

# Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication

Harwood, A. E., Pymer, S., Ibeggazene, S., Parmenter, B. & Chetter, I. C.

Published PDF deposited in Coventry University's Repository

**Original citation:**

Harwood, AE, Pymer, S, Ibeggazene, S, Parmenter, B & Chetter, IC 2021, 'Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication', Cochrane Database of Systematic Reviews, vol. 2021, no. 3, CD014677.

<https://dx.doi.org/10.1002/14651858.CD014677>

DOI 10.1002/14651858.CD014677

ESSN 1469-493X

Publisher: Wiley



**Cochrane**  
**Library**

Cochrane Database of Systematic Reviews

## Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication (Protocol)

Harwood AE, Pymer S, Ibeggazene S, Parmenter B, Chetter IC

Harwood AE, Pymer S, Ibeggazene S, Parmenter B, Chetter IC.

Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication (Protocol).

*Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No.: CD014677.

DOI: [10.1002/14651858.CD014677](https://doi.org/10.1002/14651858.CD014677).

[www.cochranelibrary.com](http://www.cochranelibrary.com)

Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication (Protocol)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

---

**TABLE OF CONTENTS**

HEADER .....	1
ABSTRACT .....	1
BACKGROUND .....	2
OBJECTIVES .....	4
METHODS .....	4
ACKNOWLEDGEMENTS .....	7
REFERENCES .....	8
ADDITIONAL TABLES .....	11
APPENDICES .....	13
HISTORY .....	15
CONTRIBUTIONS OF AUTHORS .....	15
DECLARATIONS OF INTEREST .....	16
SOURCES OF SUPPORT .....	16
NOTES .....	16

[Intervention Protocol]

# Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication

Amy Elizabeth Harwood<sup>1,2</sup>, Sean Pymer<sup>2</sup>, Saïd Ibeggazene<sup>3</sup>, Belinda Parmenter<sup>4</sup>, Ian C Chetter<sup>2</sup>

<sup>1</sup>Centre for Sport, Exercise and Life Sciences, Faculty of Health and Life Sciences, Coventry University, Coventry, UK. <sup>2</sup>Academic Vascular Surgical Unit, Hull York Medical School, Hull University Teaching Hospitals NHS Trust, Hull, UK. <sup>3</sup>College of Health, Wellbeing and Life Sciences, Sheffield Hallam University, Sheffield, UK. <sup>4</sup>Department of Exercise Physiology, Faculty of Medicine, UNSW, Sydney, Australia

**Contact address:** Amy Elizabeth Harwood, [ad5104@coventry.ac.uk](mailto:ad5104@coventry.ac.uk).

**Editorial group:** Cochrane Vascular Group.

**Publication status and date:** New, published in Issue 3, 2021.

**Citation:** Harwood AE, Pymer S, Ibeggazene S, Parmenter B, Chetter IC. Non-pharmaceutical alternatives or adjuncts to exercise programmes for people with intermittent claudication (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No.: CD014677. DOI: [10.1002/14651858.CD014677](https://doi.org/10.1002/14651858.CD014677).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Objectives

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

To assess the clinical efficacy of non-pharmaceutical, non-invasive alternatives to exercise programmes compared to standard medical care alone or to supervised exercise programmes for improving walking ability in people with intermittent claudication.

## BACKGROUND

### Description of the condition

Lower limb peripheral artery disease (PAD) refers to the obstruction or narrowing of the large arteries of the lower limbs, most commonly caused by atheromatous plaque or thrombus. The resulting stenosis or occlusion, if severe enough, can result in impairment of oxygen supply to the muscle and other tissues during exercise that results in activity-limiting symptoms. In more severe cases, blood flow becomes inadequate to meet the resting metabolic demands of the tissue, resulting in ischaemic rest pain, ischaemic ulceration or gangrene. The major risk factors for PAD are smoking, diabetes, dyslipidaemia and hypertension, and individuals with PAD are at increased risk of morbidity and mortality from cardiovascular events including myocardial infarction and stroke (Dormandy 1999; Fowkes 2008a; Hooi 2004; Pande 2011).

