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Tourniquet use for knee replacement surgery (Protocol)

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[Intervention Protocol]

Tourniquet use for knee replacement surgery

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the benefits and safety of tourniquets used in knee replacement surgery.

BACKGROUND

Description of the condition

Approximately one in two people develop symptomatic knee arthritis before the age of 85 (Murphy 2008). Knee replacement is an effective surgical procedure performed for the relief of pain from end-stage arthritis (Skou 2016). Knee replacement surgery is routinely undertaken with the aid of a tourniquet around the thigh during the procedure (Gibbs 2016).

Description of the intervention

A thigh tourniquet is an occlusive device which squeezes the upper leg and restricts distal blood flow.

Types

There are two broad designs of thigh tourniquet used for knee replacement surgery:
1. Inflatable/pneumatic: a cuff placed around the thigh is filled with compressed gas. The pressure in the cuff is maintained by a microprocessor and can be adjusted.
2. Non-inflatable: a rubber or elasticated cloth ring is placed around the thigh. A device which achieves the required pressure is applied and can not be adjusted unless it is replaced with a new device.
Prior to the tourniquet being applied, the leg can be elevated or exsanguinated (using a bandage or similar device), to help reduce the amount of pooled blood within the leg.

Duration

A thigh tourniquet can be used for the duration of the procedure or for part of the procedure (for example, just during knee replace-

ment component cementation only).
A 2010 survey found that 95% of surgeons in the USA use a tourniquet for knee replacement surgery (Zhang 2014), and the UK's National Joint Registry (NJR) reported that 93% of primary knee replacements were done with a tourniquet in 2003 (National Joint Registry 2004).

How the intervention might work

The tourniquet is designed to apply pressure to the thigh above the internal pressure of local blood vessels (limb occlusion pressure), thereby restricting both arterial and venous blood flow distally.

Why it is important to do this review

Although the effects of using a tourniquet have been the subject of systematic reviews before (Alcelik 2012; Smith 2010; Tai 2011; Zhang 2014), not all the important outcomes have been described, reviewed and evaluated together. These include:

Potential benefits

Surgical field of view
Using a tourniquet may improve the surgical field of view by limiting intraoperative blood loss (Zhang 2014).
Cementation
Most knee replacement components are cemented in place to hold and stabilise them in the correct position on the bone. Cement which is initially soft when it is inserted interdigitates into the porous bone, forming a strong bond to the bone as it sets. Some surgeons believe that using a tourniquet helps reduce bleeding from the porous bone ends and allows the soft cement to bond more effectively, and as a result improves the long-term survival of the knee implant components (Grewal 1992; Pfitzner 2016).
Blood loss
One previous systematic review (Alcelik 2012) showed that intraoperative blood loss was less when a tourniquet was used. However, when another group reviewed overall blood loss (Zhang 2014), there was no difference between intervention groups.

Potential risks

Pain and function
A tourniquet which is often applied for the duration of the procedure and tightly squeezes the thigh can cause pain both during and after surgery (Abdel-Salam 1995). In addition to pain, a tourniquet can cause bruising and swelling to the thigh muscles which it squeezes. These muscles are important for mobilisation and therefore can inhibit postoperative function.
Venous Thrombo Embolism (VTE)
A tourniquet causes both arterial and venous stasis within the lower leg for the duration that it is inflated (typically over an hour). It is therefore possible that the use of a surgical tourniquet might increase the risk of postoperative venous thromboembolism (VTE) (Tai 2011; Wauke 2002; Zhang 2014).
Systemic Emboli
VTE may not be the only thromboembolic risk associated with using a tourniquet. Systemic emboli can occur following the deflation of a tourniquet (Berman 1998). Transoesophageal echocardiography has demonstrated shower-like echogenic materials circulating from the lower limbs to the right atrium, ventricle, and pulmonary artery after the release of a thigh tourniquet, and also macroscopic emboli in the central circulation (Berman 1998). As the carotid arteries are the first branches from the aortic arch in a straight-line orientation, some of these clots may enter the cerebral circulation. Transcranial Doppler ultrasound studies show a 60% prevalence of echogenic material in the Circle of Willis after a tourniquet is released, and that microemboli can occur even in the absence of a patent foramen ovale (connection between the left and right side of the circulation within the heart) (Sulek 1999). The most likely route for emboli in these circumstances is through the pulmonary capillaries or the opening of other pulmonary vessels (Sulek 1999). The critical time is immediately after release of the tourniquet, when there is potential haemodynamic instability and evidence to suggest a five-fold increase in the amount of embolic material (Huh 2012; Parmet 1998). The presence of cerebral emboli which can cause cerebral damage may explain the higher than expected prevalence of postoperative cognitive deficit following total knee replacement (TKR). In the literature this varies from 41% to 75% at seven days to 18% to 45% at three months postoperatively (Deo 2011). These percentages are much higher than those recorded in other major lower-limb procedures with similar types of anaesthetic, but where a tourniquet is not used (Koch 2007).

