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Through-knee versus above-knee amputation for vascular and non-vascular major lower limb amputations (Protocol)

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[Intervention Protocol]

Through-knee versus above-knee amputation for vascular and non-vascular major lower limb amputations

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ABSTRACT

Objectives

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

To assess the effects of through-knee amputation compared to above-knee amputation on clinical and rehabilitation outcomes and complication rates in all patients undergoing vascular and non-vascular major lower limb amputations.

BACKGROUND

Description of the condition

Diabetes and vascular disease are the leading causes of lower limb amputation. Currently, 463 million adults are living with diabetes, and 202 million with peripheral vascular disease worldwide (Behrendt 2018; International Diabetes Federation 2017). For every 100,000 people in Europe and Australia, between seven and 41 persons undergo a major amputation every year due to diabetes or vascular disease (Behrendt 2018).

It is estimated that there are between 30 to 40 million people living with total or partial limb loss in low-income countries internationally (WHO 2005). The leading cause of amputation in these countries, and the second most common cause in the rest of the world, is severe traumatic injury (Ajibade 2013; Nwosu 2017). The population of people with limb loss due to trauma is high, as they tend to be young with a long life expectancy (Perkins 2012).

Diabetes and vascular disease are associated with significant morbidity and mortality. There is a strong link between diabetes and vascular disease, as hyperglycaemia is one of the causal factors for vascular dysfunction (Kirpichnikov 2001). Furthermore, cigarette smoking has been reported to significantly increase rates of vascular disease (Liu 2018). Vascular complications which can lead to amputation include progressive infection, major tissue loss due to infection, ischaemia, loss of limb function or intractable pain. Lower limb amputation has a significant economic burden on the individual and health services. The estimated yearly cost of inpatient amputation care to the United Kingdom (UK) National Health Service (NHS) is more than GBP 40 million (Kerr 2019). In 2007, lifetime healthcare costs for a prosthetic user were estimated to be USD 509,275 (MacKenzie 2007).

There are four main levels of major lower limb amputation: below-knee, through-knee, above-knee, and through-hip. These four types of amputation have been shown to provide the best chance of using a prosthesis, which is why amputation is not performed directly at the level of the most distal viable tissue (BSRM 2018). Instead, the level of amputation is chosen to best facilitate primary healing and optimise rehabilitation potential. Quality of life (QoL) outcomes are reported to be inversely correlated with the level of amputation up the limb. Studies have always considered below-knee versus above-knee amputation in this regard, but a direct comparison of the outcomes of through-knee versus above-knee amputation has never been done (Davie-Smith 2017; Murakami 2016).

Description of the intervention

The level of amputation affects patients' postoperative outcomes. It is accepted that below-knee amputation has preferable outcomes to above-knee amputation (Tisi 2014). People with below-knee amputation achieve a higher level of mobility with an artificial limb (prosthesis), and report a better QoL compared to those with above-knee amputation (Aulivola 2004; Davie-Smith 2017; Vogel 2014). However, below-knee amputation is not always possible and a proximal amputation is sometimes required. In these instances, an above-knee amputation is routinely performed (Aulivola 2004; Kidmas 2004; Yusof 2007).

Above-knee amputation, also referred to as 'transfemoral amputation', is an amputation of the leg through the femur, above the level of the condyles with removal of the patella. Soft tissue flaps are fashioned using the muscle from the front and back of the leg to cover the transected bone (Woodburn 2009). Above-knee amputation offers a good chance of primary healing and an even appearance with a prosthesis. However, the transected femur is associated with worse functionality for prosthetic limb users. They cannot use their transected femur as an effective physical end-point for load-bearing through a prosthesis; and may sometimes need to wear an additional suspension strap to hold the prosthesis in place, to compensate for the short length of the residuum (Gholizadeh 2014). In order to use a prosthesis safely and effectively, following above-knee amputation, the individual must have sufficient cardiovascular fitness and strength, good balance and dexterity, and good cognitive function. Achieving prosthetic ambulation, therefore, becomes more challenging with age (Bowrey 2018). In addition, the above-knee amputation prosthesis is not comfortable to sit in. If a person spends more time sitting than they do standing and mobilising, they will most likely abandon their prosthesis in favour of their wheelchair. For these reasons, prosthetic fitting post above-knee amputation is not always appropriate in the geriatric population (Bowrey 2018; Davies 2003).