Though many people with PAD may be asymptomatic, the major clinical manifestations of PAD are intermittent claudication (IC) and critical limb ischaemia (CLI). Intermittent claudication typically presents as exercise-induced ischaemic pain in the leg muscles, which typically is relieved by rest. If underlying arterial stenosis continues to progress, CLI may develop, which is both limb- and life-threatening. An individual with CLI will experience (often extreme) pain in the foot at rest, while the skin and other tissues of the affected limb may become even more susceptible to ulceration and poor wound healing, which often leads to the development of gangrene. This progression from asymptomatic disease is often categorised by the Fontaine classification criteria (Fontaine 1954). See Table 1.

The prevalence of lower limb PAD increases with age and is more common in men than women (Dormandy 2000). Globally, in 2015, an estimated 237 million people were living with PAD (Song 2019), representing an increase of 37 million since 2010 (Fowkes 2013). Worldwide, taking into account the increase in life expectancy, Fowkes and colleagues estimated an increase of 23.5% for people living with PAD between 2000 to 2010 (Fowkes 2013). This prevalence has profound consequences with regard to elevated cardiovascular disease, morbidity and mortality (Fowkes 2013), and reductions in physical activity levels (Gardner 2008). The economic burden of lower limb PAD in 2010 was approximately USD 4463 for people with intermittent claudication for one year, rising to USD 7000 after two years (Mahoney 2010). The economic burden of the disease has likely grown since that time.

### Diagnosis and treatment

Several organisations, including the National Institute for Health and Care Excellence (NICE) (NICE 2012), the American Heart Association (Hirsch 2006; Rooke 2011), and the European Society of Cardiology (Aboyans 2017), have produced guidelines addressing the diagnosis, management and optimisation of risk factors of PAD. These organisations broadly agree on the overall diagnosis and management of PAD. The main treatment is the use of a supervised exercise therapy or programme (SET), which has good evidence for its clinical and cost effectiveness (Lane 2017). Revascularisation procedures, including angioplasty (Fowkes 1998), stenting (Bachoo 2010), and bypass grafting (Fowkes 2008b), may be required for people with severe disease or those who fail to respond to non-invasive management.

Despite clinical guidelines indicating that all individuals with PAD should be offered a SET (NICE 2012), the provision of services is limited. In the United Kingdom, Harwood 2017 estimates that only 39% of vascular centres are able to provide a SET. The rates of provision are similar in other countries, such as the United States, where an estimated 54% of states have no provision for a SET (Dua 2019). Even when supervised exercise programmes are available, low uptake and low adherence to programmes compound the problem of limited provision (Harwood 2016). Fear of exercise, inability to exercise due to leg pain and inability to tolerate leg pain during exercise represent additional significant barriers to accessing SET for people with PAD (Abaraogu 2017; Harwood 2016; Harwood 2017). In response to these problems, researchers have developed numerous non-pharmaceutical, non-invasive alternatives to exercise that aim to improve symptoms and be less burdensome than attending a SET. However, there is little consensus as to the most appropriate interventions that have clinical efficacy and improve symptoms in people with PAD. Therefore, the aim of this review is to determine the clinical efficacy of various non-pharmaceutical, non-invasive alternatives to supervised aerobic exercise for people with intermittent claudication.

### Description of the intervention

Supervised exercise programmes (where available) are routinely offered to all individuals with PAD, and require a regular commitment to a programme duration of at least 12 weeks, three times per week, for at least 30 minutes and up to 60 minutes (Treat-Jacobson 2019). Numerous reviews have demonstrated the efficacy of this type of programme for improving individuals' walking distances and quality of life (QoL), amongst other key outcome measures (Lane 2017; Parmenter 2013). Due to the apparent lack of funded programmes and low uptake of supervised exercise programmes, researchers have investigated alternative interventions, including psychological, educational and therapeutic, to see if they are comparable to a standard aerobic exercise programme. These comparator interventions are not part of routine standard medical care.

