a custom-
36 built Electronic Data Capture program at the time of data collection, with a prompt for double
37 checking of the accuracy of the primary outcomes. Any inconsistencies in the data will be
38 explored and resolved. Any data completed by participants via questionnaires will be
39 recorded into the database by the research assistant.
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48 A database will be backed-up regularly on a secure network and compliant to the Note for
49 Guidance on Good Clinical Practice, according to our Data Management Plan. Study
50 personnel will only be able to access the database with a personal login and password.
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56 *Retention of documents*

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3 The study investigators will maintain adequate and accurate records to enable the conduct
4 of the study to be fully documented and the study data to be subsequently verified. These
5 documents will be classified into two separate categories (1) investigator's Study File, and
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7 (2) participant clinical source documents. The Investigator's Study File will contain the
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9 protocol/amendments, schedule of assessments, Independent Ethics Committee/Institutional
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11 Review Board and governmental approval with correspondence, sample informed consent,
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13 staff curriculum vitae and authorisation forms and other appropriate
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15 documents/correspondence.
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21 Should the study investigators wish to assign the study records to another party or move
22 them to another location, the sponsor must be notified in advance. After the completion of
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24 the study, study data will be archived by the sponsor for a minimum of 15 years.
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29 *Statistical Analysis*

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31 Treatment effectiveness analyses will be blinded and performed on an intention-to-treat
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33 basis. Statistical significance will be defined as $P < 0.025$ on the basis of a two-sided test. The
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35 three-month follow-up will be the primary endpoint. All between-group differences at all
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37 follow-up time points will be analysed with linear regression for continuous outcomes and
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39 logistic regression for dichotomous outcomes. Adjusted (sensitivity) and unadjusted (main)
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41 analyses will be presented for the main confounders. Heterogeneity between recruiting
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43 hospitals will be calculated and adjusted for in sensitivity analyses by including hospital as a
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45 covariate in the models. To elucidate if any sampling bias is present in the trial, baseline
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47 characteristics of participants in the randomised cohort will be contrasted with those in the
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49 observational cohort.
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54 In addition to a primary and secondary outcome analysis, a formal interim analysis will be
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56 conducted after two thirds of participants (n=107) have completed the 3-month follow-up of
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3 the co-primary outcome measurements (primary endpoint). The interim analysis will be
4 performed by a blinded statistician who can recommend to the Data Monitoring Committee
5 that the trial be terminated early for efficacy, defined as a between group difference greater
6 than 3 standard deviations. A recommendation to terminate the study early could also be
7 made if there is proof beyond reasonable doubt that the intervention or placebo cause an
8 unacceptable net harm. The trial will not be terminated on the grounds of futility.
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17 Sample size calculation was based on the between-group difference at all follow-ups, on co-
18 primary outcomes. A sample size of 80 per group (total of 160 participants) will achieve 90%
19 power to detect a minimum clinically important difference of 15 points on ODI (SD: 18) and
20 difference between groups in proportion of participants who have improved in the walking
21 change score (i.e. 6 or 7 on the Likert scale) of 30% (i.e. assuming 30% of participants in the
22 placebo group and 60% in the intervention group will have improved).³¹ This sample size
23 allows for a 15% loss to follow-up rate; 5% crossover between groups at three months^{38 41 42}
24 and provides enough power to detect an absolute difference of 20% in reoperation rates
25 over 2 years (the current reoperation rate for decompressive surgery is 7% and the rate of
26 surgery in the non-operative groups of previous studies is approximately 50%).⁴³
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38 *Cost-effectiveness Analysis*

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40 In the event of an observed positive treatment effect, a cost-effectiveness analysis will be
41 conducted. Intervention costs (staff, consumables, equipment, etc) will be ascertained from
42 financial statements from participating sites. Hospital admissions over the course of the
43 study in both patient arms will be recorded in patient diaries and costed on the basis of
44 published Diagnosis Related Group (DRG) cost weights. Non-hospital services will be
45 costed through individually linked Medicare data; costs of non-hospital medications will be
46 determined through individually linked Pharmaceutical Benefits Scheme data. The
47 aggregate of relevant costs to patients in both arms will be used to calculate the incremental
48 health care costs incurred (or cost-savings). Quality-adjusted life-years (QALY) will be used
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3 to determine effectiveness, and converted into a utility index, using data derived from the
4 Australian population. Average differences in QALYs will be estimated between treatment
5 and control arms. An incremental cost effectiveness ratio will be calculated based on the
6 ratio of incremental costs over incremental QALYs. Sensitivity analyses will be conducted to
7 determine robustness of the results to key assumptions made in the analyses.
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14 **Ethics and dissemination**

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16 The SuccES trial will be undertaken across multiple sites in New South Wales and Victoria,
17 Australia and a report of the trial findings will be prepared according to the CONSORT
18 statement. Authorship eligibility guidelines of publications arising from the SuccES study
19 will follow those outlined by the International Committee of Medical Journal Editors
20 (<http://www.icmje.org/>). Findings from the study will be disseminated via journal publications
21 and presentations at national and international conferences. The study is sponsored by The
22 University of Sydney, Australia and centrally coordinated and managed by staff based at the
23 Kolling Institute/Northern Clinical School. The sponsor has no role in the design of the trial. A
24 Steering Committee is responsible for study conception, design, protocol refinement, and
25 providing the scientific direction of the study. Members of the committee have expertise in
26 the conduct of large, high quality randomised trials, surgical trials and placebo trials of
27 surgery. The current protocol is V.2.0 (15/01/2018). Any modifications to the protocol which
28 may impact the study design and conduct, potential benefit or harm of the participants, will
29 require a formal amendment to the protocol. Such amendment will be agreed upon by the
30 SC and approved by the ethics committee prior to implementation. The study adheres with
31 the Australian NHMRC ethical guidelines for human research. Ethics approval has been
32 granted by the South Eastern Sydney Local Health District Human Research Ethics
33 Committee (reference:17/247/POWH/601) and the Monash University Human Research
34 Ethics Committee (reference: 12371). The study has been registered with the Australian and
35 New Zealand Clinical Trials Registry (ACTRN12617000884303p) and endorsed by the
36 Australian & New Zealand Musculoskeletal Clinical Trials Network.
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Discussion

This manuscript outlines the design of SUcceSS, the first randomised placebo-controlled trial of surgery for LSS. The trial has been endorsed by the Australia and New Zealand Musculoskeletal (ANZMUSC) Clinical Trials network; reflecting its robust design. The design of the SUcceSS trial is the result of an ongoing and close collaboration among researchers, health economists, biostatisticians, consumers and surgeons. SUcceSS will address the main limitations of previous surgical trials via its unique study design and use of a placebo arm. The inclusion of a placebo intervention will ensure blinding of participants and assessors to treatment allocation, limiting treatment crossover; and account for any placebo effect associated with decompression surgery. As a result, the study will provide high-quality evidence for the efficacy of decompressive surgery in treating LSS.

Our trial conforms to the ethical framework for the use of placebo procedures in clinical trials proposed by Horng & Miller, 2002.⁴⁴ According to the framework, the conduct of a placebo-controlled trial is ethical when: (i) it involves an important research question that cannot be answered without a placebo control. This is the case in surgical trials of LSS, given most commonly used outcome measures are self-reported and blinding of participants is impossible in 'open label' trials or those involving a no treatment control arm. In this case, there is no alternative to placebo and no other sufficiently rigorous trial design that has less risk (any other option will affect blinding); (ii) although the risks are greater than minimal they are likely to be equal in both groups. Past research has shown that the risk associated with placebo surgery is not greater than that of active surgery. Moreover, there are no anticipated extra risks and hazards to patients allocated to the placebo intervention group, since there will be no bone removal²⁵; (iii) risks associated with the placebo and active interventions do not exceed a threshold of acceptable research risk. We have been working closely with an ethicist to ensure all potential risks involved with participating in any of the interventions are appropriately disclosed to the participant; (iv) any risk in either arm is minimised by involving

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3 highly experienced and trained surgeons, following a carefully designed protocol and
4 establishing a data monitoring committee; and (vi) informed consent is sought prior to any
5 study-related procedures being conducted.
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10 One debate is whether the comparator for full surgical treatment should be placebo or sham
11 surgery. Placebo surgery is a surgical treatment performed in exactly the same way as the
12 procedure under investigation, but omitting the critical surgical element or mechanism, given
13 the mechanism by which it potentially obtains benefit has been questioned.⁴⁵ Placebo is
14 designed to cause the same effects on the participant as definitive surgical treatment (such
15 as discomfort), except for the critical element (canal decompression). It differs from sham
16 intervention which has only superficial similarity with definitive surgery, such as skin incision
17 only. Placebo surgery is frequently associated with larger beneficial effects on the participant
18 than a sham. Furthermore, placebo surgery also allows for more reliable blinding of patients
19 and assessors, than any other comparator (i.e. no treatment, non-surgical care and sham).
20 Therefore, to ensure a more robust design and given we currently lack strong evidence
21 supporting the therapeutic mechanism of decompression surgery (i.e. widening of the spinal
22 canal), the SucceSS trial team have opted to include a placebo surgical intervention.
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For peer review only

References

1. Fritz JM, Lurie JD, Zhao W, et al. Associations between physical therapy and long-term outcomes for individuals with lumbar spinal stenosis in the SPORT study. *Spine J* 2014;14(8):1611-21. doi: 10.1016/j.spinee.2013.09.044
2. Amundsen T, Weber H, Lilleas F, et al. Lumbar spinal stenosis. Clinical and radiologic features. *Spine (Phila Pa 1976)* 1995;20(10):1178-86. [published Online First: 1995/05/15]
3. Ishimoto Y, Yoshimura N, Muraki S, et al. Associations between radiographic lumbar spinal stenosis and clinical symptoms in the general population: the Wakayama Spine Study. *Osteoarthritis Cartilage* 2013;21(6):783-8. doi: 10.1016/j.joca.2013.02.656
4. de Schepper EI, Overvest GM, Suri P, et al. Diagnosis of lumbar spinal stenosis: an updated systematic review of the accuracy of diagnostic tests. *Spine (Phila Pa 1976)* 2013;38(8):E469-81. doi: 10.1097/BRS.0b013e31828935ac [published Online First: 2013/02/07]
5. Ishimoto Y, Yoshimura N, Muraki S, et al. Prevalence of symptomatic lumbar spinal stenosis and its association with physical performance in a population-based cohort in Japan: the Wakayama Spine Study. *Osteoarthritis Cartilage* 2012;20(10):1103-8.
6. Haig AJ, Tong HC, Yamakawa KS, et al. Spinal stenosis, back pain, or no symptoms at all? A masked study comparing radiologic and electrodiagnostic diagnoses to the clinical impression. *Arch Phys Med Rehabil* 2006;87(7):897-903. doi: 10.1016/j.apmr.2006.03.016 [published Online First: 2006/07/04]
7. NASS Evidence-Based Clinical Guidelines Committee. Diagnosis and Treatment of Degenerative Lumbar Spinal Stenosis. Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care. Illinois, USA, 2011.
8. Ammendolia C, Stuber KJ, Rok E, et al. Nonoperative treatment for lumbar spinal stenosis with neurogenic claudication. *Cochrane Database Syst Rev* 2013(8):CD010712. doi: 10.1002/14651858.CD010712 [published Online First: 2013/09/03]
9. Birkmeyer NJ, Weinstein JN, Tosteson AN, et al. Design of the Spine Patient outcomes Research Trial (SPORT). *Spine (Phila Pa 1976)* 2002;27(12):1361-72.
10. Machado GC, Ferreira PH, Yoo RI, et al. Surgical options for lumbar spinal stenosis. *Cochrane Database Syst Rev* 2016;11:CD012421. doi: 10.1002/14651858.CD012421
11. Overvest GM, Moojen WA, Arts MP, et al. Management of lumbar spinal stenosis: a survey among Dutch spine surgeons. *Acta Neurochir (Wien)* 2014;156(11):2139-45. doi: 10.1007/s00701-014-2186-6