Through-knee amputation is an alternative to above-knee amputation. The conflicting evidence surrounding through-knee amputation describes varying postoperative levels of success. Earlier papers recommended above-knee amputation for the best chance of primary healing (Chilvers 1971; Jamieson 1976), as delayed wound healing increases length of hospital stay, increases time taken to achieve mobility with a prosthesis, and decreases level of mobility achieved (Nijmeijer 2017). However, recent advancement in surgical techniques for through-knee amputation are improving patient outcomes for survival, morbidity, infection and dehiscence rates (Lim 2018; Nijmeijer 2017).

A true through-knee amputation, also referred to as 'knee disarticulation', is the surgical removal of the lower half of the leg through the knee joint with the femur left intact. Revised design of this amputation has improved healing rates and prosthetic fit, and variations of the through-knee amputation have been developed (Murakami 2016). Modified techniques, such as that of Mazet, Burgess and Youkey, involve removing the patella and trimming the femoral condyles to achieve a less bulbous residual end (Burgess 1977; Mazet 1966). With Gritti-Stokes and Nellis/Van De Water amputations, the patella is attached to the distal end of the femur (Middleton 1962; Nellis 2002).

Both surgeries are appropriate for people requiring a major lower limb amputation. However, surgeons tend to perform an above-knee amputation despite the potential functional advantages that a longer, more powerful, end weight-bearing, through-knee residuum offers a prosthetic or non-prosthetic user. As a result, through-knee amputations represent less than 2% of all amputations in the United States (US) (Albino 2014; Lim 2018), and less than 1% in the UK (Moxey 2010).

How the intervention might work

Although both through-knee and above-knee amputation are suitable for most patients, an above-knee amputation is often the standard method of treatment, and the small numbers of through-knee amputations performed are reflected in the sample sizes of retrospective evidence (Bae 2007; Moxey 2010). Thus, there is no

consensus regarding who makes a good or bad candidate for a through-knee amputation.

Despite this, through-knee amputation may have the following potential advantages for patients over above-knee amputation because:

- the surgery is less traumatic, and the cartilage barrier is maintained which reduces the risk of infection or bone spurs (Bowker 2000; Jensen 1996; Pinzur 2004);
- the long end-bearing lever arm creates a strong residual limb with a reduced propensity of developing hip flexion contractures (Bowker 2000; Hughes 1983; Persson 2001; Smith 2004);
- the longer residuum provides a stable sitting platform, more efficient transfers, and reduced energy requirements (Pinzur 1992; Pinzur 2004; Siev-Ner 2000); and
- the residuum supports superior ambulatory stability, prosthetic sockets are more comfortable and pressure inside the socket is reduced (Hughes 1983; Pinzur 2004; Smith 2004).

However, through-knee amputation may have the following potential disadvantages for patients when compared to above-knee amputation because:

- the prosthesis can have a poor cosmetic finish and issues with socket fit can occur (Jensen 1996; Persson 2001; Smith 2004);
- the positioning of the prosthetic knee when it is attached to the end of the socket causes asymmetrical knee levels (Hagberg 1992; Smith 2004); and
- it has a reputation for delayed wound healing despite documented evidence of successful healing (Ten Duis 2009).