### Experimental interventions

#### *Psychological or educational programmes*

Prior to the design of formal educational programmes, patient education regarding exercise for people with PAD consisted of simple 'stop smoking and start walking' advice. This level of education confers little benefit and results in minimal improvements in individuals' exercise behaviours, physical activity levels and QoL (Fokkenrood 2013). NICE recognises structured education programmes for clinical conditions such as diabetes mellitus (NICE 2015). The purposes of these education programmes are to improve individuals' knowledge about the disease process, engage their awareness around the importance of managing cardiovascular risk factors, facilitate face-to-face support and encourage individuals to engage with exercise or facilitate improvements in exercise behaviour (Tew 2015). NICE recommends that education should happen early in the diagnosis of the condition and be reviewed annually as an ongoing process to adapt to individuals' needs (NICE 2015).

## Therapeutic interventions

Non-pharmaceutical, non-invasive therapeutic interventions may play a role in the treatment of PAD. They have been used in isolation (i.e. instead of an exercise programme), prior to an exercise programme or as an adjunct to a SET. Many interventions come under the therapeutic bracket, such as intermittent pneumatic compression, negative pressure therapy, electrical muscle stimulation or electrical nerve stimulation, unloading shoes, heat therapy, hydrotherapy, osteopathic manipulation and extracorporeal shockwave therapy. Another Cochrane Review is currently investigating extracorporeal shockwave therapy (Fan 2019); thus, this intervention will not be included in this review.

## How the intervention might work

People with PAD often have an extremely limited walking capacity, have low levels of fitness, adopt sedentary lifestyle behaviours and report poor QoL (Treat-Jacobson 2019). The major treatment goals for individuals are to improve walking ability, reduce pain, increase functional status and physical activity behaviours and QoL (Treat-Jacobson 2019). The primary method for achieving these outcomes is for individuals to participate in a walking-based SET (Parmenter 2011; Parmenter 2015), with mechanisms underpinning improvements leading to changes in cardiorespiratory fitness, endothelial function, muscular conditioning and mitochondrial function (Harwood 2015). However, people may not take part in a SET for a variety of reasons, including accessibility, limited understanding of the benefits and pain experienced during walking (Abaraogu 2017). Some people may find alternative non-invasive treatment modalities more accessible and acceptable. These treatments may also be efficacious in achieving the aforementioned outcomes and therefore have the potential to improve individuals' engagement in non-invasive strategies.

## Psychological or educational programmes

People with PAD often have a limited understanding of the disease process (Harwood 2018), and have high levels of uncertainty which contribute to reductions in self-efficacy (Abaraogu 2017). Studies have also demonstrated a high prevalence of depressive symptoms in people with PAD which may be chronic in nature (Smolderen 2008). Low self-efficacy and depressive symptoms are associated with poor adherence to lifestyle and behaviour change and reduced QoL (Whooley 2009). A small pilot study by Tew 2015 demonstrated that structured education programmes may have a role in improving functional capacity and walking distance in people with PAD by educating participants about the disease, and improving awareness about how their symptoms can be managed. Interventions such as a cognitive behavioural intervention may also provide benefit to individuals in terms of improvement in health-related QoL, mood and exercise behaviour. In a trial of 194 participants, a group-mediated cognitive behavioural intervention programme lasting six months significantly improved participants' six-minute walking performance (McDermott 2013). These types of education programmes may be particularly beneficial when people cannot access a SET.