Other effects

Alcelik 2012 concluded that minor complications were more common when a tourniquet is used; similarly, Zhang 2014 showed reduced complications, including infection, blister, haematoma, wound oozing, bruising, nerve palsy and re-operation.
We propose a review of the effects of tourniquet use during TKR surgery which, in addition to measuring effects on pain, function, quality of life and blood loss, will capture field of view, cognitive function, adverse events including VTE, systemic emboli (including cerebral stroke), revision surgery and death.

OBJECTIVES

To determine the benefits and safety of tourniquets used in knee replacement surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised

We will include studies in which participants are randomised to intervention groups and studies in which allocation to interventions are quasi-randomised (i.e. not strictly random, for example by date of birth, hospital record number or alternation).

Non-randomised

Randomised studies, particularly in the field of this review, are unlikely to include more than 1000 participants. To help improve estimates of the potential risks, e.g. adverse events of the intervention, many of which may be rare events (VTE approximately < 5% (Zhang 2014)), we will include the following non-randomised study types:

- Observational cohort studies and unselected case series of 1000 or more participants, which include concurrent comparison groups, e.g. published data from joint replacement registries, for example the National Joint Registry 2015.

To minimise selection bias within non-randomised studies, we will include only studies that use statistical adjustment for baseline case mix, e.g. multivariable analyses to adjust for age, comorbidity and type of knee replacement (unicondylar knee replacement, total knee replacement, primary or revision).

Types of participants

We will include participants who are undergoing knee replacement surgery for any indication, regardless of age. We will include all types of knee replacement, including partial (e.g. unicondylar, patellofemoral) and revision surgery.

Types of interventions

We will include studies of all types of thigh tourniquet (inflatable or non-inflatable) used for the duration or part of the knee replacement surgery. Comparators could be:

1. Placebo: this may include a sham tourniquet, for example one that is applied but not inflated.
2. No tourniquet
3. Alternative measures to improve the surgical field of view or reduce intraoperative blood loss, e.g. this may include tranexamic acid.

Types of outcome measures

Major outcomes

According to the OMERACT core outcome set (Bellamy 1997), pain, function/disability, global assessment of success and health-related quality of life are the major outcomes. We will prioritise them according to previous evidence on the hierarchy of patient-reported outcomes (Juhl 2012).

1. Pain

Measured using mean pain or mean change in pain, on a visual analogue scale (VAS), a numerical rating scale or another scale.

2. Function

Measured with instruments such as: Knee Society Score (KSS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Oxford Knee Score (OKS). We will extract all available function scores and present total scores in the primary analysis and subscores as additional analyses when available.

3. Global assessment of success

As reported by the participant, e.g. proportion of participants reporting overall successful treatment and participant satisfaction.

4. Health-related quality of life

Measured with instruments such as Short Form-36 (SF-36), or EuroQoL 5D (EQ-5D).

We will also assess the following as major outcomes:

5. Serious Adverse events (SAE)

A serious adverse event is an adverse event that fulfils one of more of the following criteria: results in death, immediately life-threatening, requires hospitalisation or prolongation of existing hospitalisation, or is an important medical condition. We will report the complications and morbidity associated with the use (nerve damage, ischaemia, bruising and pain) or non-use of tourniquets (e.g. death, deep-joint infection, VTE, systemic emboli and re-operation, excluding revision for implant failure).

6. Cognitive function

Measured with instruments such as Mini-Mental State Examination (MMSE), Oxford Cognitive Screen (OCS) and Montreal Cognitive Assessment (MoCA).

7. Survival of the implant

Measured as time to failure. The preferred marker of implant failure will be revision surgery.
We will prioritise the major outcomes in numerical order, as given above.