12. Weber C, Lonne G, Rao V, et al. Surgical management of lumbar spinal stenosis: a survey among Norwegian spine surgeons. *Acta Neurochir (Wien)* 2017;159(1):191-97. doi: 10.1007/s00701-016-3020-0
13. Deyo RA, Mirza SK, Martin BI, et al. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA* 2010;303(13):1259-65. doi: 303/13/1259 [pii] 10.1001/jama.2010.338 [published Online First: 2010/04/08]
14. Zaina F, Tomkins-Lane C, Carragee E, et al. Surgical versus non-surgical treatment for lumbar spinal stenosis. *Cochrane Database Syst Rev* 2016;1:CD010264. doi: 10.1002/14651858.CD010264.pub2
15. Ammendolia C, Stuber KJ, Rok E, et al. Nonoperative treatment for lumbar spinal stenosis with neurogenic claudication. *Cochrane Database Syst Rev* 2013;8:CD010712. doi: 10.1002/14651858.CD010712 [published Online First: 2013/09/03]
16. Kovacs FM, Urrutia G, Alarcon JD. Surgery versus conservative treatment for symptomatic lumbar spinal stenosis: a systematic review of randomized controlled trials. *Spine (Phila Pa 1976)* 2011;36(20):E1335-51. doi: 10.1097/BRS.0b013e31820c97b1
17. May S, Comer C. Is surgery more effective than non-surgical treatment for spinal stenosis, and which non-surgical treatment is more effective? A systematic review. *Physiotherapy* 2013;99(1):12-20.
18. Moojen WA, Arts MP, Bartels RH, et al. Effectiveness of interspinous implant surgery in patients with intermittent neurogenic claudication: a systematic review and meta-analysis. *Eur Spine J* 2011;20(10):1596-606. doi: 10.1007/s00586-011-1873-8 [published Online First: 2011/06/15]
19. Ma XL, Zhao XW, Ma JX, et al. Effectiveness of surgery versus conservative treatment for lumbar spinal stenosis: A system review and meta-analysis of randomized controlled trials. *Int J Surg* 2017;44:329-38. doi: 10.1016/j.ijssu.2017.07.032
20. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *The New England Journal of Medicine* 2008;358(8):794-810. doi: 358/8/794
21. Delitto A, Piva SR, Moore CG, et al. Surgery versus nonsurgical treatment of lumbar spinal stenosis: a randomized trial. *Ann Intern Med* 2015;162(7):465-73. doi: 10.7326/M14-1420
22. Brim RL, Miller FG. The potential benefit of the placebo effect in sham-controlled trials: implications for risk-benefit assessments and informed consent. *J Med Ethics*

- 2013;39(11):703-7. doi: 10.1136/medethics-2012-101045 [published Online First: 2012/12/15]
23. Cobb LA, Thomas GI, Dillard DH, et al. An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med* 1959;260(22):1115-8. doi: 10.1056/NEJM195905282602204 [published Online First: 1959/05/28]
24. Dimond EG, Kittle CF, Crockett JE. Comparison of internal mammary artery ligation and sham operation for angina pectoris. *Am J Cardiol* 1960;5:483-6. [published Online First: 1960/04/01]
25. Wartolowska K, Judge A, Hopewell S, et al. Use of placebo controls in the evaluation of surgery: systematic review. *BMJ* 2014;348:g3253. doi: 10.1136/bmj.g3253 [published Online First: 2014/05/23]
26. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687. doi: 10.1136/bmj.g1687 [published Online First: 2014/03/13]
27. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. *Rev Panam Salud Publica* 2015;38(6):506-14. [published Online First: 2016/07/22]
28. Schizas C, Theumann N, Burn A, et al. Qualitative grading of severity of lumbar spinal stenosis based on the morphology of the dural sac on magnetic resonance images. *Spine (Phila Pa 1976)* 2010;35(21):1919-24. doi: 10.1097/BRS.0b013e3181d359bd [published Online First: 2010/07/31]
29. Fairbank J, Pynsent P. The Oswestry Disability Index. *Spine* 2000;25(22):2940-53.
30. Tomkins-Lane CC, Battie MC, Macedo LG. Longitudinal construct validity and responsiveness of measures of walking capacity in individuals with lumbar spinal stenosis. *Spine J* 2014;14(9):1936-43. doi: 10.1016/j.spinee.2013.11.030 [published Online First: 2013/12/03]
31. Tomkins-Lane CC, Battie MC, Macedo LG. Longitudinal construct validity and responsiveness of measures of walking capacity in individuals with lumbar spinal stenosis. *Spine Journal: Official Journal of the North American Spine Society* 2014;14(9):1936-43.
32. Pratt RK, Fairbank JC, Virr A. The reliability of the Shuttle Walking Test, the Swiss Spinal Stenosis Questionnaire, the Oxford Spinal Stenosis Score, and the Oswestry Disability Index in the assessment of patients with lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2002;27(1):84-91. [published Online First: 2002/01/24]
33. Giannadakis C, Solheim O, Jakola AS, et al. Surgery for Lumbar Spinal Stenosis in Individuals Aged 80 and Older: A Multicenter Observational Study. *J Am Geriatr Soc* 2016;64(10):2011-18.

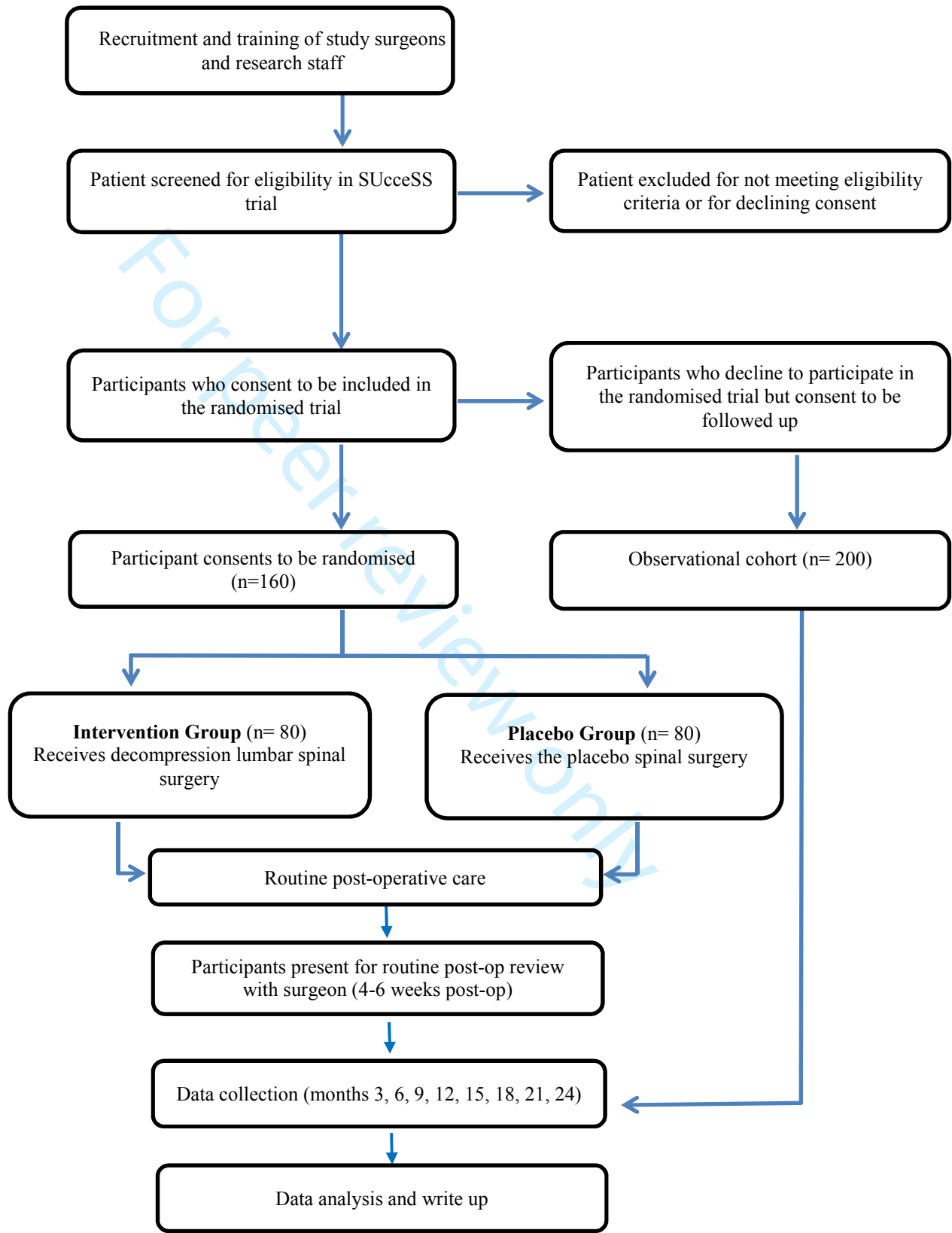
- 1
2
3 34. Lonne G, Johnsen LG, Rossvoll I, et al. Minimally invasive decompression versus x-stop
4 in lumbar spinal stenosis: a randomized controlled multicenter study. *Spine*
5 2015;40(2):77-85. doi: <https://dx.doi.org/10.1097/BRS.0000000000000691>
6
7 35. Hawthorne G, Korn S, Richardson J. Population norms for the AQL derived from the
8 2007 Australian National Survey of Mental Health and Wellbeing. *Aust N Z J Public*
9 *Health* 2013;37(1):7-16. doi: 10.1111/1753-6405.12004 [published Online First:
10 2013/02/06]
11
12 36. Hawthorne G, Richardson J, Day N. A comparison of the assessment of quality of life
13 (AQL) with four other generic utility instruments. *Annals of Medicine*
14 2001;33(5):358-70.
15
16 37. Moojen WA, Arts MP, Jacobs WC, et al. Interspinous process device versus standard
17 conventional surgical decompression for lumbar spinal stenosis: randomized
18 controlled trial. *BMJ* 2013;347:f6415. doi: 10.1136/bmj.f6415 [published Online First:
19 2013/11/16]
20
21 38. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for
22 lumbar spinal stenosis. *N Engl J Med* 2008;358(8):794-810. doi:
23 10.1056/NEJMoa0707136
24
25 39. Yee A, Adjei N, Do J, et al. Do patient expectations of spinal surgery relate to functional
26 outcome? *Clin Orthop* 2008;466(5):1154-61.
27
28 40. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr*
29 *Scand* 1983;67(6):361-70.
30
31 41. Barendse G, Berg S, Kessels A, et al. Randomized controlled trial of percutaneous
32 intradiscal radiofrequency thermocoagulation for chronic discogenic back pain: lack
33 of effect from a 90-second 70 C lesion. *Spine* 2001; 26(3).
34
35 42. Delitto A, Piva S, Moore C, et al. Surgery versus nonsurgical treatment of lumbar spinal
36 stenosis : A randomized trial. *Ann Intern Med* 2015;162(7):465-73.
37
38 43. Deyo RA, Martin BI, Kreuter W, et al. Revision surgery following operations for lumbar
39 stenosis. *Journal of Bone and Joint Surgery* 2011;93(21):1979-86. doi:
40 10.2106/JBJS.J.01292 [published Online First: 2011/11/04]
41
42 44. Horng S, Miller FG. Is placebo surgery unethical? *N Engl J Med* 2002;347(2):137-9. doi:
43 10.1056/NEJMsb021025
44
45 45. Beard D, Rees J, Rombach I, et al. The CSAW Study (Can Shoulder Arthroscopy
46 Work?) - a placebo-controlled surgical intervention trial assessing the clinical and
47 cost effectiveness of arthroscopic subacromial decompression for shoulder pain:
48 study protocol for a randomised controlled trial. *Trials* 2015;16:210. doi:
49 10.1186/s13063-015-0725-y
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3 **Authors statement:** MLF, IAH, RB and CGM had the original idea. MLF, IAH, GAD, RS,
4 DJB, QL, SJ, RM CGM, JL and RB were involved in the study design and secured funding.
5 All authors were involved in the protocol development. DBA and MLF wrote the first draft. All
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24 **Conflict of interest statement:** The authors declare they hold no conflict of interest with the
25 submitted work.
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Figure 1. The flowchart of the SUcceSS study design



