



## **Protocol for a single-centre, parallel-arm, randomised controlled superiority trial evaluating the effects of transcatheter arterial embolisation of abnormal knee neovasculation on pain, function and quality of life in people with knee osteoarthritis**

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# BMJ Open Protocol for a single-centre, parallel-arm, randomised controlled superiority trial evaluating the effects of transcatheter arterial embolisation of abnormal knee neovascularity on pain, function and quality of life in people with knee osteoarthritis

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## ABSTRACT

**Introduction** Symptomatic knee osteoarthritis (OA) is common. Advanced knee OA is successfully treated with joint replacement surgery, but effectively managing mild to moderate knee OA can be difficult. Angiogenesis increases with OA and might contribute to pain and structural damage. Modifying angiogenesis is a potential treatment pathway for OA. The aim of the current study is to determine whether transcatheter arterial embolisation of abnormal neovascularity arising from the genicular arterial branches improves knee pain, physical function and quality of life in people with mild to moderate symptomatic knee OA.

**Methods and analysis** The study is a single centre, parallel-arm, double-blinded (participant and assessor), randomised controlled superiority trial with 1:1 random block allocation. Eligible participants have mild to moderate symptomatic knee OA and will be randomly assigned to receive either embolisation of aberrant knee neovascularity of genicular arterial branches or a placebo intervention. Outcome measures will be collected prior to the intervention and again 1, 6 and 12 months postintervention. The primary outcome is change in knee pain between baseline and 12 month assessment as measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS). Secondary outcomes include change in self-reported physical function (KOOS), self-reported quality of life (KOOS, EuroQol: EQ-5D-5L), self-reported knee joint stiffness (KOOS), self-reported global change, 6 min walk test performance, and 30 s chair-stand test performance. Intention-to-treat analysis will be performed including all participants as randomised. To detect a mean between group difference in change pain of 20% at the one year reassessment with a two-sided significance level of  $\alpha=0.05$  and power of 80% using a two-sample t-test, we require 29 participants per arm which allows for 20% of participants to drop out.

**Ethics and dissemination** Barwon Health Human Research Ethics Committee, 30 May 2016, (ref:15/101).

## Strengths and limitations of this study

- First randomised controlled trial to investigate vascular embolisation for treating knee pain
- Internal validity optimised by study design
- External validity limited by single-site study
- The study has implications for large numbers of people with knee osteoarthritis

Study results will be disseminated via peer-reviewed publications and conference presentations.

**Trial registration number** Universal trial number U1111-1183-8503, Australian New Zealand Clinical Trials Registry, ACTRN12616001184460, approved 29 August 2016.

## INTRODUCTION

Knee osteoarthritis (OA) is common and its prevalence is rising due to an ageing population and the obesity epidemic.<sup>1</sup> In 2010, radiographically confirmed symptomatic knee OA affected approximately 3.8% of people worldwide, and knee and hip OA ranked as the 11th highest contributor to global disability.<sup>2</sup> The prevalence and burden of knee OA presents a major challenge for health systems globally.<sup>2</sup>

Knee OA is a complex, multifactorial disease with no known cure. Knee OA risk factors include joint injury, bone and joint shape, muscle strength and mass, obesity, gender, metabolic factors, nutrition and vitamin factors, bone density, psychological health and occupation.<sup>3–5</sup> Treatment seeks to manage symptoms, but adequate symptom control can be difficult to achieve.<sup>6</sup> Core

evidence-based treatment options for knee OA include intra-articular corticosteroids, exercise (land based and water based), education, weight management, and oral medications such as paracetamol and non-steroidal anti-inflammatories.<sup>7</sup> Joint replacement is generally reserved for those with severe joint disease, pain and functional limitations.<sup>8,9</sup>