Why it is important to do this review

People live with postoperative limitations after both through-knee and above-knee amputation. Incidence of return to theatre and revision to above-knee amputation remains an issue with through-knee amputation (Lim 2018), and it is unknown how all postoperative outcomes compare between above-knee amputation and through-knee amputation. An earlier systematic review compared through-knee techniques to establish if through-knee amputation is suitable for the dysvascular patient (Murakami 2016). Murakami reported that a more substantial body of evidence would be necessary to establish the effects between different surgical techniques for mobility outcomes and gait biomechanics to determine if through-knee amputation is a useful treatment option for dysvascular patients. Murakami recommended that there should be future research that compared through-knee and above-knee amputation in the dysvascular population over a suitable follow-up period. Retrospective data suggests that reamputation rates range from 0% to 21% for through-knee cases (Murakami 2016), compared to 8% to 12% for above-knee amputations (Conte 2019). However, poor rehabilitation outcomes are common amongst people with above-knee amputation, with less than 30% able to mobilise with a prosthesis outdoors (Davies 2003), whereas through-knee amputation mobility rates have been reported to range from 13% to 75% (Murakami 2016). Sufficient wound healing is essential to successful prosthetic rehabilitation and these factors must be considered carefully when deciding on level of amputation (Conte 2019). The ability to mobilise with a prosthesis has a direct impact on a person's QoL (Agrawal 2017; Davie-Smith 2017). People with through-knee amputation theoretically have gait biomechanical benefits, though some of these are potentially mitigated by the shorter lower leg segment, limited prosthetic knee joint options, and lack of prosthetist experience (Schuett 2018; Smith 2004). Recent global vascular guidelines for the management of chronic limb-threatening ischaemia set a research priority to determine whether the primary healing rates, postoperative mobility and prosthetic use, and quality of life data justify through-knee amputation rather than above-knee amputation (Conte 2019). A recent patient and public involvement (PPI) group conducted by the authors of the current review confirmed that QoL, time taken to achieve independent mobility and level of walking ability are considered research priorities by people post-amputation, and their family members. The review authors attended a UK artificial limb centre and spoke with service users in the waiting room to better understand these research priorities. The National Institute for Health Research (NIHR) recommend using PPI to improve quality and relevance of research (NIHR INVOLVE).

For these reasons, it is important to determine which level of amputation provides a lower complication rate (in terms of delayed wound healing, pain and patient survival), alongside improved postoperative, rehabilitation and QoL outcomes. The aim of this Cochrane Review is to compare the clinical and rehabilitation outcomes and complication rates of through-knee amputation with those of above-knee amputation. We will collate and evaluate evidence to facilitate discussions and shared-decision making between physicians and patients about which level of amputation offers improved healing rates, chance of survival, and QoL, and improves the potential for successful rehabilitation outcomes. We will present available evidence supporting decision-making for each clinical or patient group. We anticipate that the findings of the Cochrane Review will serve as a base to incorporate both amputation levels into a body of consensus guidelines, such as the Vascular Society of Great Britain and Northern Ireland (VSGBI), British Association of Chartered Physiotherapists in Amputation Rehabilitation (BACPAR), British Orthopaedic Association (BOA), and British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS).

OBJECTIVES

To assess the effects of through-knee amputation compared to above-knee amputation on clinical and rehabilitation outcomes and complication rates in all patients undergoing vascular and non-vascular major lower limb amputations.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials (RCTs) that compare through-knee amputation with above-knee amputation for all aetiologies. We will incorporate studies that include amputations at all above-knee levels if through-knee outcomes are reported separately. We will exclude studies where we are unable to obtain separate through-knee amputation data.

Types of participants

We will include participants of both sexes and all ages undergoing major unilateral lower limb amputation at or above the knee

(between but not including the levels of below-knee and through-hip) in all countries of origin. We will include participants with any level of pre-existing function and co-morbidities, with the exception of major lower limb amputation on the contralateral side. The indications for amputation include vascular or diabetic indications, such as infection, tissue loss, pain and ischaemia; as well as non-vascular indications, such as trauma, malignancy and congenital malformation. Participants may have had previous major or minor lower limb surgery, including salvage attempts, limb reconstruction, revascularisation, below-knee or other distal lower limb amputations.

Types of interventions

We will include RCTs that compare through-knee amputation versus above-knee amputation. We will use the umbrella term 'through-knee amputation' to refer to all variations including:

- Standard through-knee (through-knee, knee disarticulation);
- Modified through-knee (Mazet, Burgess, Youkey); and
- Gritti-Stokes and Nellis/Van De Water.

Above-knee amputations are amputations of all levels through the femur for all aetiologies. We will exclude below-knee and through-hip amputations (hip disarticulation). We will compare any through-knee amputation with any above-knee amputation.