## Therapeutic interventions

There are a number of non-invasive, alternative 'therapeutic interventions' that may be used either in isolation (particularly where people cannot access a SET), prior to the start of a SET, or as an adjunct to a SET. The majority of these interventions

have the same goals as a SET, such as improvements in walking distances, QoL and behavioural changes. They may encourage greater adherence to exercise programmes. Electrical stimulation devices, such as transcutaneous electrical nerve stimulation (TENS) or neuromuscular electrical stimulation (NMES), induce sensory stimulation and are mainly used for their analgesic properties (Johnson 2007). These devices tend to be portable and often utilise electrodes on the skin or provide stimulation through the feet. They may be set to various intensities (frequency of impulse) and stimulation profiles (continuous or intermittent). These devices were first used in PAD to try to reduce ischaemic pain experienced during walking and potential vasodilatory effects. Evidence suggests that they may have some vasodilatory properties (Labrunee 2015), and produce modest improvements in walking distances (Seenan 2016). Devices such as negative pressure therapy (NPT) and intermittent pneumatic compression (IPC) consist of the application of a 'boot' or bandage to the affected limb. The boot or bandage is set to a certain pressure (mmHg) which is most commonly delivered anatomically at the calf muscle. Evidence suggests that this type of intervention improves popliteal artery velocity and flow, and increases pain-free and maximum walking distance (Williams 2017). Likely contributing mechanisms for improvement include reduction in venous leg pressure, increased arterial flow and release of vasodilators (such as nitric oxide), all of which help to widen the artery. The benefits of these devices have been shown to be sustained up to 12 months after treatment. Clinical trials have demonstrated that IPC and NPT should be used for up to three hours per day for maximum benefits (Kalodiki 2007).

Heat therapy has been used for many years in various populations and has clear benefits for reductions in cardiovascular and all-cause mortality (Laukkanen 2015). In addition, heat therapy has been shown to reduce blood pressure, improve blood glucose control and may increase peripheral blood flow (Brunt 2016). There is less evidence for its use in people with PAD, with various methodologies employed, such as water perfused trousers, leg-showering, hydrotherapy or full immersion (i.e. hot baths). Acute changes for individuals receiving heat therapy include reductions in circulating inflammatory markers, blood pressure and popliteal flow, which are driven by the heat therapy inducing a cardiovascular stimulus similar to what is achieved during exercise (Neff 2016; Pellingier 2019; Thomas 2017).

Research demonstrates that pain experienced by people with PAD during walking may be influenced by a variety of factors, including ground surface, incline, speed of walking and the shoes worn (Gorely 2012). Particularly with regard to the type or design of shoe, the amount of support that the shoe provides to the ankle may influence the metabolic demands on the gastrocnemius muscle during walking and could therefore influence occurrence and intensity of claudication pain (Hutchins 2012). Researchers have investigated 'unloading' or 'rocking' shoes in people with PAD as an adjunct treatment. The shoes aim to reduce the sagittal plane ankle range of motion by at least 25%, which in turn reduces the metabolic cost to the gastrocnemius and improves the efficiency of calf muscle power (Tew 2017). There is limited evaluation of the role of these shoes for people with PAD.

Osteopathic manipulation therapy (OMT) is a type of therapy that manipulates bones, muscles and tendons to promote blood flow through the tissues, with one of the purported mechanisms of

improvement being an increase in nitric oxide release (Salamon 2004). Techniques used include myofascial release, craniocervical manipulation and soft tissue massage. A study by Lombardini and colleagues reported improvements in pain-free and maximum walking distance following a six-month programme of OMT (Lombardini 2009).

There is no consensus within the literature regarding the most appropriate intervention for therapeutic use.

### Why it is important to do this review

The prevalence of PAD is high, with global estimates suggesting that over 236 million people currently live with PAD (Song 2019). The major clinical manifestation of PAD is intermittent claudication which presents as exercise-induced ischaemic pain, mostly felt in the calf but which may appear in the thigh or buttocks. People with intermittent claudication often have an extremely limited walking capacity, have low levels of fitness, adopt sedentary lifestyle behaviours and experience poor QoL (Treat-Jacobson 2019). Many treatments are available that reduce symptoms and improve walking capacity and QoL. However, there is no consensus as to the most appropriate therapeutic interventions (Dua 2019; Harwood 2017). Many of the barriers to standard treatments may be overcome via alternative therapies. However, these therapies are diverse in nature and there has been no synthesis of the available evidence for the efficacy of these treatments. This Cochrane Review aims to assess the evidence on the clinical efficacy of these therapies (i.e. improvements in pain-free and maximum walking distance). This will enable clinicians to make informed decisions on the best management for individuals in whom a traditional walking SET is not suitable or affordable, in order to provide clinical benefit.