An in-depth understanding of OA pathophysiology is still emerging.<sup>1,3</sup> Recently, angiogenesis has been implicated in OA by contributing to structural damage, inflammation and pain.<sup>10</sup> Angiogenesis is blood vessel outgrowth from pre-existing vasculature and is essential for growth, development and tissue repair.<sup>10</sup> However, in OA, angiogenesis increases in articular cartilage, synovium, meniscus, and osteophytes, and at the osteochondral junction.<sup>11–15</sup> Because angiogenesis is accompanied by sensory nerve growth, perivascular nerve growth into normally aneural structures such as articular cartilage and meniscus is thought to contribute to OA pain through chemical and mechanical stimulation of newly formed nerves. Modifying angiogenesis and associated nerve growth is a potential treatment pathway to affect the pathogenesis and symptoms of OA.<sup>10</sup> Angiogenesis inhibitor treatment decreased pain-related behaviour in animal models.<sup>11</sup> The mechanism of symptomatic relief is unclear but could include reduced synovitis, reduced periarticular innervation and nociception, and maintaining the integrity of the osteochondral junction.<sup>10,11</sup> Okuno *et al* investigated the effects of embolising abnormal blood vessels about the knee on pain in people with mild to moderate knee OA.<sup>6</sup> Fourteen participants received transcatheter arterial embolisation of abnormal branches of the genicular artery using imipenem and cilastatin sodium or 75 µm Embosphere microspheres. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain and function scores improved substantially at 1, 4 and 12 months post procedure. No major adverse events occurred. One participant had a moderate subcutaneous haemorrhage at the puncture site that resolved within 1 week.

The current study seeks to elaborate on Okuno *et al*'s single-arm trial<sup>6</sup> by using a randomised controlled design with a larger cohort of people.

## OBJECTIVES

The primary objective of the study is to determine whether transcatheter arterial embolisation of abnormal neovasculature arising from the genicular arterial branches improves knee pain 12 months post intervention compared with a placebo intervention.

A secondary objective is to determine whether transcatheter arterial embolisation of abnormal neovasculature arising from the genicular arterial branches compared with a placebo intervention improves knee pain 1 and 6 months post intervention. Other secondary objectives are to determine whether the intervention compared with the placebo at 1, 6 and 12 months post intervention improves:

1. self-reported physical function;
2. self-reported quality of life;
3. self-reported knee joint stiffness;
4. self-reported global change;
5. six-minute walk test performance;
6. thirty-second chair stand test performance.

The tertiary objective of the study is to determine whether transcatheter arterial embolisation of abnormal neovasculature arising from the genicular arterial branches compared with a placebo intervention reduces pharmacotherapy (frequency and dosage) for knee pain 1, 6 and 12 months post intervention.

## METHODS AND ANALYSIS

### Study design

The study is a single-centre, parallel-arm, double-blinded (participant and assessor), randomised controlled superiority trial with 1:1 random block allocation. The study will be conducted at a large regional public health service in Victoria, Australia. Vascular embolisation is routinely conducted at the study site. Table 1 summarises the study schedule.

### Eligibility criteria

Eligible participants must have the following characteristics:

1. 18–75 years of age;
2. grade 2 knee OA on X-ray (including Rosenberg radiograph) as per Kellgren-Lawrence Grading Scale<sup>16</sup>;
3. knee pain for at least 6 months;
4. moderate to severe unilateral knee pain:
  - a.  $\geq 3/10$  knee pain on at least half the days in the preceding month according to an 11-point numeric scale with 0 representing 'no pain' and 10 'the worst pain imaginable';
5. pain resistant to conservative treatment for at least 6 months:
  - a. Conservative treatment might include medication (eg, paracetamol, anti-inflammatories), intra-articular injections, physiotherapy or exercise, or weight loss;
6. willing, able and mentally competent to provide informed consent (able to read and understand the Patient Information and Consent Form which is written in English language).

People who have the following characteristics are not eligible:

1. local infection;
2. active malignancy;
3. rheumatoid arthritis or seronegative arthropathies;
4. prior ipsilateral knee surgery excluding arthroscopic surgery more than 6 months ago;
5. ipsilateral knee intra-articular injection in the last 6 months;
6. grade 3 or 4 knee OA on X-ray as per Kellgren-Lawrence Grading Scale;<sup>16</sup>

**Table 1** Study schedule

	Prerandomisation	Day 0	Postintervention		
			1 month	6 months	12 months
<b>Enrolment</b>					
Eligibility screen	X				
Informed consent	X				
Randomisation		X			
<b>Interventions</b>					
Embolisation		X			
Placebo		X			
<b>Assessments</b>					
Demographic variables	X				
KOOS	X		X	X	X
EQ-5D-5L	X		X	X	X
Global change	X		X	X	X
Six-minute walk test	X		X	X	X
Thirty-second chair stand test	X		X	X	X
Analgesia	X		X	X	X

EQ-5D-5L: EuroQol.