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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

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

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

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

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| | | Reporting Item | Page Number |
|---|-----|--|-------------|
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | #3 | Date and version identifier | 18 |
| Funding | #4 | Sources and types of financial, material, and other support | 25 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 25 |
| Roles and responsibilities: | #5b | Name and contact information for the trial sponsor | 18 |

| | | | | |
|----|----------------------|------|---|--------|
| 1 | sponsor contact | | | |
| 2 | information | | | |
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| 4 | Roles and | #5c | Role of study sponsor and funders, if any, in study design; | 18 and |
| 5 | responsibilities: | | collection, management, analysis, and interpretation of | 25 |
| 6 | sponsor and funder | | data; writing of the report; and the decision to submit the | |
| 7 | | | report for publication, including whether they will have | |
| 8 | | | ultimate authority over any of these activities | |
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| 12 | Roles and | #5d | Composition, roles, and responsibilities of the coordinating | 18 |
| 13 | responsibilities: | | centre, steering committee, endpoint adjudication | |
| 14 | committees | | committee, data management team, and other individuals or | |
| 15 | | | groups overseeing the trial, if applicable (see Item 21a for | |
| 16 | | | data monitoring committee) | |
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| 19 | | | | |
| 20 | Background and | #6a | Description of research question and justification for | 5-7 |
| 21 | rationale | | undertaking the trial, including summary of relevant studies | |
| 22 | | | (published and unpublished) examining benefits and harms | |
| 23 | | | for each intervention | |
| 24 | | | | |
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| 27 | Background and | #6b | Explanation for choice of comparators | 5-7 |
| 28 | rationale: choice of | | | |
| 29 | comparators | | | |
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| 32 | Objectives | #7 | Specific objectives or hypotheses | 7-8 |
| 33 | | | | |
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| 35 | Trial design | #8 | Description of trial design including type of trial (eg, parallel | 7-8 |
| 36 | | | group, crossover, factorial, single group), allocation ratio, | |
| 37 | | | and framework (eg, superiority, equivalence, non-inferiority, | |
| 38 | | | exploratory) | |
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| 42 | Study setting | #9 | Description of study settings (eg, community clinic, | 8 |
| 43 | | | academic hospital) and list of countries where data will be | |
| 44 | | | collected. Reference to where list of study sites can be | |
| 45 | | | obtained | |
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| 48 | Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, | 8-10 |
| 49 | | | eligibility criteria for study centres and individuals who will | |
| 50 | | | perform the interventions (eg, surgeons, psychotherapists) | |
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| 54 | Interventions: | #11a | Interventions for each group with sufficient detail to allow | 10-11 |
| 55 | description | | replication, including how and when they will be | |
| 56 | | | administered | |
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| 1 | Interventions: | #11b | Criteria for discontinuing or modifying allocated | 14-15 |
| 2 | modifications | | interventions for a given trial participant (eg, drug dose | |
| 3 | | | change in response to harms, participant request, or | |
| 4 | | | improving / worsening disease) | |
| 5 | | | | |
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| 8 | Interventions: | #11c | Strategies to improve adherence to intervention protocols, | 14-15 |
| 9 | adherence | | and any procedures for monitoring adherence (eg, drug | |
| 10 | | | tablet return; laboratory tests) | |
| 11 | | | | |
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| 13 | Interventions: | #11d | Relevant concomitant care and interventions that are | 10-11 |
| 14 | concomitant care | | permitted or prohibited during the trial | |
| 15 | | | | |
| 16 | | | | |
| 17 | Outcomes | #12 | Primary, secondary, and other outcomes, including the | 12-14 |
| 18 | | | specific measurement variable (eg, systolic blood pressure), | |
| 19 | | | analysis metric (eg, change from baseline, final value, time | |
| 20 | | | to event), method of aggregation (eg, median, proportion), | |
| 21 | | | and time point for each outcome. Explanation of the clinical | |
| 22 | | | relevance of chosen efficacy and harm outcomes is strongly | |
| 23 | | | recommended | |
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| 27 | | | | |
| 28 | Participant timeline | #13 | Time schedule of enrolment, interventions (including any | Figure 1 |
| 29 | | | run-ins and washouts), assessments, and visits for | |
| 30 | | | participants. A schematic diagram is highly recommended | |
| 31 | | | (see Figure) | |
| 32 | | | | |
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| 35 | Sample size | #14 | Estimated number of participants needed to achieve study | 16 |
| 36 | | | objectives and how it was determined, including clinical and | |
| 37 | | | statistical assumptions supporting any sample size | |
| 38 | | | calculations | |
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| 42 | Recruitment | #15 | Strategies for achieving adequate participant enrolment to | 8 |
| 43 | | | reach target sample size | |
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| 46 | Allocation: sequence | #16a | Method of generating the allocation sequence (eg, | 11 |
| 47 | generation | | computer-generated random numbers), and list of any | |
| 48 | | | factors for stratification. To reduce predictability of a random | |
| 49 | | | sequence, details of any planned restriction (eg, blocking) | |
| 50 | | | should be provided in a separate document that is | |
| 51 | | | unavailable to those who enrol participants or assign | |
| 52 | | | interventions | |
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| 57 | Allocation | #16b | Mechanism of implementing the allocation sequence (eg, | 11 |
| 58 | concealment | | central telephone; sequentially numbered, opaque, sealed | |
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| 1 | mechanism | | envelopes), describing any steps to conceal the sequence | |
| 2 | | | until interventions are assigned | |
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| 4 | Allocation: | #16c | Who will generate the allocation sequence, who will enrol | 11 |
| 5 | implementation | | participants, and who will assign participants to | |
| 6 | | | interventions | |
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| 9 | Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, | 11 |
| 10 | | | trial participants, care providers, outcome assessors, data | |
| 11 | | | analysts), and how | |
| 12 | | | | |
| 13 | | | | |
| 14 | Blinding (masking): | #17b | If blinded, circumstances under which unblinding is | 11 |
| 15 | emergency | | permissible, and procedure for revealing a participant's | |
| 16 | unblinding | | allocated intervention during the trial | |
| 17 | | | | |
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| 20 | Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, | 11 |
| 21 | | | and other trial data, including any related processes to | |
| 22 | | | promote data quality (eg, duplicate measurements, training | |
| 23 | | | of assessors) and a description of study instruments (eg, | |
| 24 | | | questionnaires, laboratory tests) along with their reliability | |
| 25 | | | and validity, if known. Reference to where data collection | |
| 26 | | | forms can be found, if not in the protocol | |
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| 31 | Data collection plan: | #18b | Plans to promote participant retention and complete follow- | 11 |
| 32 | retention | | up, including list of any outcome data to be collected for | |
| 33 | | | participants who discontinue or deviate from intervention | |
| 34 | | | protocols | |
| 35 | | | | |
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| 38 | Data management | #19 | Plans for data entry, coding, security, and storage, including | 15 |
| 39 | | | any related processes to promote data quality (eg, double | |
| 40 | | | data entry; range checks for data values). Reference to | |
| 41 | | | where details of data management procedures can be | |
| 42 | | | found, if not in the protocol | |
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| 46 | Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary | 16-18 |
| 47 | | | outcomes. Reference to where other details of the statistical | |
| 48 | | | analysis plan can be found, if not in the protocol | |
| 49 | | | | |
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| 51 | Statistics: additional | #20b | Methods for any additional analyses (eg, subgroup and | 16-18 |
| 52 | analyses | | adjusted analyses) | |
| 53 | | | | |
| 54 | | | | |
| 55 | Statistics: analysis | #20c | Definition of analysis population relating to protocol non- | 16-18 |
| 56 | population and | | adherence (eg, as randomised analysis), and any statistical | |
| 57 | missing data | | methods to handle missing data (eg, multiple imputation) | |
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|----|--------------------|------|--|-------|
| 1 | Data monitoring: | #21a | Composition of data monitoring committee (DMC); summary | 15 |
| 2 | formal committee | | of its role and reporting structure; statement of whether it is | |
| 3 | | | independent from the sponsor and competing interests; and | |
| 4 | | | reference to where further details about its charter can be | |
| 5 | | | found, if not in the protocol. Alternatively, an explanation of | |
| 6 | | | why a DMC is not needed | |
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| 11 | Data monitoring: | #21b | Description of any interim analyses and stopping guidelines, | 16 |
| 12 | interim analysis | | including who will have access to these interim results and | |
| 13 | | | make the final decision to terminate the trial | |
| 14 | | | | |
| 15 | | | | |
| 16 | Harms | #22 | Plans for collecting, assessing, reporting, and managing | 14-15 |
| 17 | | | solicited and spontaneously reported adverse events and | |
| 18 | | | other unintended effects of trial interventions or trial conduct | |
| 19 | | | | |
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| 21 | Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, | 14 |
| 22 | | | and whether the process will be independent from | |
| 23 | | | investigators and the sponsor | |
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| 27 | Research ethics | #24 | Plans for seeking research ethics committee / institutional | 18 |
| 28 | approval | | review board (REC / IRB) approval | |
| 29 | | | | |
| 30 | | | | |
| 31 | Protocol | #25 | Plans for communicating important protocol modifications | 18 |
| 32 | amendments | | (eg, changes to eligibility criteria, outcomes, analyses) to | |
| 33 | | | relevant parties (eg, investigators, REC / IRBs, trial | |
| 34 | | | participants, trial registries, journals, regulators) | |
| 35 | | | | |
| 36 | | | | |
| 37 | Consent or assent | #26a | Who will obtain informed consent or assent from potential | 10 |
| 38 | | | trial participants or authorised surrogates, and how (see | |
| 39 | | | Item 32) | |
| 40 | | | | |
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| 43 | Consent or assent: | #26b | Additional consent provisions for collection and use of | 10 |
| 44 | ancillary studies | | participant data and biological specimens in ancillary | |
| 45 | | | studies, if applicable | |
| 46 | | | | |
| 47 | | | | |
| 48 | Confidentiality | #27 | How personal information about potential and enrolled | 15 |
| 49 | | | participants will be collected, shared, and maintained in | |
| 50 | | | order to protect confidentiality before, during, and after the | |
| 51 | | | trial | |
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| 55 | Declaration of | #28 | Financial and other competing interests for principal | 25 |
| 56 | interests | | investigators for the overall trial and each study site | |
| 57 | | | | |
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| 59 | Data access | #29 | Statement of who will have access to the final trial dataset, | 15-16 |
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and disclosure of contractual agreements that limit such access for investigators

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| 4 | Ancillary and post | #30 | Provisions, if any, for ancillary and post-trial care, and for | 10-11 |
| 5 | trial care | | compensation to those who suffer harm from trial | |
| 6 | | | participation | |
| 7 | | | | |
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| 9 | Dissemination policy: | #31a | Plans for investigators and sponsor to communicate trial | 18 |
| 10 | trial results | | results to participants, healthcare professionals, the public, | |
| 11 | | | and other relevant groups (eg, via publication, reporting in | |
| 12 | | | results databases, or other data sharing arrangements), | |
| 13 | | | including any publication restrictions | |
| 14 | | | | |
| 15 | | | | |
| 16 | | | | |
| 17 | Dissemination policy: | #31b | Authorship eligibility guidelines and any intended use of | 18 |
| 18 | authorship | | professional writers | |
| 19 | | | | |
| 20 | | | | |
| 21 | Dissemination policy: | #31c | Plans, if any, for granting public access to the full protocol, | n/a |
| 22 | reproducible | | participant-level dataset, and statistical code | |
| 23 | research | | | |
| 24 | | | | |
| 25 | | | | |
| 26 | | | | |
| 27 | Informed consent | #32 | Model consent form and other related documentation given | n/a |
| 28 | materials | | to participants and authorised surrogates | |
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| 30 | | | | |
| 31 | Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of | n/a |
| 32 | | | biological specimens for genetic or molecular analysis in the | |
| 33 | | | current trial and for future use in ancillary studies, if | |
| 34 | | | applicable | |
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 38 BY-ND 3.0. This checklist was completed on 21. June 2018 using <http://www.goodreports.org/>, a tool
 39 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