## OBJECTIVES

To assess the clinical efficacy of non-pharmaceutical, non-invasive alternatives to exercise programmes compared to standard medical care alone or to supervised exercise programmes for improving walking ability in people with intermittent claudication.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include all randomised controlled trials (RCTs) and quasi-RCTs on non-pharmaceutical, non-invasive alternatives to exercise programme interventions versus standard medical care alone or to supervised exercise programmes. Any methods of randomisation are eligible.

#### Types of participants

We will include all participants aged 18 years and older, diagnosed with PAD Fontaine Classification IIa/IIb or Rutherford Classification 1 to 3, diagnosed clinically using general or systemic examination using ankle brachial arterial index (ABI < 0.9), doppler scan, magnetic resonance (MR) or computerised tomography (CT) angiography.

### Types of interventions

We will include studies that investigate any non-pharmaceutical, non-invasive alternatives to exercise programme interventions for treatment of intermittent claudication (IC). This will include:

- psychological or educational programmes (including cognitive behavioural therapy);
- intermittent pneumatic compression;
- negative pressure therapy (vacuum therapy);
- electrical stimulation (including transcutaneous electrical nerve stimulation (TENS) or neuromuscular electrical stimulation (NMES));
- hydrotherapy;
- heat therapy;
- unloading footwear ('unloading' or 'rocker shoes'); and
- osteopathic manipulation (including myofascial release, craniocervical manipulation and soft tissue massage).

We will exclude any studies on pharmacological interventions and extracorporeal shockwave therapy (ESWT), as these are investigated in other Cochrane Reviews (Bedenis 2014; de Backer 2012; Fan 2019). We will also exclude studies that focus on supplements. We will also exclude studies on supervised exercise programmes versus standard medical care as this is investigated in another Cochrane review (Hageman 2018). However, 'non-pharmaceutical, non-invasive alternatives to exercise programme interventions' may include elements of exercise as part of the intervention. We propose to perform sensitivity analysis to assess the impact of such studies.

We will compare these interventions to:

- standard medical care (best medical therapy plus basic walking advice). We have defined standard medical care as individuals receiving best medical therapy (i.e. statin and aspirin therapy) plus basic walking advice; and
- supervised exercise therapy (SET) that consists predominantly of a walking intervention and any form of alternative aerobic training programme (such as Nordic walking, cycling or swimming).

It is expected that standard medical care will be equal across study arms.

### Types of outcome measures

#### Primary outcomes

- Maximum walking distance (MWD). Assessed with a six-minute walking distance (6MWD) or maximal constant or progressive grade treadmill time (converted to distance where needed)

#### Secondary outcomes

- Pain-free walking distance (PFWD). Assessed with the 6MWD or measured via treadmill testing
- Ankle brachial index (ABI)
- Adherence to treatment (compliance to treatment)
- Quality of life (QoL), as measured using validated quality of life scales (i.e. Short Form 36 or EQ-5D-L)
- Adverse events due to intervention (such as onset of coronary signs or symptoms, myocardial infarction or death)

- Pain (measured using validated scales)
- Psychosocial outcomes including self-efficacy, measured with validated scales (i.e. Hospital Anxiety and Depression Scale (HADS))
- Mortality

## 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:

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web);
- 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, MEDLINE Daily and MEDLINE) (from 1946 onwards);
- Embase Ovid (from 1974 onwards);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 onwards);
- AMED Ovid (Allied and Complementary Medicine; from 1985 onwards);
- PsychINFO Ovid (from 1806 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](http://who.int/trialsearch));
- ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)).