Global change: overall change, change in pain, change in physical function.

KOOS, Knee Injury and Osteoarthritis Outcome Score (five scales: pain, symptoms, function in daily living, function in sports and recreational activities, quality of life).

7. pregnant or trying to become pregnant during the study period;
8. known history of allergy to contrast media;
9. reduced kidney function or failure (chronic or acute):
  - a. estimated glomerular filtration rate  $<30 \text{ ml/min/1.73 m}^2$ ;
10. body weight greater than 200 kg;
11. platelets  $<100 \times 10^9/\text{L}$ ;
12. international normalised ratio  $>1.5$ ;
13. approved for knee joint replacement surgery;
14. moderate to severe pain in other lower limb joints;
15. history of allergy to carbapenem (eg, imipenem, ertapenem or meropenem), or having an immediate or severe hypersensitivity reaction to a penicillin or cephalosporin antibiotic;
16. history of seizures or using valproate.

Participants will be recruited at the study site's physiotherapist-led outpatient screening clinic that routinely assesses people's eligibility for knee joint replacement surgery following referral from the person's general practitioner or rheumatologist. Physiotherapists will be trained by study investigators to assess and record participant eligibility and provide eligible participants with written information regarding the study. Physiotherapists will receive training from the principal investigator to grade knee X-rays with the Kellgren-Lawrence scale in a manner similar to that used by others.<sup>17</sup> Physiotherapists will receive descriptions of the scale, together with X-ray examples of each grade. An orthopaedic doctor will be provided with the same training material as the

physiotherapist and will also grade X-rays of potential participants. The physiotherapist and orthopaedic doctor will discuss any discrepancies until consensus is reached. The principal investigator will adjudicate if the physiotherapist and orthopaedic doctor cannot reach consensus regarding the grading. A study coordinator or investigator will guide interested people through written informed consent. Recruitment is expected to occur over an 18-month period, commencing in 2017.

Participation in the study is voluntary; no financial incentives will be offered. The participant's general practitioner will be informed by letter that the patient is taking part in the study; the general practitioner will not be informed of group allocation.

### Randomisation

People who meet eligibility requirements and provide informed consent will be randomly allocated to either intervention or control groups with a 1:1 allocation ratio. The allocation sequence will be computer generated by the trial statistician (SEL) prior to trial commencement and use randomly selected block sizes. Block sizes will not be disclosed to the interventionalist, assessors or other investigators. Allocation will be concealed until immediately prior to the participant's intervention, at which time the interventionalist will access the allocation code for that participant via the web-based project and data management tool.<sup>18</sup> Participants randomised to the control group will be offered the intervention at the completion of the study should it demonstrate effectiveness.

## Blinding

Participants and assessors will be blinded to group allocation throughout the study. Due to the nature of the intervention, it is not possible to blind the interventionist to group allocation. To assess the effectiveness of blinding, participants will be asked within 4 hours of the intervention which group they believed they were allocated to, and again 1 and 12 months post intervention.

## Interventions

The treatment group will receive angiography and embolisation; the control group will receive a placebo embolisation procedure. One interventional radiologist (SL), who is trained in vascular embolisation, will perform all procedures. The procedure, real or placebo, will take 30–60 min to complete.

Participants in the treatment group will receive light sedation with midazolam and fentanyl and a local anaesthetic injected into their groin. Femoral artery access will be obtained with a 3 French sheath and a microcatheter introduced. An angiogram will identify abnormal knee neovasculature arising from the genicular arterial branches. The abnormal vessels will be embolised with a suspension of 0.5 g imipenem and cilastatin sodium (Primaxin; Merck & Co, Whitehouse Station, New Jersey, USA) in 5 mL of iodinated contrast agent (prepared by pumping syringes for 10 s) by injecting 0.2 mL increments until blood flow stagnates. The guide wire will be removed. A dressing will be applied to the puncture site.