Types of outcome measures

Primary outcomes

- Limb-fitted and not limb-fitted: measured as whether patients are referred for limb fitting and successfully fitted with a prosthetic limb, or not fitted with a prosthetic limb
- Uncomplicated primary wound healing (30 day)

Secondary outcomes

- Time taken to achieve independent mobility with a prosthesis, with or without the use of a walking aid
- Health-related QoL: reported using a validated QoL outcome measure, including those relevant to life as a prosthetic limb user, such as the 36-Item Short Form Survey (SF-36), the EuroQol-5D (EQ-5D) or the Prosthetic Patient Satisfaction Survey
- Walking speed: measured as the distance walked during a time period divided by the time taken to walk that distance. This will be converted and reported as metres per second (m/s) (Peel 2012).
- Pain (postoperative, phantom limb and pain associated with prosthetic limb-wearing) reported using a validated pain measure such as the Visual Analogue Scale (VAS) or Short Form McGill Pain Questionnaire
- 30-day patient survival

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist aims to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

The Information Specialist will search the following databases for relevant trials:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) (1946 onwards);
- EMBASE Ovid (from 1974 onwards);
- CINAHL Ebsco (from 1982 onwards).

The Information Specialist has devised a draft search strategy for RCTs for MEDLINE which is displayed in Appendix 1. This will be used as the basis for search strategies for the other databases listed.

The Information Specialist will search the following trials registries:

- the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch); and
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

Two review authors will independently check the bibliographies of included trials and non-Cochrane systematic reviews for further references of interest. We will contact the authors of the included trials for any possible unpublished data. We will also liaise with professionals within relevant specialities to identify any as yet unpublished RCTs.

Data collection and analysis

Selection of studies

Two review authors (HC and GB) will independently review the titles and abstracts and determine which studies are eligible for inclusion, discussing any conflicts with the review team to reach consensus when necessary. We will repeat this process with full texts of the studies that are initially evaluated as appropriate for inclusion. We will illustrate the study selection process in a PRISMA diagram (Liberati 2009). We will list all articles excluded after full text assessment in a 'Characteristics of excluded studies' table and will provide the reasons for their exclusion.

Data extraction and management

Two review authors (HC and GB) will independently extract and collect the relevant data from the included studies using a data extraction form provided by Cochrane Vascular. We will contact the authors for the raw data if through-knee amputation outcomes are used within the population but not reported. We will resolve any disagreement by discussion within the review team. We will collect the following information:

- publication details: year, country, authors;
- methods: study design, randomisation, total duration of study, number of study centres and location, study setting, withdrawals, date of study;
- participants: number, setting, demographic characteristics, aetiology, presence or absence of multimorbidities, previous lower-limb surgery, inclusion criteria, exclusion criteria;
- interventions: amputation level, surgical technique;
- outcomes: primary and secondary outcomes specified and collected, time points reported.

Assessment of risk of bias in included studies

Two review authors (HC and GB) will independently assess the included studies for risk of bias using Cochrane's 'Risk of bias' tool, as defined in Section 8.5 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will rate each domain as low risk, high risk or unclear risk of bias. We will resolve any disagreements between the two authors by discussion and, if necessary, a discussion with the review team. A random subset of papers (10 to 20%), will be reviewed by a senior author for risk of bias, as quality control.

We will assess the risk of bias in the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other sources of bias

We will report the judgement for each individual study in the 'Risk of bias' tables located in the 'Characteristics of included studies' section. We will contact study authors for further clarification if required.

Measures of treatment effect

We will calculate and report odds ratios (OR) with 95% confidence interval (CI) to investigate the pooled estimate of effect for dichotomous data (limb-fitted and not limb-fitted, uncomplicated primary wound healing, and 30 day patient survival). We will calculate the mean difference (MD) between treatment groups with 95% CIs for the continuous outcomes measures (health-related QoL, walking speed, and pain). Standardised mean difference (SMD) will be used if difference scales are used to measure the same concept. We will calculate time-to-event outcomes (time to achieve independent mobility) as a hazard ratio (HR) with a 95% CI. If sufficient data are not reported, we will contact study authors.

Unit of analysis issues

We will consider the unit of analysis within each trial to be the participant. If a trial allows participants who have a through-knee amputation that is reamputated to an above-knee amputation in the same admission to remain in the trial, they will also be included.