### Searching other resources

We will review the references cited in all relevant papers identified by the search strategy for relevant studies not already identified by the above search strategy. We will also check additional grey literature sources such as conference proceedings and unpublished theses.

## Data collection and analysis

### Selection of studies

Two review authors (AH and SP) will independently assess the titles and abstracts of each study to identify those that meet the above inclusion criteria. We will retrieve the full-text publications of studies that meet the inclusion criteria. Two review authors (AH and SP) will independently screen the full-text articles to determine inclusion in the review. We will resolve any disagreements about the inclusion or exclusion of papers through discussion, or by consultation with a third review author (BP) if necessary. 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 (AH and SP) will independently extract data from the eligible studies using a standard data collection form provided by Cochrane Vascular, with any additional data to be extracted agreed a priori and added to the data extraction form where necessary. We will resolve any disagreements through discussion or by consultation with a third review author (BP) if necessary. One review author (AH) will enter the data in Review Manager 5 ([Review Manager 2020](#)). A second review author (SP) will check the data entry for accuracy and consistency against the data extraction sheets. We will contact trial authors for missing data if required. We will extract the following data.

- Lead author, date.
- Study participant inclusion and exclusion criteria.
- Country where the research was conducted.
- Participants' sex and age.
- Study design, randomisation processes, allocation concealment.
- Recruitment rates.
- Descriptions of interventions (frequency, intensity, duration of intervention, duration of session, adherence).
- Intervention settings (e.g. home, hospital, gym) and resources required (expertise and numbers of staff, time per intervention).
- Number of participants in each trial arm, withdrawals, dropouts, and losses to follow-up.
- Length of follow-up.
- Outcome measures and time points for assessing outcomes.
- Adverse events.
- Funding source of trial and declarations of interest of trialists.

### Assessment of risk of bias in included studies

Two review authors (AH and SI) will independently assess the risk of bias in each study, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (hereafter referred to as the *Cochrane Handbook*, [Higgins 2017](#)). We will assess the risk of bias using the following criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective outcome reporting (reporting bias).
- Other sources of bias.

We will allocate each criterion a score of 'low', 'high' or 'unclear' risk of bias, and provide a statement to support each judgement. We will resolve any disagreements between review authors through discussion or by consultation with a third review author (BP) if necessary. We will contact study authors should further information be required for the risk of bias assessment. We will present our judgements of risk of bias using a risk of bias graph and a risk of bias summary. We will assess the likely magnitude and



direction of bias and whether it is likely to impact on findings using sensitivity analyses (see [Sensitivity analysis](#)).

## Measures of treatment effect

### Dichotomous data

For dichotomous outcomes, we will analyse the data based on the number of people assessed in the intervention and comparison groups and use outcomes to calculate a standard estimation of the risk ratio (RR) and associated 95% confidence intervals (CIs).

### Continuous data

For continuous outcomes, we will estimate the mean difference (MD). If not reported, MD will be calculated by subtracting baseline from post-treatment values for both control and intervention groups. For maximum walking distance, we will take into account methodological differences, should they arise in the analysis (for example, graded versus constant load treadmill testing) using standardised mean difference (SMD). We will calculate SMD with 95% CIs in order to combine data from trials that measure the same outcome using different scales. ([Higgins 2017](#)).

### Unit of analysis issues

We will consider the unit of analysis to be each individual participant. We will analyse parallel-group and cross-over trials separately and only use the first period from cross-over trials.

### Dealing with missing data

We will perform all analyses using an intention-to-treat approach, whereby all participants and their outcomes remain within the groups to which they were allocated, regardless of whether they received the intervention, when possible. If required, we will contact study authors to request missing data. We will report and assess loss to follow-up as a potential source of bias.