Minor outcomes

Following discussion between the senior review authors, we will prioritise the minor outcomes in numerical order as shown below.

1. Blood loss:

a) Total blood loss during surgery (intra-operative blood loss).
b) Postoperative blood loss measured from drainage systems and blood transfusion rates.
Example outcome measures include: change in haematocrit, change in haemoglobin level and number of units of postoperative blood transfusions.

2. Economic

a) Resource usage: direct healthcare and societal costs, to facilitate a cost-effectiveness analysis.
b) Duration of surgery: we will report the definition of surgery start and finish times where available.
c) Length of hospital stay.

3. Implant stability: v

Validated methods such as radiostereometric analysis (RSA).

4. Adverse events

We will report adverse events which are not classified as serious adverse events, based on the criteria above.

Timing of outcome assessment

Studies are likely to report the outcomes discussed at several time points. We therefore plan to group these assessments into three categories: short-term (up to and including three months), medium-term (after three months and up to and including 12 months) and long-term follow-up (greater than one year).

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase.
We will also conduct a search of ClinicalTrials.gov and the WHO trials portal (www.who.int/ictrp/en/).
We will search all databases from their inception to the present, and will impose no restriction by language of publication.
See Appendix 1 for the MEDLINE search strategy for RCTs.
See Appendix 2 for the MEDLINE search strategy for observational studies

Searching other resources

We will check reference lists of all primary studies and review articles for additional references.
We will search the following established joint registry programmes for relevant published reports and use these contacts to identify any missing joint registry programmes:
Australasia
Australian Orthopaedic Association National Joint Replacement Registry: aoanjrr.sahmri.com/
New Zealand National Joint Register: nzoa.org.nz/nz-joint-registry
Europe
Danish Knee Arthroplasty Register: www.kea.au.dk/en/ClinicalQuality/KneeArthroplastyRegistry.html
European Arthroplasty Register: www.ear.efort.org/
Scottish Arthroplasty Project: www.arthro.scot.nhs.uk/
Slovak National Arthroplasty Register: sar.mfn.sk/the-slovak-arthroplasty-register.348.html
Swedish Knee Arthroplasty Register: www.myknee.se/en/
National Joint Registry of England and Wales: www.njrcentre.org.uk/njrcentre/default.aspx
Norwegian Arthroplasty Register: nrlweb.ihelse.net/eng/
Portugese Arthroplasty Register: www.rpa.spot.pt/
RIPO Bologna, Italy: ripo.cineca.it/
Romanian Arthroplasty Register: www.rne.ro/?lang=en
North America
American Joint Replacement Registry: www.ajrr.net/

Canadian Joint Replacement Register: www.cihi.ca/en/types-of-care/specialized-services/joint-replacements/canadian-joint-replacement-registry
Health East Joint Replacement Registry: www.healtheast.org/orthopaedics/registry.html
Kaiser Permanente National Implant Registries: www.kpimplantregistries.org/
Western Slope Study Group: www.wssgco.com/
We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (IA and PW) will independently screen titles and abstracts of all the potential studies for inclusion that we identify as a result of the search. We will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. After retrieving the full-text study reports/publications, two review authors (IA and PW) will independently screen them and identify studies for inclusion, and will identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (MU). We will identify and exclude duplicates and collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (IA) will extract study characteristics from the included studies. A second review author (PW) will cross-check study characteristics for accuracy against the trial report. We will extract the following study characteristics:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and dates of study.
2. Participants: number (N), mean age, age range, sex, disease duration, comorbidities, inclusion criteria, and exclusion criteria.
3. Interventions: type of surgery, number of participants in tourniquet group, number of participants in comparator group (sham/no tourniquet/other).
4. Outcomes: major and minor outcomes specified and collected, and time points reported.
5. Characteristics of the design of the trial as outlined in the Assessment of risk of bias in included studies section below.
6. Notes: funding for trial, and notable declarations of interest of trial authors.