SUcceSS: Surgery for Spinal Stenosis – protocol of a randomised, placebo-controlled trial

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Manuscripts

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Title: SUCceSS: Surgery for Spinal Stenosis – protocol of a randomised, placebo-controlled trial

Authors

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5 **Abstract**
6

7 **Introduction:** Central lumbar spinal canal stenosis (LSS) is a common cause of pain and reduced
8 function and quality of life in older adults. Current management of LSS includes surgery to
9 decompress the spinal canal and alleviate symptoms. However, evidence supporting surgical
10 decompression derives from unblinded randomised trials with high cross-over rates or cohort
11 studies showing modest benefits. This protocol describes the design of SUcceSS (SUrgery for
12 Spinal Stenosis) - the first randomised placebo-controlled trial of decompressive surgery for
13 symptomatic LSS.
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16 **Methods and analysis:** SUcceSS will be a prospectively registered, randomised placebo-
17 controlled trial of decompressive spinal surgery. 160 eligible participants (80 participants/group)
18 with symptomatic LSS will be randomised to either surgical spine decompression or placebo
19 surgical intervention. The placebo surgical group is identical in all other ways with the exception
20 of removal of any bone or ligament. All participants and assessors will be blinded to treatment
21 allocation. Outcomes will be assessed at baseline and at 3, 6, 12, and 24 months. The co-primary
22 outcomes will be function measured with the Oswestry Disability Index (ODI) and the proportion
23 of participants who have meaningfully improved their walking capacity at 3 months post-
24 randomisation. Secondary outcomes include back pain intensity, lower limb pain intensity,
25 disability, quality of life, anxiety and depression, neurogenic claudication score, perceived
26 recovery, treatment satisfaction, adverse events, reoperation rate, and rehospitalisation rate.
27
28 Those who decline to be randomised will be invited to participate in a parallel observational cohort.
29
30 Data analysis will be blinded and by intention-to-treat. A trial-based cost-effectiveness analysis
31 will determine the potential incremental cost per quality adjusted life year gained.
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34 **Ethics and dissemination:** Ethics approval has been granted by the NSW Health
35 (reference:17/247/POWH/601) and the Monash University (reference: 12371) Human Research
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3 Ethics Committees. Dissemination of results will be via journal articles and presentations at
4 national and international conferences.
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7 **Trial registration number** ACTRN12617000884303 (registered on 16/06/2017; updated and
8 approved 18/09/2018).
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11 **Key words:** randomised controlled trial, placebo controlled trial, surgery, lumbar spinal stenosis

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13 **Word count:** 4,759
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Article Summary

- This will be the first randomised placebo-controlled trial of surgery for symptomatic LSS.
- Participants and study assessors will be blinded to treatment allocation.
- The placebo intervention will resemble surgical decompression, but exclude removal of the bone and ligament (i.e. to increase the diameter of the spinal canal)
- The findings of this study will provide Level 1 evidence for the treatment efficacy, safety and cost-effectiveness of decompression for LSS.

Introduction

Lumbar spinal stenosis (LSS) is a common source of pain and reduced function in those over the age of 50.¹ The condition is attributed to a reduction in the diameter of the lumbar spinal canal from age-related degenerative changes of the surrounding structures, including the intervertebral discs, facet joints and ligaments.²⁻⁴ Symptoms typically include neurogenic claudication, which is defined as pain, paraesthesia, and/or fatigue in the gluteal area and/or legs that is aggravated by walking, and relieved by bending forward or sitting.⁵

In the Japanese population, approximately three quarters of those over 40 years of age have MRI signs of moderate central canal stenosis (i.e. narrowing by one third of the canal area).³ Thirty percent have severe stenosis (narrowing by two thirds), but only around one fifth of those report clinical symptoms.³ A case-multiple control study from the USA and including 126 individuals (50 with a clinical diagnosis of lumbar stenosis, 44 with back pain and no diagnosis of stenosis and 32 with no pain) found no correlation between imaging findings and clinical diagnosis of stenosis, with approximately 50% (n=13/32) of the asymptomatic participants being diagnosed with stenosis by blinded assessors.⁶ The diagnosis of LSS therefore, requires both the presence of clinical symptoms (i.e. neurogenic claudication) and evidence of stenosis on diagnostic imaging (e.g. Magnetic Resonance Imaging (MRI)).³ Current guidelines recommend symptomatic LSS be managed initially with non-operative treatment⁷, including oral medication (i.e. non-steroidal anti-inflammatory drugs and analgesics) and physical therapies (e.g. exercise therapy or manual therapy).⁸ If patients with symptomatic LSS fail to improve with non-operative treatment, referral for surgical assessment is recommended.⁷⁻⁹

Surgical management of LSS involves decompression of the spinal canal via laminectomy or laminotomy.¹⁰⁻¹² The procedure is the most common form of spinal surgery in adults over the age of 65.¹³ Recent data from the USA estimates an adjusted rate of lumbar stenosis surgery of 135.5

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3 per 100,000 Medicare beneficiaries, with a resulting aggregated hospital bill of \$1.65 billion per
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5 year. The evidence supporting this practice is however, inconclusive. The latest Cochrane review
6
7 assessing the efficacy of surgery compared to non-surgical care for this population included five
8
9 randomised controlled trials (643 participants) and concluded there is low quality evidence that
10
11 surgery provides little benefit after two years follow up compared to non-surgical treatment (a
12
13 difference in the Oswestry Disability Index of 4.43, which is less than the accepted minimally
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15 clinically important difference of 15).¹⁴ This is in part attributed to the methodological limitations
16
17 of existing trials, including lack of participant and assessor blinding, imprecise results due to small
18
19 samples and high treatment crossovers.¹⁵⁻¹⁹ For example, the Spine Patient Outcome Research
20
21 Trial (SPORT trial) published in 2008, evaluated the effects of surgery for spinal canal stenosis²⁰
22
23 in an open randomised parallel group design. Over one third of participants assigned to surgery
24
25 did not undergo surgery, and almost half (43%) of those assigned to non-operative management
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27 underwent surgery. Given patients' often have strong preferences for one treatment over the
28
29 other, treatment cross-overs are common in pragmatic open trials of surgical interventions.^{20 21}
30
31 The results of the as-treated analysis in the SPORT trial favoured surgery in reducing pain and
32
33 disability, but these results were not confirmed in the intention-to-treat analyses. A more recent
34
35 trial by Delitto et al (2015) that randomised 169 patients to either decompressive surgery or
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37 physical therapy²¹ also failed to find any clinically important differences in pain improvement or
38
39 physical function between treatment groups. Given the lack of robust evidence confirming the
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41 superiority of surgery compared to non-surgical care; the benefits of surgery observed in clinical
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43 practice might be attributable to non-specific effects, including regression to the mean and the
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45 placebo effects associated with invasive procedures.²² These findings highlight the need for a
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47 placebo-controlled trial of surgical decompression in this population.
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54 The importance of a placebo surgical intervention is that it is indistinguishable (i.e. to the
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56 participant) from the traditional surgical procedure in many aspects. These include pre-operative
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3 and anaesthetic management; incision length and surgical dissection; and post-operative
4 discomfort and management. By design and intention, the observable differences between
5 participants receiving placebo surgical intervention and those receiving the traditional surgical
6 procedure are more reliably due to the procedure itself and not the events surrounding the
7 procedure. In the case of lumbar surgical decompression, this means that the placebo surgical
8 intervention must include muscle dissection down to the bone of the lumbar lamina, but no
9 removal of bone or ligamentum flavum. Placebo interventions also differ from sham in that a sham
10 intervention might only involve a skin incision; falling short of replicating the experience of the
11 traditional surgical procedure, including absence of post-surgical pain from muscle dissection, or
12 any potential benefits from denervation effects of surgical dissection.
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26 Placebo-controlled trials of surgical interventions are not new. In the late 1950s two landmark
27 randomised trials for patients with severe angina pectoris compared the common practice of
28 internal mammary artery ligation to placebo intervention.^{23 24} The observation that the placebo
29 intervention resulted in similar and sustained symptom relief as true ligation surgery disproved
30 the rationale of the procedure to increase coronary artery blood flow. A recent systematic review
31 identified a total of 53 randomised placebo-controlled trials of surgery published between 1946
32 and 2013, with about half showing the index procedure was superior to a placebo comparator,
33 while the other half showed no superiority of the surgical procedure.²⁵ The review also found that
34 placebo trials can be safe, and that placebo interventions are, in general, associated with less
35 frequent and less severe adverse events than the experimental group.
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49 Given the growing rates of surgical management of symptomatic LSS and the inconclusive
50 evidence supporting its efficacy, we have designed and will conduct the first placebo-controlled
51 trial of surgical decompression for this population. The aim of the SUCceSS trial is to evaluate the
52 efficacy, safety and cost-effectiveness of decompressive surgery for people with severe LSS who
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3 have failed to respond to non-operative care. We will evaluate relevant participant outcomes
4 related to LSS, including disability, walking capacity, pain, quality of life, serious adverse events
5 and reoperation rates. Our study hypothesis is that decompression surgery is more effective,
6 more cost-effective and safer than placebo intervention in improving pain and function in patients
7 with LSS. The study will also include a parallel observational study of eligible participants who
8 decline to be randomised to the placebo-controlled trial to test for any selection bias.
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18 **Methods**

19 *Study Design*

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21 This paper describes a research protocol for the SUcCeSS (SUrgery for Spinal Stenosis) trial, a
22 prospectively registered, randomised placebo-controlled trial of decompressive spinal surgery
23 for LSS. The participants, investigators other than the surgical team performing the procedure,
24 and outcome assessors will be blinded to treatment allocation. The protocol was developed in
25 accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials),
26 and TIDieR (Template for Intervention Description and Replication) statements.^{26 27} The study
27 design appears in Figure 1.
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39 *Participants and Recruitment*

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41 Consecutive patients who present to one of the study surgeons in New South Wales or Victoria,
42 Australia will be assessed for eligibility and invited to participate. All study surgeons will be
43 qualified Orthopaedic Spine Surgeons or Neurosurgeons, and are required to have current
44 registration to perform spinal decompression surgery in Australia.
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52 *Inclusion criteria*

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54 Participants will need to meet all the following inclusion criteria:
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- Be 50 years of age or older;
- Present with complaints of neurogenic claudication for at least three months. Neurogenic claudication is defined as pain, numbness and/or fatigue below the gluteal line with or without back pain (if back pain is present, leg pain is greater than back pain) that is precipitated by walking and alleviated by sitting or other posture of lumbar flexion.
- Have grades C or D stenosis as defined by Schizas et al²⁸ indicating occlusion (absent cerebrospinal fluid signal) of the central lumbar spinal canal at one or two levels on T2 weighted MRI or CT-Myelogram;
- Be considered by a study surgeon to be in need of single or dual-level decompressive surgery;
- Have not improved with non-surgical treatment (e.g. physiotherapy, medication).

Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

- Are pregnant;
- Are under a worker's compensation claim;
- Have been diagnosed with serious spinal pathology including: cancer, infection, cauda equina syndrome, spinal fracture;
- Present with active Paget's disease of the spine;
- Have a diagnosis of lumbar instability defined as more than 4mm translation or 10 degrees of angular motion between flexion and extension on upright lateral radiographs (to exclude participants who might need to undergo concurrent surgical fusion);
- Have had previous lumbar spine surgery at the same levels;
- Inadequate English to complete outcome measures;
- Motor deficit related to lumbar compression (Medical Research Council (MRC) grades 0-4) and the motor deficit interferes with walking ability;

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- 3 - Presence of significant scoliosis (Cobb angle $>25^\circ$) or other spinal deformities;
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- 5 - Presence of known or demonstrated peripheral vascular disease causing vascular
- 6 claudication i.e. claudication accompanied by absent foot pulse or vascular insufficiency
- 7 detected with Doppler Ultrasound or CT angiography;
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- 11 - Meyerding Classification grade 2 or greater spondylolisthesis;
- 12
- 13 - Symptomatic hip disease with symptoms reproduced with external or internal rotation of
- 14 the hip joint; and
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- 16
- 17 - Cognitive impairment interfering with participant's ability to give full and informed consent
- 18 or complete the baseline or follow-up assessments.
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23 If a study surgeon determines the participant has met the trial eligibility criteria, the participant will
24 be provided with information about the trial and asked if they consent for a study researcher to
25 contact them. As part of consent, participants will be informed they could be allocated on a 50:50
26 basis to receive either conventional decompression surgery or placebo intervention (no
27 decompression). A researcher will then contact them, provide detailed trial information, obtain
28 written informed consent, and collect all baseline assessments. A subject/participant identification
29 (ID) number will then be allocated and the participant booked for surgery at the earliest available
30 date. When surgery cannot be scheduled within six weeks from baseline, baseline assessments
31 will be repeated to ensure a maximum of six weeks from baseline assessment to randomisation.
32 Eligible patients who do not consent to participate in the randomised trial will be invited to
33 participate in a parallel observational cohort. Participants who consent to participate in the
34 observational cohort will be followed up for the duration of the trial and the same outcome
35 measures will be collected at all time points.
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52 *Study Treatment*

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3 On the scheduled day of surgery, each participant will be admitted to the hospital of the recruiting
4 study surgeon and follow the hospital's routine admission protocol. Participants will receive
5 general anaesthesia, venous thromboembolism prophylaxis and prophylactic antibiotics. Based
6 upon each individual surgeon's standard surgical practice, local anaesthetic may be infiltrated into
7 the subcutaneous tissues, with a single midline or dual paramedian longitudinal skin incision
8 made through skin and adipose layers. The posterior spinal muscles will then be dissected in a
9 subperiosteal fashion to expose lumbar laminae, and self-retaining retractors placed. Participants
10 will be randomised to treatment groups following muscle dissection. If the patient is randomised
11 to placebo, the surgeon will progress no further and close the wound. In this case, the lumbar
12 spinal canal will not be entered or the dural sac decompressed. If the patient is randomised to
13 receive surgery involving decompression, the surgeon will proceed to remove bone from the
14 lamina, and underlying ligamentum flavum in order to enter the lumbar spinal canal and
15 decompress the dural sac. Following the decompression or placebo intervention, routine post-
16 operative care will follow as per the standard of care from the operating hospital (e.g. mobility
17 advice, wound care).

36 *Randomisation*

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38 Central randomisation will be utilised to ensure concealment of treatment allocation. An interactive
39 voice response will be used for automatic, 24 hours/day, 7 days/week allocation of participants
40 and delivered to participating surgeons at the time of surgery. The randomisation will be obtained
41 by a study trained theatre nurse who will contact the central randomisation service following
42 muscle dissection, but prior to decompression. Randomisation will be by random permuted blocks
43 of 4 and 6 and stratified by surgeon.

53 *Blinding*

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3 Participants, assessors and investigators other than the treating surgical team will be blinded to
4 treatment allocation. Randomisation will occur in the surgical theatre to eliminate treatment bias
5 by any of the surgical team prior to the procedure. Members of the surgical team will not be
6 involved in patient care after the procedure. Arrangements will be made for surgical colleagues
7 who are unaware of the treatment given to provide post-operative care
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16 *Data Collection*

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18 Blinded research staff will collect all baseline data including demographic data (e.g. work status,
19 socioeconomic status, symptom duration etc), and outcome data, serious adverse events, and
20 hospital admissions and medications. Outcomes will be collected at baseline and at 3, 6, 12 and
21 24 months (with adverse events and hospital admissions additionally collected at 9, 15, 18 and
22 21 months). All research staff will be trained to ensure data accuracy, consistency and
23 completeness.
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32 *Primary Outcomes*

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34 The co-primary outcomes will be the function measured with the Oswestry Disability Index (ODI)
35 score²⁹; and the proportion of participants who have meaningfully improved their walking
36 capacity.³⁰ Our selection of co-primary outcomes reflects the two main complaints of patients
37 with lumbar spinal stenosis (LSS): **walking capacity and function**. The ODI is a self-reported
38 questionnaire commonly used to assess function in people with spinal conditions, including
39 lumbar spinal stenosis.^{20 21 31} The outcome has been validated in this population, showing good
40 post-surgery responsiveness, excellent internal consistency (alpha Cronbach of 0.9) and test
41 retest reliability (ICC:0.89).³² The ODI is also strongly correlated with patient satisfaction after
42 surgery.³²
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3 The self-reported walking capacity measure has also been validated in people with LSS and
4 neurogenic claudication, showing strong correlation with the ODI walking section (Spearman
5 Rho:0.64) and self-paced walking test (Spearman Rho:0.65; ICC: 0.68).^{33 34} Meaningful
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7 improvement will be defined as a score of 6 or 7 on the walking capacity change scale:
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9 'How would you say your walking capacity is today compared to immediately before surgery?',
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11 where 1 is 'a great deal worse' and 7 is 'a great deal better'³⁰. Co-primary outcomes will be
12
13 measured at baseline (ODI only), 3, 6, 12, and 24 months. The primary outcome timepoint will
14
15 be 3 months because the beneficial effects of definitive surgical decompression are likely to be
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17 apparent by then, and patients with poor clinical response are more likely to undergo further
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19 spinal imaging to assess adequacy of decompression, resulting in unblinding.
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28 *Secondary Outcomes*

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30 Secondary outcomes include:

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32 1. Walking ability, using the walking section of the ODI³⁰ will be measured at baseline, 3, 6,
33 12 and 24 months;
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35 2. Assessment of Neurogenic Claudication: claudication will be measured using the Swiss
36 Spinal Stenosis Questionnaire³² and will be measured at baseline, 3, 6, 12 and 24 months.
37 Results of the symptom severity and functional subscales of the Swiss Spinal Stenosis
38 Questionnaire will be separately reported;
- 39
40 3. Average lower limb pain in the past week will be measured using the 11-point Numerical
41 Rating Scale (NRS), where 0 is 'no pain' and 10 is 'worst possible pain',^{35 36} at baseline,
42 3, 6, 12 and 24 months;
- 43
44 4. Average low back pain in the past week will be measured using the 11-point NRS scale,
45 where 0 is 'no pain' and 10 is 'worst possible pain',^{35 36} at baseline, 3, 6, 12 and 24 months;
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3 **5.** Quality of life: the Assessment of Quality of Life questionnaire will be used to assess
4 quality of life and to estimate quality-adjusted-life-years (QALYS) for the cost-
5 effectiveness analyses.^{37 38} It will be measured at baseline, 3, 6, 12 and 24 months;
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9 **6.** Self-reported perceived recovery: will be measured using a seven-point Likert scale
10 where 1 is 'worse than ever', and 7 is 'completely recovered'³⁹ will be measured at 3, 6,
11 12, and 24 months;
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15 **7.** Satisfaction with surgery: measured using section XIII of the Swiss Spinal Stenosis
16 Questionnaire, which asks "how satisfied are you with the overall result of your back
17 operation" where 1 is very satisfied and 4 is very dissatisfied³² will be measured at 3
18 months only;
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22 **8.** Re-operation and re-hospitalisation rates: data on hospital and/or privately funded
23 healthcare visits will be collected over the phone via the use of a diary which the participant
24 will keep and complete at all listed time-points. This data will be measured at 3, 6, 9, 12,
25 15, 18, 21 and 24 months⁴⁰;
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29 **9.** Healthcare utilisation will be collected from participant diaries for the cost effectiveness
30 analysis at 3, 6, 9, 12, 15, 18, 21 and 24 months;
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34 **10.** Adverse events will be collected from participant diaries at screening, baseline, 3, 6, 9, 12,
35 15, 18, 21 and 24 months following treatment;
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39 **11.** Surgical decompression and placebo intervention fidelity: an MRI scan will be performed
40 on a random 20% selection of the decompression and placebo intervention groups to
41 assess fidelity of the surgical decompression and placebo surgeries. This will be
42 completed at the 24-month follow-up only.
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52 *Other Data Collected*

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3 Demographic information, clinical data and expectation of treatment outcome will be collected at
4
5 baseline. These measures include expectation of satisfaction with treatment outcome in terms of
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7 pain and walking capacity measured as: “How much pain relief would you expect from treatment?”
8
9 and “How much improvement in your walking capacity would you expect from treatment?”.
10
11 Participants will be asked to rate their expectation of change in walking capacity and expected
12
13 pain relief using a seven-point Likert scale where 1 is ‘no improvement expected’ and 7 is ‘full
14
15 recovery expected’.⁴¹ Anxiety and Depression will be measured at baseline via the Hospital
16
17 Anxiety and Depression Scale.⁴² Blinding fidelity will be assessed by asking the patient “which
18
19 study group do you think you were in?” (decompression surgery, placebo intervention, don’t know)
20
21 and will be measured at hospital discharge following surgery; and at 3 months.
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26 *Adverse events*

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28 A Standard Operating Procedure (SOP) for clinical trial safety will be used to guide the data
29
30 collection of adverse events, serious adverse events, suspected and unexpected serious adverse
31
32 reactions in this study. This SOP will describe in detail the actions to be taken should adverse
33
34 events occur and the relevant timelines. Events will be classified according to their attribution (not
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36 related, doubtful, possible, probable, and very likely); and severity (mild; moderate; or severe).
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38 Risks and complications of surgical decompression are rare and may include cerebrospinal fluid
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40 leak, postoperative instability of the operated level, infection, nerve root damage, and bleeding.
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45 Serious Adverse events (SAE) are defined as any event that is life threatening, results in death,
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47 hospitalisation, or significant disability.⁴⁰ Any SAE will be immediately reported to the Data
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49 Monitoring committee by a notified study member. The Steering Committee will investigate the
50
51 nature of the adverse event and whether unblinding of treatment allocation is necessary. The
52
53 ethics committee will also be informed of all serious adverse events.
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Treatment Fidelity

All staff involved in the delivery of the study will be required to undertake research training. This will include study surgeons, anaesthetists and nurses involved in the care of participants.

Regular research meetings will be conducted with study staff, and site visits of participating hospitals completed. Study patients will be provided with a study pamphlet that can be shown to their other treating health care professionals (eg, physiotherapists, GPs etc). The pamphlet explains the trial and their participation in it.

Unblinding

Unblinding will be carried out in the case of serious adverse events where knowledge of the participant's treatment allocation is necessary for further medical management of the participant, or in cases where the participant requests to be unblinded due to his/her withdrawal from the study. Following unblinding, the following information must be provided: the reason for unblinding, details of the clinician, the date and time the decision was made, and any supporting documentation. Regardless of unblinding, a follow-up schedule for data collection will be attempted, to enable full analysis of all participant data on an intention-to-treat basis. At the end of the trial, participants may be notified of the study results and treatment allocation if they wish to be.

Data Integrity

A Data Monitoring Committee has been convened and will overview data collection and integrity. Data collected by the trained research staff will be directly entered into a custom-built Electronic Data Capture program at the time of data collection, with a prompt for double checking of the accuracy of the primary outcomes. Any inconsistencies in the data will be explored and resolved. Any data completed by participants via questionnaires will be recorded into the database by the research assistant.