### Assessment of heterogeneity

We will assess heterogeneity via visual inspection of forest plots. We will assess heterogeneity for the main outcome variables using the  $\chi^2$ ,  $I^2$  and  $\tau^2$  statistics, in accordance with the *Cochrane Handbook* ([Higgins 2017](#)). We will interpret the  $I^2$  value approximately as follows:

- 0 to 40% might not be important;
- 30 to 60% may represent moderate heterogeneity;
- 50 to 90% may represent substantial heterogeneity;
- 75 to 100% indicates considerable heterogeneity.

The importance of the observed value of  $I^2$  will depend on (i) the magnitude and direction of effects, and (ii) the strength of evidence for heterogeneity (e.g. P value from the  $\chi^2$  test, or a confidence interval for  $I^2$ ) as set out in the *Cochrane Handbook* ([Higgins 2017](#)). If heterogeneity is detected, then we will further explore the reasons for this through sub-analysis.

### Assessment of reporting biases

We will investigate publication bias using funnel plots if 10 or more studies meet the inclusion criteria of the review, as recommended by the *Cochrane Handbook* ([Higgins 2017](#)). The fixed-effect model will be compared against the random-effects model to assess the possible presence of small sample bias in the published literature.

In the presence of small sample bias, the random-effects estimate of the intervention effect will be reported over the fixed-effect estimate ([Poole 1999](#)).

## Data synthesis

We will undertake statistical analyses using Review Manager 5 ([Review Manager 2020](#)). If we identify methodological, clinical or statistical heterogeneity across included trials sufficient to cause concerns, we will report results not as pooled outcomes but instead using a narrative approach. We will present the results by intervention (e.g. TENS or other alternatives versus the comparator (e.g. best medical care)). We will use the random-effects model as the default option due to expected heterogeneity for analysis, and only perform meta-analysis on studies that are clinically homogenous.

## Subgroup analysis and investigation of heterogeneity

We intend to perform these subgroup analyses (where possible):

- frequency of intervention;
- intensity of intervention;
- sex;
- severity of disease;
- age;
- location of stenosis;
- mode of treatment; and
- supervision of intervention.

## Sensitivity analysis

We will repeat analyses to include only high-quality trials (calculated from the risk of bias assessment). For the purposes of this review, we will judge trials as high quality if they have a low risk of bias for sequence generation, blinding and allocation concealment ([Higgins 2017](#)). We will repeat analyses with quasi-RCTs, which will allow us to investigate further any effects of randomisation methods used. In addition, we will perform sensitivity analysis on trials which clearly provided general exercise advice in addition to best medical therapy, to investigate any impact of trials where general exercise advice was not provided or was unclear.

## Summary of findings and assessment of the certainty of the evidence

We will present the findings of this review in a 'Summary of findings' table, based on the methods described in the *Cochrane Handbook* ([Higgins 2019](#)). We will create one table for each of the main comparisons of the review ('Psychological or educational programmes versus standard medical care'; 'Therapeutic interventions versus standard medical care'; 'Psychological or educational programmes versus SET' and 'Therapeutic interventions versus SET'). Each table will present the main outcomes which may be considered to have the most relevance to patients and clinicians, as listed below:

- changes in MWD as measured during the 6MWD;
- changes in PFWD as measured during the 6MWD;
- changes in ABI;
- adherence to treatment;

- changes in QoL, as measuring using validated quality of life scales (i.e. Short Form 36 or EQ-5D-L);
- adverse events due to intervention; and
- pain (measured using validated scales).

We will prepare a 'Summary of findings' table using the GRADE profiler ([GRADEpro GDT](#)). We will use the GRADE approach to assess the certainty of evidence as very low, low, moderate or high, based on the GRADE criteria of risk of bias, imprecision, inconsistency, indirectness and publication bias ([Atkins 2004](#)). For each assigned risk cited in the table(s), we will provide a source and rationale. If a

meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table. See [Table 2](#) for an example 'Summary of findings' table.