Participants in the control group will receive light sedation with midazolam and fentanyl and a local anaesthetic injection and incision into their groin. The radiologist will then pretend to insert a guide wire and catheter into the femoral artery and complete the embolisation procedure. No wire or catheter will be introduced. No radiation will be used. No contrast will be administered. During the placebo procedure, the participant will view prerecorded video images of an angiogram and genicular artery vascular embolisation. The duration of the placebo procedure will match the treatment group. A dressing will be applied to the incision site.

All participants will be monitored for 4 hours post procedure and any adverse events documented and managed. It is anticipated that most participants will be discharged home 4 hours post procedure.

## Outcome measures and assessment time points

Outcome measures will be collected 1–2 weeks before the intervention and 1, 6 and 12 months after the intervention.

The primary outcome is change in knee pain between baseline and 12-month follow-up assessments. Pain will be assessed with the Knee injury and Osteoarthritis Outcome Score (KOOS). The KOOS is a condition-specific, self-administered questionnaire that is commonly used in knee OA clinical trials.<sup>19</sup>

Change in KOOS pain scores at 1 and 6 months post intervention is a secondary outcome. Other secondary

outcomes include change at 1, 6 and 12 months of assessment for:

1. self-reported physical function: KOOS Function in Daily Living scale and KOOS Function in Sport and Recreation scale<sup>19</sup>;
2. self-reported quality of life: KOOS Quality of Life scale<sup>19</sup> and EQ-5D-5L<sup>20</sup>;
3. self-reported knee joint stiffness: KOOS Symptoms scale<sup>19</sup>;
4. self-reported global changes: overall change, change in knee pain, change in physical function using a 7-point ordinal scale designed by the investigators and based on a scale used by others<sup>21</sup>;
5. six-minute walk test performance<sup>22</sup>;
6. improved 30 s chair stand test performance<sup>23</sup>.

The tertiary outcome of change in pharmacotherapy to treat knee pain will be determined 1, 6 and 12 months post intervention by the participant's report of the frequency and dosage of medication taken. The study will not attempt to modify pharmacotherapy which will be determined by the participant and their relevant primary health professional. Participants in the intervention group will receive an MRI of their affected knee 12 months post intervention.

A research assistant, trained by the study investigators, will collect study data in person with each participant according to the pilot-tested study protocol. Participants will complete standardised questionnaires in paper format with assistance offered by the research assistant as required. Performance-based measures will be collected by the research assistant using standardised protocols. The research assistant will enter data into REDCap, the study's password-protected electronic data collection and management tool hosted at Barwon Health.<sup>18</sup>

The study will collect baseline demographic information including age, sex, height, body weight, medical comorbidities and highest educational status.

The study will record, but not attempt to modify throughout the study period, participants' involvement in other treatment options for knee pain such as physiotherapy.

Once participants have enrolled in the study and undergone the intervention, every reasonable effort will be made to reassess them for the entire study period. Research assistants will attempt to contact participants a maximum of four times over a 3-month period using phone, email or mail before they are considered lost to follow-up. Participants may withdraw from the study at any time and for any reason. Participants will be invited, though not required to indicate reasons for withdrawal. Participants wishing to withdraw from the study will be invited to complete questionnaire assessments via mail rather than attending reassessment/s in person.

## Adverse events and data safety and monitoring

An adverse event refers to an untoward occurrence during the study, which may or may not be causally related to the intervention.<sup>24</sup> We will collect information relating

to adverse events from the baseline assessment until the participant completes the 12-month postintervention assessment. Information regarding all adverse events will be collected at the time of the intervention and at each follow-up assessment. Participants will be asked in writing to inform the study coordinator of adverse events that occur in the interim between planned assessments and each participant's general practitioner/family doctor will be informed of the study in writing and asked to notify the study coordinator if adverse events occur. Serious adverse events (SAE) are those which result in death, are immediately life threatening, require hospitalisation, result in persistent or significant disability or incapacity, or have important clinical sequelae. SAE will be reported to the Data and Safety Management Board (DSMB) and the organisation's Human Research Ethics Committee within 24 hours of the event becoming known to the investigators. All adverse events will be reported to the DSMB once all participants have completed the 12-month assessment. Study procedures will be audited by one investigator at least annually and any deviations compromising the fidelity of the study will be reported to the investigation team and where appropriate the DSMB. Annual reports of the study's progress will be sent to the organisation's Human Research Ethics Committee.