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5 A database will be backed-up regularly on a secure network and compliant to the Note for
6 Guidance on Good Clinical Practice, according to our Data Management Plan. Study personnel
7 will only be able to access the database with a personal login and password.
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11 12 13 *Retention of documents*

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15 The study investigators will maintain adequate and accurate records to enable the conduct of the
16 study to be fully documented and the study data to be subsequently verified. These documents
17 will be classified into two separate categories (1) investigator's Study File, and (2) participant
18 clinical source documents. The Investigator's Study File will contain the protocol/amendments,
19 schedule of assessments, Independent Ethics Committee/Institutional Review Board and
20 governmental approval with correspondence, sample informed consent, staff curriculum vitae and
21 authorisation forms and other appropriate documents/correspondence.
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32 Should the study investigators wish to assign the study records to another party or move them to
33 another location, the sponsor must be notified in advance. After the completion of the study, study
34 data will be archived by the sponsor for a minimum of 15 years.
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41 42 *Statistical Analysis*

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44 Treatment effectiveness analyses of randomised trial data will be blinded and performed on an
45 intention-to-treat basis. Statistical significance will be defined as $P < 0.025$ on the basis of a two-
46 sided test. The three-month follow-up will be the primary endpoint. All between-group differences
47 at all follow-up time points will be analysed with linear regression for continuous outcomes and
48 logistic regression for dichotomous outcomes. Adjusted (sensitivity) and unadjusted (main)
49 analyses will be presented for the main confounders. Heterogeneity between recruiting hospitals
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3 will be calculated and adjusted for in sensitivity analyses by including hospital as a covariate in
4 the models. To elucidate if any sampling bias is present in the trial, baseline characteristics of
5 participants in the randomised cohort will be contrasted with those in the observational cohort.
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11 In addition to a primary and secondary outcome analysis, a formal interim analysis will be
12 conducted after two thirds of participants (n=107) have completed the 3-month follow-up of the
13 co-primary outcome measurements (primary endpoint). The interim analysis will be performed by
14 a blinded statistician who can recommend to the Data Monitoring Committee that the trial be
15 terminated early for efficacy, defined as a between group difference greater than 3 standard
16 deviations. A recommendation to terminate the study early could also be made if there is proof
17 beyond reasonable doubt that the intervention or placebo cause an unacceptable net harm. The
18 trial will not be terminated on the grounds of futility.
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31 Sample size calculation was based on the between-group difference at all follow-ups, on co-
32 primary outcomes. A sample size of 80 per group (total of 160 participants) will achieve 90%
33 power to detect a minimum clinically important difference of 15 points (of a total of 100 points) on
34 ODI (SD: 18) and difference between groups in proportion of participants who have improved in
35 the walking change score (i.e. 6 or 7 on the Likert scale) of 30% (i.e. assuming 30% of participants
36 in the placebo group and 60% in the intervention group will have improved).⁴³ This sample size
37 allows for a 15% loss to follow-up rate; 5% crossover between groups at three months^{40 44 45} and
38 provides enough power to detect an absolute difference of 20% in reoperation rates over 2 years
39 (the current reoperation rate for decompressive surgery is 7% and the rate of surgery in the non-
40 operative groups of previous studies is approximately 50%).⁴⁶
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52 53 *Cost-effectiveness Analysis* 54 55 56 57 58 59 60

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3 In the event of an observed positive treatment effect, a cost-effectiveness analysis will be
4 conducted. Intervention costs (staff, consumables, equipment, etc) will be ascertained from
5 financial statements from participating sites. Hospital admissions over the course of the study in
6 both patient arms will be recorded in patient diaries and costed on the basis of published
7 Diagnosis Related Group (DRG) cost weights. Non-hospital services will be costed through
8 individually linked Medicare data; costs of non-hospital medications will be determined through
9 individually linked Pharmaceutical Benefits Scheme data. The aggregate of relevant costs to
10 patients in both arms will be used to calculate the incremental health care costs incurred (or cost-
11 savings). Quality-adjusted life-years (QALY) will be used to determine effectiveness, and
12 converted into a utility index, using data derived from the Australian population. Average
13 differences in QALYs will be estimated between treatment and control arms. An incremental cost
14 effectiveness ratio will be calculated based on the ratio of incremental costs over incremental
15 QALYs. Sensitivity analyses will be conducted to determine robustness of the results to key
16 assumptions made in the analyses.
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35 *Patient and Public Involvement*

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37 Consumer representatives were involved in different stages of the design of this trial. Prior to the
38 protocol development phase, patients presenting to orthopaedic surgeons with lumbar spinal
39 stenosis and indication for surgical decompression were surveyed regarding their views on the
40 value of such a study and their willingness to participate in this trial. Members of the Consumer
41 Advisory Group of the Australia and New Zealand Musculoskeletal (ANZMUSC) Clinical Trials
42 Network were also consulted and asked to provide feedback on the protocol during its
43 development phase.
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54 **Ethics and dissemination**

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3 The SuceSS trial will be undertaken across multiple sites in New South Wales and Victoria,
4 Australia and a report of the trial findings will be prepared according to the CONSORT statement.
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6 Authorship eligibility guidelines of publications arising from the SUCceSS study will follow those
7 outlined by the International Committee of Medical Journal Editors (<http://www.icmje.org/>).
8
9 Findings from the study will be disseminated via journal publications and presentations at national
10 and international conferences. The study is sponsored by The University of Sydney, Australia and
11 centrally coordinated and managed by staff based at the Kolling Institute/Northern Clinical School.
12
13 The sponsor has no role in the design of the trial. A Steering Committee is responsible for study
14 conception, design, protocol refinement, and providing the scientific direction of the study.
15
16 Members of the committee have expertise in the conduct of large, high quality randomised trials,
17 surgical trials and placebo trials of surgery. The current protocol is V.3.0 (13/07/2018). Any
18 modifications to the protocol which may impact the study design and conduct, potential benefit or
19 harm of the participants, will require a formal amendment to the protocol. Such amendment will
20 be agreed upon by the SC and approved by the ethics committee prior to implementation. The
21 study adheres with the Australian NHMRC ethical guidelines for human research. Ethics approval
22 has been granted by the South Eastern Sydney Local Health District Human Research Ethics
23 Committee (reference:17/247/POWH/601) and the Monash University Human Research Ethics
24 Committee (reference: 12371). The study has been registered with the Australian and New
25 Zealand Clinical Trials Registry (ACTRN12617000884303p) and endorsed by the Australian &
26 New Zealand Musculoskeletal Clinical Trials Network.
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47 **Discussion**

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49 This manuscript outlines the design of SUCceSS, the first randomised placebo-controlled trial of
50 surgery for LSS. The trial has been endorsed by the Australia and New Zealand Musculoskeletal
51 (ANZMUSC) Clinical Trials network; reflecting its robust design. The design of the SUCceSS trial
52 is the result of an ongoing and close collaboration among researchers, health economists,
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3 biostatisticians, consumers and surgeons. SUCceSS will address the main limitations of previous
4 surgical trials via its unique study design and use of a placebo arm. The inclusion of a placebo
5 intervention will ensure blinding of participants and assessors to treatment allocation, limiting
6 treatment crossover; and account for any placebo effect associated with decompression surgery.
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8 As a result, the study will provide high-quality evidence for the efficacy of decompressive surgery
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10 in treating LSS.
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18 Our trial conforms to the ethical framework for the use of placebo procedures in clinical trials
19 proposed by Horng & Miller, 2002.⁴⁷ According to the framework, the conduct of a placebo-
20 controlled trial is ethical when: (i) it involves an important research question that cannot be
21 answered without a placebo control. This is the case in surgical trials of LSS, given most
22 commonly used outcome measures are self-reported and blinding of participants is impossible in
23 'open label' trials or those involving a no treatment control arm. In this case, there is no alternative
24 to placebo and no other sufficiently rigorous trial design that has less risk (any other option will
25 affect blinding); (ii) although the risks are greater than minimal they are likely to be equal in both
26 groups. Past research has shown that the risk associated with placebo surgery is not greater than
27 that of active surgery. Moreover, there are no anticipated extra risks and hazards to patients
28 allocated to the placebo intervention group, since there will be no bone removal²⁵; (iii) risks
29 associated with the placebo and active interventions do not exceed a threshold of acceptable
30 research risk. We have been working closely with an ethicist to ensure all potential risks involved
31 with participating in any of the interventions are appropriately disclosed to the participant; (iv) any
32 risk in either arm is minimised by involving highly experienced and trained surgeons, following a
33 carefully designed protocol and establishing a data monitoring committee; and (vi) informed
34 consent is sought prior to any study-related procedures being conducted.
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3 One debate is whether the comparator for full surgical treatment should be placebo or sham
4 surgery. Placebo surgery is a surgical treatment performed in exactly the same way as the
5 procedure under investigation, but omitting the critical surgical element or mechanism, given the
6 mechanism by which it potentially obtains benefit has been questioned.⁴⁸ Placebo is designed to
7 cause the same effects on the participant as definitive surgical treatment (such as discomfort),
8 except for the critical element (canal decompression). It differs from sham intervention which has
9 only superficial similarity with definitive surgery, such as skin incision only. Placebo surgery is
10 frequently associated with larger beneficial effects on the participant than a sham. Furthermore,
11 placebo surgery also allows for more reliable blinding of patients and assessors, than any other
12 comparator (i.e. no treatment, non-surgical care and sham). Therefore, to ensure a more robust
13 design and given we currently lack strong evidence supporting the therapeutic mechanism of
14 decompression surgery (i.e. widening of the spinal canal), the SucceSS trial team have opted to
15 include a placebo surgical intervention.
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34 **Figure Legends**

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36 Figure 1. The flowchart of the SUCceSS study design.
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54 **References**

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- 1
2
3 1. Fritz JM, Lurie JD, Zhao W, et al. Associations between physical therapy and long-term
4 outcomes for individuals with lumbar spinal stenosis in the SPORT study. *Spine J*
5 2014;14(8):1611-21.
6
7
- 8 2. Amundsen T, Weber H, Lilleas F, et al. Lumbar spinal stenosis. Clinical and radiologic
9 features. *Spine (Phila Pa 1976)* 1995;20(10):1178-86.
10
- 11 3. Ishimoto Y, Yoshimura N, Muraki S, et al. Associations between radiographic lumbar spinal
12 stenosis and clinical symptoms in the general population: the Wakayama Spine Study.
13 *Osteoarthritis Cartilage* 2013;21(6):783-8.
14
- 15 4. de Schepper EI, Overvest GM, Suri P, et al. Diagnosis of lumbar spinal stenosis: an
16 updated systematic review of the accuracy of diagnostic tests. *Spine (Phila Pa 1976)*
17 2013;38(8):E469-81.
18
- 19 5. Ishimoto Y, Yoshimura N, Muraki S, et al. Prevalence of symptomatic lumbar spinal stenosis
20 and its association with physical performance in a population-based cohort in Japan: the
21 Wakayama Spine Study. *Osteoarthritis Cartilage* 2012;20(10):1103-8.
22
- 23 6. Haig AJ, Tong HC, Yamakawa KS, et al. Spinal stenosis, back pain, or no symptoms at all? A
24 masked study comparing radiologic and electrodiagnostic diagnoses to the clinical
25 impression. *Arch Phys Med Rehabil* 2006;87(7):897-903.
26
- 27 7. NASS Evidence-Based Clinical Guidelines Committee. Diagnosis and Treatment of
28 Degenerative Lumbar Spinal Stenosis. Evidence-Based Clinical Guidelines for
29 Multidisciplinary Spine Care. Illinois, USA, 2011.
30
- 31 8. Ammendolia C, Stuber KJ, Rok E, et al. Nonoperative treatment for lumbar spinal stenosis
32 with neurogenic claudication. *Cochrane Database Syst Rev* 2013(8):CD010712.
33
- 34 9. Birkmeyer NJ, Weinstein JN, Tosteson AN, et al. Design of the Spine Patient outcomes
35 Research Trial (SPORT). *Spine (Phila Pa 1976)* 2002;27(12):1361-72.
36
- 37 10. Machado GC, Ferreira PH, Yoo RI, et al. Surgical options for lumbar spinal stenosis.
38 *Cochrane Database Syst Rev* 2016;11:CD012421.
39
- 40 11. Overvest GM, Moojen WA, Arts MP, et al. Management of lumbar spinal stenosis: a
41 survey among Dutch spine surgeons. *Acta Neurochir (Wien)* 2014;156(11):2139-45.
42
- 43 12. Weber C, Lonne G, Rao V, et al. Surgical management of lumbar spinal stenosis: a survey
44 among Norwegian spine surgeons. *Acta Neurochir (Wien)* 2017;159(1):191-97.
45
- 46 13. Deyo RA, Mirza SK, Martin BI, et al. Trends, major medical complications, and charges
47 associated with surgery for lumbar spinal stenosis in older adults. *JAMA*
48 2010;303(13):1259-65.
49
50
51
52
53
54
55
56
57
58
59
60