Dealing with missing data

We will analyse all available data and will contact authors to request any missing data. We will allow six weeks for response before treating the data as missing. We will aim to perform an intention-to-treat analysis and will report incidents of loss to follow-up.

Assessment of heterogeneity

We will consider clinical, methodological, and statistical heterogeneity of included studies. We will assess heterogeneity using Chi^2 and I^2, and use the below guidance for interpretation as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011):

- 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%: considerable heterogeneity.

Assessment of reporting biases

Reporting biases may occur when the dissemination of research findings is influenced by the nature and direction of results (Higgins 2011). We will examine small study effects. We will use funnel plots and seek statistical advice for their interpretation for outcomes with more than 10 studies (Higgins 2011).

Data synthesis

We will synthesise the data using Review Manager 5 software (Review Manager 2014). We will use statistical analysis in agreement with the statistical guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will use the fixed-effect model of meta-analysis when there is minimal or no heterogeneity. If there is a high level of heterogeneity, we will use a random-effects model. If we are unable to carry out meta-analysis, we will use a narrative approach to data synthesis instead.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analysis if sufficient data are available.

- Aetiology. We anticipate that participants' surgical, QoL and mobility outcomes may differ between the underlying causes of amputation. The large range of reamputation rates of through-knee amputation (0% to 21%) is due to the difference between aetiology from studies using single aetiology samples (Murakami 2016). Similarly, we expect that participants are more like to experience delayed wound healing or require reamputation if the presenting cause for the amputation is diabetes or vascular rather than for non-vascular causes or trauma. We will investigate any effect on the outcomes from vascular or non-vascular causes of amputation by using subgroup analysis when possible.
- Gender (Heidari 2016). It has been reported that female amputees are less likely to mobilise with a prosthesis and they are less satisfied with the cosmetic appearance of a through-knee amputation (Singh 2008). However, Davie-Smith 2017 described being male as one of the most significant factors to negatively affect QoL post major lower limb amputation. We will carry out subgroup analysis to provide evidence for any gender impact.
- Age. It is claimed that through-knee amputation is more suitable for paediatric patients to retain growth plates (Smith 2004). We will investigate any effect on the outcomes due to the age of participant at time of amputation by comparing participants under age 18 with those age 18 years and older (Le 2015; NHS 2013; Rijnders 2000).
- Surgical technique. We will use subgroup analysis to investigate any effect difference between through-knee, modified through-knee, Gritti-Stokes and Nellis/Van De Water amputation techniques.

Sensitivity analysis

We will use sensitivity analysis to investigate the robustness of the findings for the primary and secondary outcomes, by excluding studies we judge as having high risk of methodological bias. We will

classify trials as being at high risk of methodological bias if they are at high risk of bias for random sequence generation and allocation concealment.

Summary of findings and assessment of the certainty of the evidence

We will present the review findings in a 'Summary of findings' table, based on the methods in Chapter 11 of the *Cochrane Handbook* (Higgins 2011). We will create a table for the comparison 'Through-knee versus above-knee amputation for vascular and non-vascular major lower limb amputations'. If sufficient data are available we will create separate tables for specific through-knee variations (such as Gritti-Stokes, etc.) versus any above-knee amputation. We will include the following outcomes in each table: limb-fitted or not limb-fitted, uncomplicated primary wound healing within 30 days, time taken to achieve independent mobility, QoL, walking speed, pain, and 30 day patient survival. We will assess the certainty of the evidence for each outcome using the GRADE approach (Atkins 2004; Higgins 2011). We will assign the certainty of the evidence as high, moderate, low or very low, based on the overall risk of bias, inconsistency, indirectness, imprecision and publication bias. We will prepare the 'Summary of findings' tables using GRADEpro GDT software (GRADEpro GDT 2015). We have included a draft 'Summary of findings' table in this protocol (see Table 1).

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ADDITIONAL TABLES

Table 1. Example Summary of findings

Through-knee amputation compared with above-knee amputation for vascular and non-vascular major lower limb amputations

Patient or population: participants with through-knee or above-knee amputation

Settings: all settings (surgical wards, rehabilitation centres, artificial limb units, community settings etc.)