A DSMB has been established. DSMB membership is exclusive of the study investigators and includes two senior radiologists, one of whom is an interventional radiologist, a senior radiographer and a senior orthopaedic surgeon. DSMB members have no competing interests with the study. The DSMB's main function is to oversee trial safety. The study investigators will inform the unblinded DSMB of any SAE and the DSMB will recommend to the investigators whether to modify or cease the study.

### Statistical analysis plan

Intention-to-treat analysis will be performed and include all participants as randomised. The primary analysis will assess differences between the two treatment arms for percentage change in KOOS pain scores from baseline to 12-month assessment using a two-sample t-test if no dropouts occur and all data are available on each participant. Normality of the outcomes will be assessed and if the assumptions are not met, the primary analysis will be conducted using the Wilcoxon rank-sum test. In the case of dropouts or missing data at 12 months, the primary analysis will be conducted using linear regression, with random effects accounting for intraindividual correlations.

Secondary outcomes assessed at baseline and follow-up will first be analysed as the difference between the two treatment arms in percentage change from baseline to 12-month assessment using two-sample t-tests if no dropouts occur and all data are available on each participant. Normality of the outcomes will be assessed and if the assumptions are not met, analyses will be conducted using the Wilcoxon rank-sum test. In the case of dropouts or missing data, analyses will be conducted under a

linear regression model, with random effects accounting for intraindividual correlations. Outcome data that are available at multiple time points will also be analysed using linear regression models, with random effects accounting for intraindividual correlations. Differences between intervention and placebo arms will be analysed and presented for each time point using a time-by-intervention product term.

Participant reported global change since the intervention will be dichotomised as 'improved' (moderately or much better) or 'not improved' (slightly better or below). Between-group comparisons will be made using log binomial regression and presented as relative risks.<sup>21</sup>

Tests will be two sided and considered significant if p values are less than 0.05.

### Sample size

The sample size was calculated on the basis of the primary outcome. Using data provided by Okuno *et al*,<sup>6</sup> we estimated that the SD of change in pain 12 months post intervention was 19.9%. Given the small sample size and the observational nature of Okuno *et al*'s study, we chose a conservative approach and used the upper limit of the 80% CI for the SD. The SD was calculated via bootstrapping and was equal to 23.9%. For the mean between-group difference for change in pain, we used a minimum important difference (MID) of 20%. KOOS guidelines suggest a MID of 8–10 points for sample size calculations,<sup>25</sup> and assuming baseline pain scores between 48 and 70 for adults with knee OA,<sup>26 27</sup> MID as a percentage of baseline pain would be 11%–21%, from which we chose a conservative estimate of 20%. To detect a mean between-group difference of 20% for change in pain (SD=23.9%) with a two-sided significance level of  $\alpha=0.05$  and power of 80% using a two-sample t-test, we require 24 participants per arm. Allowing for a 20% dropout rate, 29 participants per treatment arm will be recruited, equalling 58 participants in total.

### Ethics and dissemination

Barwon Health Human Research Ethics Committee, Geelong, Australia, approved the study including the protocol and the participant information and consent form (reference 15/101, 30 May 2016). The ethics committee will be notified of any adverse events relating to the study or any changes to the study protocol. The study complies with the National Statement on Ethical Conduct in Research.<sup>28</sup> The study is registered with the Australian New Zealand Clinical Trials Registry.<sup>29</sup>

All investigators and the trial statistician will have access to the final dataset. Key study results will be shared with interested participants in writing using plain English. Results will be disseminated at national and international conferences and in peer-reviewed journals. Authorship eligibility for disseminated material will be determined according to international criteria.<sup>30</sup>

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**Contributors** SL and AH conceived the study. All authors (SL, AH, BH, NM, RH, SEL, SDG, RP) contributed to the design of the study protocol, assisted with drafting the manuscript and approved the final version of the manuscript. SEL developed the statistical analysis plan as senior biostatistician, Research Directorate, Barwon Health.

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**Competing interests** None declared.