Two review authors (IA and PW) will independently extract outcome data from the included studies. We will extract the number of events and number of participants in each treatment group for dichotomous outcomes, and means and standard deviations and number of participants in each treatment group for continuous outcomes. For non-randomised trials we will extract adjusted outcome measures.
We aim to use non-randomised studies to extract outcomes of interest which are rare, for example: VTE and implant failure rate.
We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way and when data were transformed or estimated from a graph. We will resolve disagreements by consensus or by involving a third review author (MU). One review author (IA) will transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the review with the study reports.
Our a priori decision rules to extract data in the event of multiple outcome reporting in trials are as follows:
Where trialists report both final values and change from baseline values for the same outcome, we plan to extract change from baseline values.
Where trialists report both unadjusted and adjusted-for-baseline values for the same outcome, we plan to extract unadjusted baseline values.
Where trialists report data analysed based on the intention-to treat (ITT) sample and another sample (e.g. per protocol, as treated), we plan to extract ITT-analysed data.
Where trials do not include a measure of overall pain but include one or more other measures of pain, for the purpose of pooling data we will combine overall pain with other types of pain in the following hierarchy: unspecified pain, pain at rest, pain with activity, or daytime pain.
Where trialists report multiple pain outcome measures, for the purposes of pooling data we will extract one measure using the following hierarchy: visual analogue scale, numerical or cognitive rating scale, McGill pain questionnaire, or other scale.
Where trialists report multiple measures of function or disability, for the purposes of pooling data we will extract a single measure using the following hierarchy: Oxford knee score (OKS), Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Society Score (KSS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) or other scale.

Assessment of risk of bias in included studies

Randomised studies

Two review authors (IA and PW) will independently assess risks of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will resolve any disagreements by discussion or by involving another review author (MU). We will assess the risks of bias according to the following domains:

1. Random sequence generation (only for randomised studies).
2. Allocation concealment (only for randomised studies).
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other potential bias, e.g. discrepancies between groups for comorbidities which could act as confounding factors, for example clotting disorders.

We will grade each potential source of bias as high, low or unclear, and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be different than for a participant-reported pain scale). We will also consider the impact of missing data by key outcomes.

Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will present the figures generated by the 'Risk of bias' tool to provide summary assessments of the risks of bias.

Non-randomised studies

We will use ROBINS-I, a tool for assessing risk of bias in non-randomised studies of interventions (Sterne 2016). This will involve three stages for each study:

Stage 1

Specify the research question, list the confounding domains, list co-interventions and specify the outcomes you are collecting.

Confounding factors which may influence outcomes include:

1. Comorbidities such as vascular disease;
2. Previous VTE disease;
3. Prothombotic conditions such as malignancy;
4. Use and type of VTE prophylaxis (such as low molecular weight heparin, aspirin, intermittent calf pump);
5. Type of implant used;
6. Use of cement;
7. Basic participant demographics, including age, body mass index (BMI), and American Society of Anaesthesiologists (ASA) grade.

Stage 2

Risk of bias assessment for specific result.

Stage 3

Overall risk of bias assessment, 'triangulated' across studies.

The tool will evaluate the following areas of bias:

1. Confounding
2. Selection bias
3. Bias in measurement classification of interventions
4. Bias due to deviations from intended interventions
5. Bias due to missing data
6. Bias in measurement of outcomes
7. Bias in selection of the reported result

We will report bias as low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, no information.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We will use risk ratios (RRs) with a 95% confidence intervals (CI) to report categorical outcomes. We will analyse continuous data as the mean difference (MD) or standardised mean difference (SMD), depending on whether the same scale is used to measure an outcome, with a 95% confidence interval. We will enter data presented as a scale with a consistent direction of effect across studies.

When different scales are used to measure the same conceptual outcome (e.g. disability), we will calculate the SMDs, with a corresponding 95% CI. We will back-translate the SMD to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical among-person standard deviation (SD), e.g. the standard deviation of the control group at baseline from the most representative trial, as described in Chapter 12 of the *Cochrane Handbook* (Schünemann 2011b).

For non-randomised studies we will assess the treatment effect using the risk ratio, provided the follow-up periods are consistent and we are reporting categorical data.

In the 'Effects of intervention' Results section and the 'Comments' column of the 'Summary of findings' table we will provide the absolute per cent difference, the relative per cent change from baseline, and the number needed to treat for an additional beneficial outcome (NNTB); we will calculate the NNTB only when the outcome shows a statistically significant difference.

For dichotomous outcomes, such as serious adverse events, we will calculate the NNTB from the control group event rate and the risk ratio, using the Visual Rx NNT calculator (Cates 2008). We will calculate the NNTB for continuous measures using the Wells calculator (available at the CMSG Editorial office, musculoskeletal.cochrane.org/).