Intervention: through-knee amputation

Comparison: above-knee amputation

Outcomes	Anticipated absolute effects *		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with above-knee amputation	Risk with through-knee amputation				

Table 1. Example Summary of findings *(Continued)*

Limb-fitted and not limb-fitted (follow-up: upon completion of prosthetic rehabilitation)	**Study population**		**OR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			
Uncomplicated primary wound healing (follow-up: within 30 days)	**Study population**		**OR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			
Time to achieve independent mobility (follow-up)	**Study population**		**HR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			
Health related QoL (any validated QoL outcome measure) (follow-up)	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Walking speed (m/s) (follow-up: upon completion of prosthetic rehabilitation)	The mean [outcome] ranged across control groups from [value][measure]	The mean [outcome] in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Pain	The mean [outcome] ranged	The mean [outcome] in the intervention groups was **[value] [lower/higher]**		[value]	⊕⊖⊖⊖ **very low**

Table 1. Example Summary of findings *(Continued)*

(any validated pain measure) (follow-up)	across control groups from [value][measure]	[(value to value lower/higher)]		([value])	⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Patient survival (follow-up: within 30 days)	**Study population**		**OR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
	[value] per 1000	**[value] per 1000** ([value] to [value])			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval;**HR:** hazard ratio; **OR**: odds ratio; **QoL:** quality of life;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix 1. Medline search strategy

1 exp Knee/su [Surgery]

2 exp Knee Joint/su [Surgery]

3 Knee*.ti,ab.

4 "above-knee".ti,ab.

5 "Through-knee".ti,ab.

6 "trans femoral".ti,ab.

7 or/1-6

8 exp Amputation/

9 exp Amputation Stumps/

10 exp Amputees/

11 "residua* limb*".ti,ab.

12 (phantom adj6 limb*).ti,ab.

13 amput*.ti,ab.

14 disarticulat*.ti,ab.

15 exarticulat*.ti,ab.

16 postamputation*.ti,ab.

17 post-amputation*.ti,ab.

18 stump*.ti,ab.

19 Gritti-Stokes.ti,ab.

20 Mazet.ti,ab.

21 Burgess.ti,ab.

22 or/8-21

23 7 and 22

24 randomized controlled trial.pt.

25 controlled clinical trial.pt.

26 randomized.ab.

27 placebo.ab.

28 drug therapy.fs.

29 randomly.ab.

30 trial.ab.

31 groups.ab.

32 or/24-31

33 exp animals/ not humans.sh.

34 32 not 33

35 23 and 34

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

HC: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting and future review updates, guarantor of the review

GB: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting and future review updates, guarantor of the review

DC: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting and future review updates

NV: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting and future review updates

MT: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting and future review updates

GES: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting and future review updates

DECLARATIONS OF INTEREST

HC: has declared that her institution received a research bursary of £2000 from the British Association of Chartered Physiotherapists in Amputee Rehabilitation (BACPAR). This was solely for participant costs for qualitative interviews conducted with through-knee and above-knee amputees for her PhD

GB: has declared that her institution received £1000 from Help for Health solely to cover the costs of participant incentives and their travel costs when completing data collection for her PhD

DC: has received consultancy fees from Medtronic relating to venous treatment policy, and travel expenses from All Party Parliamentary Group on Vascular Disease, NICE, MHRA to provide expert advice.

NV: has received payment for Editorial board membership (Associate Editor) for the Journal of Sports Sciences. She is Chief Investigator on a study funded by the National Institute for Health Research (PB-PG-0816-20029). This study is to assess the feasibility of conducting an RCT about the effectiveness and cost-effectiveness of a novel prosthesis for older patients with vascular-related below the knee amputations and multi-morbidities. It is not relevant to this review

MT: none known

GES: has in the past received consulting fees from BSN Medical for consulting on NICE technology appraisal application, speakers fees from BSN medical and Bayer with regard to presenting research related to their products. GES reports that in the past his institution has received unconditional funding from Diomed/Angiodynamics. This was used to help fund a research nurse to assist with objective assessments in the context of randomised controlled trials.

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- No sources of support supplied

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NOTES

Parts of the methods section of this protocol are based on a standard template established by Cochrane Vascular.