14. Zaina F, Tomkins-Lane C, Carragee E, et al. Surgical versus non-surgical treatment for lumbar spinal stenosis. *Cochrane Database Syst Rev* 2016;1:CD010264.
15. Ammendolia C, Stuber KJ, Rok E, et al. Nonoperative treatment for lumbar spinal stenosis with neurogenic claudication. *Cochrane Database Syst Rev* 2013;8:CD010712.
16. Kovacs FM, Urrutia G, Alarcon JD. Surgery versus conservative treatment for symptomatic lumbar spinal stenosis: a systematic review of randomized controlled trials. *Spine (Phila Pa 1976)* 2011;36(20):E1335-51.
17. May S, Comer C. Is surgery more effective than non-surgical treatment for spinal stenosis, and which non-surgical treatment is more effective? A systematic review. *Physiotherapy* 2013;99(1):12-20.
18. Moojen WA, Arts MP, Bartels RH, et al. Effectiveness of interspinous implant surgery in patients with intermittent neurogenic claudication: a systematic review and meta-analysis. *Eur Spine J* 2011;20(10):1596-606.
19. Ma XL, Zhao XW, Ma JX, et al. Effectiveness of surgery versus conservative treatment for lumbar spinal stenosis: A system review and meta-analysis of randomized controlled trials. *Int J Surg* 2017;44:329-38.
20. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *The New England Journal of Medicine* 2008;358(8):794-810.
21. Delitto A, Piva SR, Moore CG, et al. Surgery versus nonsurgical treatment of lumbar spinal stenosis: a randomized trial. *Ann Intern Med* 2015;162(7):465-73.
22. Brim RL, Miller FG. The potential benefit of the placebo effect in sham-controlled trials: implications for risk-benefit assessments and informed consent. *J Med Ethics* 2013;39(11):703-7.
23. Cobb LA, Thomas GI, Dillard DH, et al. An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med* 1959;260(22):1115-8.
24. Dimond EG, Kittle CF, Crockett JE. Comparison of internal mammary artery ligation and sham operation for angina pectoris. *Am J Cardiol* 1960;5:483-6.
25. Wartolowska K, Judge A, Hopewell S, et al. Use of placebo controls in the evaluation of surgery: systematic review. *BMJ* 2014;348:g3253.
26. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687. doi: 10.1136/bmj.g1687 [published Online First: 2014/03/13]
27. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. *Rev Panam Salud Publica* 2015;38(6):506-14.

- 1
2
3 28. Schizas C, Theumann N, Burn A, et al. Qualitative grading of severity of lumbar spinal
4 stenosis based on the morphology of the dural sac on magnetic resonance images.
5 *Spine (Phila Pa 1976)* 2010;35(21):1919-24.
6
7
8 29. Fairbank J, Pynsent P. The Oswestry Disability Index. *Spine* 2000;25(22):2940-53.
9
10 30. Tomkins-Lane CC, Battie MC, Macedo LG. Longitudinal construct validity and
11 responsiveness of measures of walking capacity in individuals with lumbar spinal
12 stenosis. *Spine J* 2014;14(9):1936-43.
13
14 31. Forsth P, Olafsson G, Carlsson T, et al. A Randomized, Controlled Trial of Fusion Surgery
15 for Lumbar Spinal Stenosis. *N Engl J Med* 2016;374(15):1413-23. doi:
16 10.1056/NEJMoa1513721
17
18 32. Pratt RK, Fairbank JC, Virr A. The reliability of the Shuttle Walking Test, the Swiss Spinal
19 Stenosis Questionnaire, the Oxford Spinal Stenosis Score, and the Oswestry Disability
20 Index in the assessment of patients with lumbar spinal stenosis. *Spine (Phila Pa 1976)*
21 2002;27(1):84-91.
22
23 33. Tomkins-Lane CC, Battie MC. Validity and reproducibility of self-report measures of walking
24 capacity in lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2010;35(23):2097-102. doi:
25 10.1097/BRS.0b013e3181f5e13b [published Online First: 2010/10/13]
26
27 34. Conway J, Tomkins CC, Haig AJ. Walking assessment in people with lumbar spinal
28 stenosis: capacity, performance, and self-report measures. *Spine J* 2011;11(9):816-23.
29 doi: 10.1016/j.spinee.2010.10.019 [published Online First: 2010/12/15]
30
31 35. Giannadakis C, Solheim O, Jakola AS, et al. Surgery for Lumbar Spinal Stenosis in
32 Individuals Aged 80 and Older: A Multicenter Observational Study. *J Am Geriatr Soc*
33 2016;64(10):2011-18.
34
35 36. Lonne G, Johnsen LG, Rossvoll I, et al. Minimally invasive decompression versus x-stop in
36 lumbar spinal stenosis: a randomized controlled multicenter study. *Spine* 2015;40(2):77-
37 85.
38
39 37. Hawthorne G, Korn S, Richardson J. Population norms for the AQoL derived from the 2007
40 Australian National Survey of Mental Health and Wellbeing. *Aust N Z J Public Health*
41 2013;37(1):7-16. doi: 10.1111/1753-6405.12004 [published Online First: 2013/02/06]
42
43 38. Hawthorne G, Richardson J, Day N. A comparison of the assessment of quality of life
44 (AQoL) with four other generic utility instruments. *Annals of Medicine* 2001;33(5):358-70.
45
46 39. Moojen WA, Arts MP, Jacobs WC, et al. Interspinous process device versus standard
47 conventional surgical decompression for lumbar spinal stenosis: randomized controlled
48 trial. *BMJ* 2013;347:f6415. doi: 10.1136/bmj.f6415 [published Online First: 2013/11/16]
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3 40. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar
4 spinal stenosis. *N Engl J Med* 2008;358(8):794-810. doi: 10.1056/NEJMoa0707136
5
6 41. Yee A, Adjei N, Do J, et al. Do patient expectations of spinal surgery relate to functional
7 outcome? *Clin Orthop* 2008;466(5):1154-61.
8
9 42. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*
10 1983;67(6):361-70.
11
12 43. Tomkins-Lane CC, Battie MC, Macedo LG. Longitudinal construct validity and
13 responsiveness of measures of walking capacity in individuals with lumbar spinal
14 stenosis. *Spine Journal: Official Journal of the North American Spine Society*
15 2014;14(9):1936-43.
16
17 44. Barendse G, Berg S, Kessels A, et al. Randomized controlled trial of percutaneous
18 intradiscal radiofrequency thermocoagulation for chronic discogenic back pain: lack of
19 effect from a 90-second 70 C lesion. *Spine* 2001; 26(3).
20
21 45. Delitto A, Piva S, Moore C, et al. Surgery versus nonsurgical treatment of lumbar spinal
22 stenosis : A randomized trial. *Ann Intern Med* 2015;162(7):465-73.
23
24 46. Deyo RA, Martin BI, Kreuter W, et al. Revision surgery following operations for lumbar
25 stenosis. *Journal of Bone and Joint Surgery* 2011;93(21):1979-86. doi:
26 10.2106/JBJS.J.01292 [published Online First: 2011/11/04]
27
28 47. Horng S, Miller FG. Is placebo surgery unethical? *N Engl J Med* 2002;347(2):137-9. doi:
29 10.1056/NEJMs021025
30
31 48. Beard D, Rees J, Rombach I, et al. The CSAW Study (Can Shoulder Arthroscopy Work?) - a
32 placebo-controlled surgical intervention trial assessing the clinical and cost effectiveness
33 of arthroscopic subacromial decompression for shoulder pain: study protocol for a
34 randomised controlled trial. *Trials* 2015;16:210. doi: 10.1186/s13063-015-0725-y
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3 **Authors statement:** MLF, IAH, RB and CGM had the original idea. MLF, IAH, GAD, RS, DB,
4
5 QL, SJ, RM CGM, JL and RB were involved in the study design and secured funding. DBA,
6
7 MLF, IAH, GAD, RS, DB QL, JS, RM, CGM, RY, TZ, JL, RB were involved in the protocol
8
9 development. DBA and MLF wrote the first draft. All authors have approved the final draft.
10
11

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28 submitted work.
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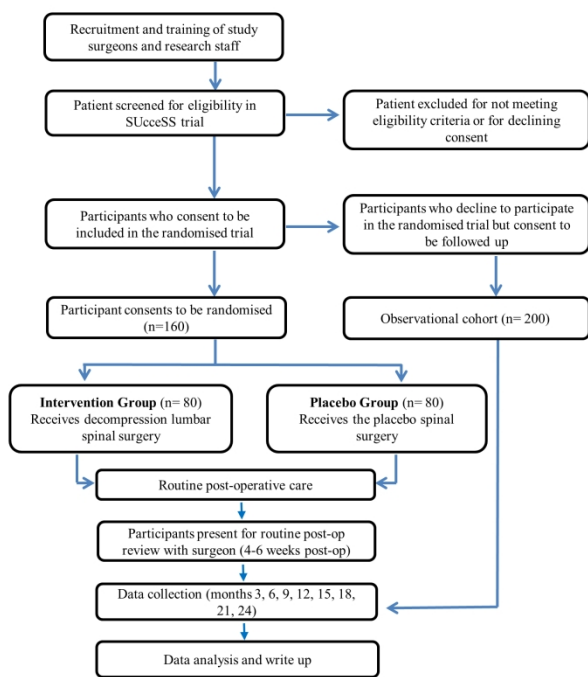


Figure 1. The flowchart of the SUcceSS study design.