For dichotomous outcomes, we will derive the absolute risk difference using the Risk Difference statistic in Review Manager 5, and will express the result as a percentage. For continuous outcomes, we will calculate the absolute risk difference as the improvement in the intervention group minus the improvement in the control group, in the original units.

We will calculate the relative per cent change for dichotomous data as the RR minus 1, expressed as a percentage. For continuous outcomes, we will calculate the relative difference in the change from baseline as the absolute benefit divided by the baseline mean of the control group.

Unit of analysis issues

We expect most studies to be simple parallel-group designs. However, if we find other designs (e.g. cluster-randomised), we will use generic inverse variance methods to combine data. For analysis, we plan to use details of intra-class correlation coefficients (ICCs) and cluster sizes for trials of this type, if reported effects have not been adjusted for clustering.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

We do not expect any crossover trials, but if we do include them we will report the findings at the end of the first treatment period only.

We will prefer trials that report a unit of analysis at the participant level, to maintain independence of the outcome variable.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only, or when data are not available for all participants). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis**.** We will clearly describe any assumptions and imputations for handling missing data, and will explore the effect of imputation by sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate the withdrawal rate using the number of participants randomised in the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD based on the number of participants analysed at that time point. If the number of participants analysed is not presented for each time point, we will use the number of randomised participants in each group at baseline.

Where possible, we will compute missing standard deviations from other statistics such as standard errors, confidence intervals or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*. If we cannot estimate standard deviations, we will impute them (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

We will assess clinical and methodological diversity in terms of participants, interventions, outcomes and study characteristics for the included studies, to determine whether a meta-analysis is appropriate. We will assess statistical heterogeneity by visual inspection of the forest plot to assess for obvious differences in results between the studies, and by using the I^2 and Chi^2 statistical tests. As recommended in the *Cochrane Handbook* (Deeks 2011), the interpretation of an I^2 value of 0% to 40% 'might not be important'; 30% to 60% may represent 'moderate heterogeneity'; 50% to 90% may represent 'substantial heterogeneity'; and 75% to 100% represents 'considerable heterogeneity'. As noted in the *Cochrane Handbook*, we will keep in mind that the importance of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity.

We will interpret a Chi^2 test with a P value of 0.10 or less as evidence of statistical heterogeneity.

If we identify substantial heterogeneity we will report it and investigate possible causes by following the recommendations in section 9.6 of the *Cochrane Handbook*.

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small-study biases. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry, as outlined in section 10.4 of the *Cochrane Handbook,* and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, and will follow the recommendations in section 10.4 of the *Cochrane Handbook* (Sterne 2011).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1st July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (apps.who.int/trialssearch) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will pool outcomes of clinically and methodologically homogeneous studies, where meaningful, using a random-effects model. We will perform analysis using Review Manager 5 and will produce forest plots for all analyses.

We will only pool outcomes of non-randomised studies if the studies are clinically homogeneous, using a random-effects model which will allow for different study variances. We will use log-RR

data (with corresponding standard errors (SEs) on the log scale) and will pool outcomes using the generic inverse variance method. We will use non-randomised studies to analyse only outcomes which are rare, for example VTE and implant failure rate. We will assess clinical homogeneity based on participants, intervention (procedure performed with a tourniquet), outcomes (VTE and implant failure) and study characteristics, including study design. Two review authors (IA and PW) will determine if at least three of these features are matching between each study in order to pool the data.

'Summary of findings' table

We will create a 'Summary of findings' (SoF) table using the following outcomes:

1. Pain
2. Function
3. Global assessment of success
4. Health-related quality of life
5. Serious adverse events
6. Cognitive function
7. Survival of the implant

The comparison in the first SoF table will be: *Tourniquet versus no tourniquet.* For the second SoF table the comparator will be: *Tourniquet versus sham tourniquet.*

Two review authors (IA and PW) will independently assess the quality of the evidence. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5, 8.7, Chapter 11 and Chapter 13 section 13.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Schünemann 2011a), using GRADEpro software. We will justify all decisions to down- or upgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Different surgical procedures that may affect outcome, e.g. unicompartmental knee replacement, primary knee replacement and revision knee replacement.
2. Different types of tourniquet that may affect outcome, e.g. inflatable or non-inflatable.
3. Duration of tourniquet use that may affect outcome, e.g. used for the whole procedure or used for part of the procedure. We will do this by predefining subgroups based on stages of the procedure.