**Ethics approval** Barwon Health Human Research Ethics Committee 15/101.

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## REFERENCES

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115–26.
2. Cross M, Smith E, Hoy D, *et al.* The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323–30.
3. Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. *Curr Opin Rheumatol* 2015;27:276–83.
4. Litwic A, Edwards MH, Dennison EM, *et al.* Epidemiology and burden of osteoarthritis. *Br Med Bull* 2013;105:185–99.
5. Blagojevic M, Jinks C, Jeffery A, *et al.* Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2010;18:24–33.
6. Okuno Y, Korchi AM, Shinjo T, *et al.* Transcatheter arterial embolization as a treatment for medial knee pain in patients with mild to moderate osteoarthritis. *Cardiovasc Intervent Radiol* 2015;38:336–43.
7. McAlindon TE, Bannuru RR, Sullivan MC, *et al.* OARSJ guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363–88.
8. Dieppe P, Basler HD, Chard J, *et al.* Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. *Rheumatology* 1999;38:73–83.
9. Dieppe P, Lim K, Lohmander S. Who should have knee joint replacement surgery for osteoarthritis? *Int J Rheum Dis* 2011;14:175–80.
10. Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol* 2012;8:390–8.
11. Ashraf S, Mapp PI, Walsh DA. Contributions of angiogenesis to inflammation, joint damage, and pain in a rat model of osteoarthritis. *Arthritis Rheum* 2011;63:2700–10.
12. Ashraf S, Wibberley H, Mapp PI, *et al.* Increased vascular penetration and nerve growth in the Meniscus: a potential source of pain in osteoarthritis. *Ann Rheum Dis* 2011;70:523–9.
13. Mapp PI, Avery PS, McWilliams DF, *et al.* Angiogenesis in two animal models of osteoarthritis. *Osteoarthritis Cartilage* 2008;16:61–9.
14. Suri S, Gill SE, Massena de Camin S, *et al.* Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Ann Rheum Dis* 2007;66:1423–8.
15. Walsh DA, Bonnet CS, Turner EL, *et al.* Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. *Osteoarthritis Cartilage* 2007;15:743–51.
16. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis* 1957;16:494–502.
17. Riddle DL, Jiranek WA, Hull JR. Validity and reliability of radiographic knee osteoarthritis measures by arthroplasty surgeons. *Orthopedics* 2013;36:e25–e32.
18. Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
19. Roos EM, Roos HP, Lohmander LS, *et al.* Knee Injury and Osteoarthritis Outcome score (KOOS)—development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96.
20. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337–43.
21. Bennell KL, Egerton T, Martin J, *et al.* Effect of physical therapy on pain and function in patients with hip osteoarthritis: a randomized clinical trial. *JAMA* 2014;311:1987–97.
22. Enright PL. The six-minute walk test. *Respir Care* 2003;48:783–5.
23. Wright AA, Cook CE, Baxter GD, *et al.* A comparison of 3 methodological approaches to defining Major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. *J Orthop Sports Phys Ther* 2011;41:319–27.
24. Ioannidis JP, Evans SJ, Gøtzsche PC, *et al.* Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004;141:781–8.
25. KOOS FAQs. <http://www.koos.nu/>. accessed 20 Dec 2016.
26. Mills KA, Naylor JM, Eyles JP, *et al.* Examining the minimal important difference of Patient-reported Outcome measures for individuals with knee osteoarthritis: a Model using the knee Injury and Osteoarthritis Outcome score. *J Rheumatol* 2016;43:395–404.
27. Sabirli F, Paker N, Bugdayci D. The relationship between knee Injury and Osteoarthritis Outcome score (KOOS) and timed up and go test in patients with symptomatic knee osteoarthritis. *Rheumatol Int* 2013;33:2691–4.
28. The National Health and Medical Research Council, the Australian Research Council and the Australian Vice-Chancellors' Committee. *National statement on ethical conduct in human research 2007*. Canberra: Commonwealth of Australia, 2015.
29. Australian New Zealand clinical trial registry (ANZCTR). <http://www.anzctr.org.au/>.
30. ICMJE. International Committee of Medical Journal Editors). *recommendations for the Conduct, Reporting, Editing, and publication of Scholarly Work in Medical Journals. Updated* 2016.

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