254x190mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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

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

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

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

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| | | Reporting Item | Page Number |
|---|-----|--|-------------|
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | #3 | Date and version identifier | 18 |
| Funding | #4 | Sources and types of financial, material, and other support | 25 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 25 |
| Roles and responsibilities: | #5b | Name and contact information for the trial sponsor | 18 |

| | | | | |
|----|----------------------|------|---|--------|
| 1 | sponsor contact | | | |
| 2 | information | | | |
| 3 | | | | |
| 4 | Roles and | #5c | Role of study sponsor and funders, if any, in study design; | 18 and |
| 5 | responsibilities: | | collection, management, analysis, and interpretation of | 25 |
| 6 | sponsor and funder | | data; writing of the report; and the decision to submit the | |
| 7 | | | report for publication, including whether they will have | |
| 8 | | | ultimate authority over any of these activities | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | Roles and | #5d | Composition, roles, and responsibilities of the coordinating | 18 |
| 13 | responsibilities: | | centre, steering committee, endpoint adjudication | |
| 14 | committees | | committee, data management team, and other individuals or | |
| 15 | | | groups overseeing the trial, if applicable (see Item 21a for | |
| 16 | | | data monitoring committee) | |
| 17 | | | | |
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| 19 | | | | |
| 20 | Background and | #6a | Description of research question and justification for | 5-7 |
| 21 | rationale | | undertaking the trial, including summary of relevant studies | |
| 22 | | | (published and unpublished) examining benefits and harms | |
| 23 | | | for each intervention | |
| 24 | | | | |
| 25 | | | | |
| 26 | | | | |
| 27 | Background and | #6b | Explanation for choice of comparators | 5-7 |
| 28 | rationale: choice of | | | |
| 29 | comparators | | | |
| 30 | | | | |
| 31 | | | | |
| 32 | Objectives | #7 | Specific objectives or hypotheses | 7-8 |
| 33 | | | | |
| 34 | | | | |
| 35 | Trial design | #8 | Description of trial design including type of trial (eg, parallel | 7-8 |
| 36 | | | group, crossover, factorial, single group), allocation ratio, | |
| 37 | | | and framework (eg, superiority, equivalence, non-inferiority, | |
| 38 | | | exploratory) | |
| 39 | | | | |
| 40 | | | | |
| 41 | | | | |
| 42 | Study setting | #9 | Description of study settings (eg, community clinic, | 8 |
| 43 | | | academic hospital) and list of countries where data will be | |
| 44 | | | collected. Reference to where list of study sites can be | |
| 45 | | | obtained | |
| 46 | | | | |
| 47 | | | | |
| 48 | Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, | 8-10 |
| 49 | | | eligibility criteria for study centres and individuals who will | |
| 50 | | | perform the interventions (eg, surgeons, psychotherapists) | |
| 51 | | | | |
| 52 | | | | |
| 53 | | | | |
| 54 | Interventions: | #11a | Interventions for each group with sufficient detail to allow | 10-11 |
| 55 | description | | replication, including how and when they will be | |
| 56 | | | administered | |
| 57 | | | | |
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| 1 | Interventions: | #11b | Criteria for discontinuing or modifying allocated | 14-15 |
| 2 | modifications | | interventions for a given trial participant (eg, drug dose | |
| 3 | | | change in response to harms, participant request, or | |
| 4 | | | improving / worsening disease) | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | Interventions: | #11c | Strategies to improve adherence to intervention protocols, | 14-15 |
| 9 | adherence | | and any procedures for monitoring adherence (eg, drug | |
| 10 | | | tablet return; laboratory tests) | |
| 11 | | | | |
| 12 | | | | |
| 13 | Interventions: | #11d | Relevant concomitant care and interventions that are | 10-11 |
| 14 | concomitant care | | permitted or prohibited during the trial | |
| 15 | | | | |
| 16 | | | | |
| 17 | Outcomes | #12 | Primary, secondary, and other outcomes, including the | 12-14 |
| 18 | | | specific measurement variable (eg, systolic blood pressure), | |
| 19 | | | analysis metric (eg, change from baseline, final value, time | |
| 20 | | | to event), method of aggregation (eg, median, proportion), | |
| 21 | | | and time point for each outcome. Explanation of the clinical | |
| 22 | | | relevance of chosen efficacy and harm outcomes is strongly | |
| 23 | | | recommended | |
| 24 | | | | |
| 25 | | | | |
| 26 | | | | |
| 27 | | | | |
| 28 | Participant timeline | #13 | Time schedule of enrolment, interventions (including any | Figure 1 |
| 29 | | | run-ins and washouts), assessments, and visits for | |
| 30 | | | participants. A schematic diagram is highly recommended | |
| 31 | | | (see Figure) | |
| 32 | | | | |
| 33 | | | | |
| 34 | | | | |
| 35 | Sample size | #14 | Estimated number of participants needed to achieve study | 16 |
| 36 | | | objectives and how it was determined, including clinical and | |
| 37 | | | statistical assumptions supporting any sample size | |
| 38 | | | calculations | |
| 39 | | | | |
| 40 | | | | |
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| 42 | Recruitment | #15 | Strategies for achieving adequate participant enrolment to | 8 |
| 43 | | | reach target sample size | |
| 44 | | | | |
| 45 | | | | |
| 46 | Allocation: sequence | #16a | Method of generating the allocation sequence (eg, | 11 |
| 47 | generation | | computer-generated random numbers), and list of any | |
| 48 | | | factors for stratification. To reduce predictability of a random | |
| 49 | | | sequence, details of any planned restriction (eg, blocking) | |
| 50 | | | should be provided in a separate document that is | |
| 51 | | | unavailable to those who enrol participants or assign | |
| 52 | | | interventions | |
| 53 | | | | |
| 54 | | | | |
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| 57 | Allocation | #16b | Mechanism of implementing the allocation sequence (eg, | 11 |
| 58 | concealment | | central telephone; sequentially numbered, opaque, sealed | |
| 59 | | | | |
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|----|------------------------|------|--|-------|
| 1 | mechanism | | envelopes), describing any steps to conceal the sequence | |
| 2 | | | until interventions are assigned | |
| 3 | | | | |
| 4 | Allocation: | #16c | Who will generate the allocation sequence, who will enrol | 11 |
| 5 | implementation | | participants, and who will assign participants to | |
| 6 | | | interventions | |
| 7 | | | | |
| 8 | | | | |
| 9 | Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, | 11 |
| 10 | | | trial participants, care providers, outcome assessors, data | |
| 11 | | | analysts), and how | |
| 12 | | | | |
| 13 | | | | |
| 14 | Blinding (masking): | #17b | If blinded, circumstances under which unblinding is | 11 |
| 15 | emergency | | permissible, and procedure for revealing a participant's | |
| 16 | unblinding | | allocated intervention during the trial | |
| 17 | | | | |
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| 20 | Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, | 11 |
| 21 | | | and other trial data, including any related processes to | |
| 22 | | | promote data quality (eg, duplicate measurements, training | |
| 23 | | | of assessors) and a description of study instruments (eg, | |
| 24 | | | questionnaires, laboratory tests) along with their reliability | |
| 25 | | | and validity, if known. Reference to where data collection | |
| 26 | | | forms can be found, if not in the protocol | |
| 27 | | | | |
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| 30 | | | | |
| 31 | Data collection plan: | #18b | Plans to promote participant retention and complete follow- | 11 |
| 32 | retention | | up, including list of any outcome data to be collected for | |
| 33 | | | participants who discontinue or deviate from intervention | |
| 34 | | | protocols | |
| 35 | | | | |
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| 38 | Data management | #19 | Plans for data entry, coding, security, and storage, including | 15 |
| 39 | | | any related processes to promote data quality (eg, double | |
| 40 | | | data entry; range checks for data values). Reference to | |
| 41 | | | where details of data management procedures can be | |
| 42 | | | found, if not in the protocol | |
| 43 | | | | |
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| 46 | Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary | 16-18 |
| 47 | | | outcomes. Reference to where other details of the statistical | |
| 48 | | | analysis plan can be found, if not in the protocol | |
| 49 | | | | |
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| 51 | Statistics: additional | #20b | Methods for any additional analyses (eg, subgroup and | 16-18 |
| 52 | analyses | | adjusted analyses) | |
| 53 | | | | |
| 54 | | | | |
| 55 | Statistics: analysis | #20c | Definition of analysis population relating to protocol non- | 16-18 |
| 56 | population and | | adherence (eg, as randomised analysis), and any statistical | |
| 57 | missing data | | methods to handle missing data (eg, multiple imputation) | |
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| 1 | Data monitoring: | #21a | Composition of data monitoring committee (DMC); summary | 15 |
| 2 | formal committee | | of its role and reporting structure; statement of whether it is | |
| 3 | | | independent from the sponsor and competing interests; and | |
| 4 | | | reference to where further details about its charter can be | |
| 5 | | | found, if not in the protocol. Alternatively, an explanation of | |
| 6 | | | why a DMC is not needed | |
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| 11 | Data monitoring: | #21b | Description of any interim analyses and stopping guidelines, | 16 |
| 12 | interim analysis | | including who will have access to these interim results and | |
| 13 | | | make the final decision to terminate the trial | |
| 14 | | | | |
| 15 | | | | |
| 16 | Harms | #22 | Plans for collecting, assessing, reporting, and managing | 14-15 |
| 17 | | | solicited and spontaneously reported adverse events and | |
| 18 | | | other unintended effects of trial interventions or trial conduct | |
| 19 | | | | |
| 20 | | | | |
| 21 | Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, | 14 |
| 22 | | | and whether the process will be independent from | |
| 23 | | | investigators and the sponsor | |
| 24 | | | | |
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| 27 | Research ethics | #24 | Plans for seeking research ethics committee / institutional | 18 |
| 28 | approval | | review board (REC / IRB) approval | |
| 29 | | | | |
| 30 | | | | |
| 31 | Protocol | #25 | Plans for communicating important protocol modifications | 18 |
| 32 | amendments | | (eg, changes to eligibility criteria, outcomes, analyses) to | |
| 33 | | | relevant parties (eg, investigators, REC / IRBs, trial | |
| 34 | | | participants, trial registries, journals, regulators) | |
| 35 | | | | |
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| 37 | Consent or assent | #26a | Who will obtain informed consent or assent from potential | 10 |
| 38 | | | trial participants or authorised surrogates, and how (see | |
| 39 | | | Item 32) | |
| 40 | | | | |
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| 43 | Consent or assent: | #26b | Additional consent provisions for collection and use of | 10 |
| 44 | ancillary studies | | participant data and biological specimens in ancillary | |
| 45 | | | studies, if applicable | |
| 46 | | | | |
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| 48 | Confidentiality | #27 | How personal information about potential and enrolled | 15 |
| 49 | | | participants will be collected, shared, and maintained in | |
| 50 | | | order to protect confidentiality before, during, and after the | |
| 51 | | | trial | |
| 52 | | | | |
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| 55 | Declaration of | #28 | Financial and other competing interests for principal | 25 |
| 56 | interests | | investigators for the overall trial and each study site | |
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| 59 | Data access | #29 | Statement of who will have access to the final trial dataset, | 15-16 |
| 60 | | | | |

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| 1 | | | and disclosure of contractual agreements that limit such | |
| 2 | | | access for investigators | |
| 3 | | | | |
| 4 | Ancillary and post | #30 | Provisions, if any, for ancillary and post-trial care, and for | 10-11 |
| 5 | trial care | | compensation to those who suffer harm from trial | |
| 6 | | | participation | |
| 7 | | | | |
| 8 | | | | |
| 9 | Dissemination policy: | #31a | Plans for investigators and sponsor to communicate trial | 18 |
| 10 | trial results | | results to participants, healthcare professionals, the public, | |
| 11 | | | and other relevant groups (eg, via publication, reporting in | |
| 12 | | | results databases, or other data sharing arrangements), | |
| 13 | | | including any publication restrictions | |
| 14 | | | | |
| 15 | | | | |
| 16 | | | | |
| 17 | Dissemination policy: | #31b | Authorship eligibility guidelines and any intended use of | 18 |
| 18 | authorship | | professional writers | |
| 19 | | | | |
| 20 | | | | |
| 21 | Dissemination policy: | #31c | Plans, if any, for granting public access to the full protocol, | n/a |
| 22 | reproducible | | participant-level dataset, and statistical code | |
| 23 | research | | | |
| 24 | | | | |
| 25 | | | | |
| 26 | | | | |
| 27 | Informed consent | #32 | Model consent form and other related documentation given | n/a |
| 28 | materials | | to participants and authorised surrogates | |
| 29 | | | | |
| 30 | | | | |
| 31 | Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of | n/a |
| 32 | | | biological specimens for genetic or molecular analysis in the | |
| 33 | | | current trial and for future use in ancillary studies, if | |
| 34 | | | applicable | |
| 35 | | | | |
| 36 | | | | |

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 38 BY-ND 3.0. This checklist was completed on 21. June 2018 using <http://www.goodreports.org/>, a tool
 39 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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