The types of surgical procedure vary in complexity and may therefore impact upon both the duration of tourniquet use and the risk of complications.

We will use the following outcomes in subgroup analyses:

1. Pain
2. Function
3. Adverse events

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014), and will use caution in the interpretation of subgroup analyses, as advised in section 9.6 of the *Cochrane Handbook*. We will compare the magnitude of the effects between the subgroups by assessing the overlap of the confidence intervals of the summary estimates. Non-overlap of the confidence intervals indicates statistically significant differences.

Sensitivity analysis

If studies were to differ markedly from most other studies (outcome is different) and we deem it necessary to exclude them, then we will conduct sensitivity analyses to report whether the overall effect changes when these studies are removed.

Where we have sufficient studies, we will perform sensitivity analyses to assess the impact on primary outcomes, e.g. adverse events, global assessment of quality, cognitive function, pain, and function of quasi-randomisation and bias attributable to unclear or inadequate treatment allocation and blinding of the surgeon or the outcome assessor.

Interpreting results and reaching conclusions

We will follow the guidelines in the *Cochrane Handbook*, Chapter 12 (Schünemann 2011b) for interpreting results, and will be aware of distinguishing a lack of evidence of effect from a lack of effect. We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in this area.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Medline search strategy for RCTs

Ovid MEDLINE(R) 1946 to August Week 5 2016
1. arthroplasty, replacement,knee/ (17166)
2. knee Prosthesis/ (10303)
3. Tkr.ti,ab. (1338)
4. exp knee. (12724)
5. Knee.ti,ab. (96425)
6. 4 or 5 (101075)
7. exp arthroplasty/ (52275)
8. joint prosthesis/ (9921)
9. (arthroplasty$ or prosthe$ or replac$).ti,ab. (419747)
10. or/7-9 (433269)
11. 6 and 10 (29324)
12. or/1-3,11 (32468)
13. exp tourniquet/ (3407)
14. Tourniquet.ti,ab. (4412)
15. Esmarch.ti,ab (117)
16. Lofquist.ti,ab (3)
17. Cuff.ti,ab. (19634)
18. Or/13-17 (24490)
19. 12 and 18 (633)
20. randomized controlled trial.pt (430183)
21. Controlled clinical trial.ot (91662)
22. Randomized.ab. (326206)
23. Placebo.ab. (164485)
24. Clinical trials as topic.sh. (179377)
25. randomly.ab. (228844)
26. Trial.ti. (143168)
27. Or/21-26 (873089)
28. Exp animals/ not humans.sh (4313283)
29. 27 not 28 (794647)
30. 19 and 29 (192)

Appendix 2. Medline search stratedgy for observational studies

Ovid MEDLINE(R) 1946 to August Week 5 2016
1. arthroplasty, replacement,knee/ (26264)
2. knee Prosthesis/ (10437)
3. Tkr.ti,ab. (1445)
4. exp knee. (13018)
5. Knee.ti,ab. (102713)
6. 4 or 5 (107341)
7. exp arthroplasty/ (54920)
8. joint prosthesis/ (9917)
9. (arthroplasty$ or prosthe$ or replac$).ti,ab. (410606)
10. or/7-9 (446439)
11. 6 and 10 (28919)
12. or/1-3,11 (40006)
13. exp tourniquet/ (3536)

14. Tourniquet.ti,ab. (4613)
15. Esmarch.ti,ab (123)
16. Lofquist.ti,ab (4)
17. Cuff.ti,ab. (20336)
18. Or/13-17 (25912)
19. 12 and 18 (908)
20. Case-control studies/ or Case control.mp (268947)
21. Cohort studies/ or Cohort.mp (428924)
22. Case series. mp (45861)
23. Observational studies.mp or Observational study/ (57501)
24. Or/ 20-23 (749956)
25. Exp animals/ not humans.sh (4438472)
26. 24 not 25 (739494)
28. 19 and 26(85)

CONTRIBUTIONS OF AUTHORS

All authors contributed to writing of the protocol and approval of final draft.

DECLARATIONS OF INTEREST

Two of the review authors (AM and AP) are Consultant Orthopaedic Surgeons who routinely undertake independent TKR surgery.

Both AM and AP currently routinely perform TKR surgery with a tourniquet unless their patients express a preference or there are contraindications to using a tourniquet.

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