## ACKNOWLEDGEMENTS

The authors, and the Cochrane Vascular Editorial base, are grateful to the following peer reviewers for their time and comments: Dr Marianne Brodmann, Medical University of Graz, Austria; Dr Chris Seenan, School of Health and Life Sciences, Glasgow Caledonian University, UK; Stella O'Brien, UK; Dr Rengarajan Rajagopal, India.

## REFERENCES

### Additional references

#### Abaraogu 2017

Abaraogu UO, Dall PM, Seenan CA. The effect of structured patient education on physical activity in patients with peripheral arterial disease and intermittent claudication: a systematic review. *European Journal of Vascular and Endovascular Surgery* 2017;**54**:58-68.

#### Aboyans 2017

Aboyans V, Ricco JB, Bartelink ML, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO), the Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *European Heart Journal* 2017;**39**(9):763-816.

#### Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *British Medical Journal* 2004;**328**(7454):1490-4.

#### Bachoo 2010

Bachoo P, Thorpe PA, Maxwell H, Welch K. Endovascular stents for intermittent claudication. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No: CD003228. [DOI: [10.1002/14651858.CD003228.pub2](https://doi.org/10.1002/14651858.CD003228.pub2)]

#### Bedenis 2014

Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G. Cilostazol for intermittent claudication. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No: CD003748. [DOI: [10.1002/14651858.CD003748.pub4](https://doi.org/10.1002/14651858.CD003748.pub4)]

#### Brunt 2016

Brunt VE, Howard MJ, Franciisco MA, Ely BR, Minson CT. Passive heat therapy improves endothelial function, arterial stiffness and blood pressure in sedentary humans. *Journal of Physiology* 2016;**594**(18):5329-42.

#### de Backer 2012

de Backer TL, Vander Stichele R, Lehert P, Van Bortel L. Naftidrofuryl for intermittent claudication. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No: CD001368. [DOI: [10.1002/14651858.CD001368.pub4](https://doi.org/10.1002/14651858.CD001368.pub4)]

#### Dormandy 1999

Dormandy J, Heck L, Vig S. The natural history of claudication: risk to life and limb. *Seminars in Vascular Surgery* 1999;**12**(2):123-37.

#### Dormandy 2000

Dormandy JA, Rutherford RB, TransAtlantic Inter-Society Consensus (TASC) Working Group. Management of peripheral

arterial disease (PAD). *Journal of Vascular Surgery* 2000;**31**(Pt 2):1-296.

#### Dua 2019

Dua A, Gologorsky R, Savage D, Rens N, Gandhi N, Brooke B, et al. National assessment of availability, awareness, and utilization of supervised exercise therapy for peripheral artery disease patients with intermittent claudication. *Journal of Vascular Surgery* 2019;**P2 S0741-5214**(19):32184-61 [Epub ahead of print].

#### Fan 2019

Fan W, Yang B, Liang N, Liang S. Extracorporeal shockwave therapy for peripheral arterial disease. *Cochrane Database of Systematic Reviews* 2019, Issue 12. Art. No: CD013509. [DOI: [10.1002/14651858.CD013509](https://doi.org/10.1002/14651858.CD013509)]

#### Fokkenrood 2013

Fokkenrood HJ, Bendermacher BL, Lauret GJ, Wiligendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No: CD005263. [DOI: [10.1002/14651858.CD005263.pub3](https://doi.org/10.1002/14651858.CD005263.pub3)]

#### Fontaine 1954

Fontaine VR, Kim M, Kiény R. Surgical treatment for peripheral vascular disease [Die chirurgische Behandlung der peripheren Durchblutungsstörungen]. *Helvetica Chirurgica Acta* 1954;**21**:499-533.

#### Fowkes 1998

Fowkes G, Gillespie IN. Angioplasty (versus non surgical management) for intermittent claudication. *Cochrane Database of Systematic Reviews* 1998, Issue 2. Art. No: CD000017. [DOI: [10.1002/14651858.CD000017](https://doi.org/10.1002/14651858.CD000017)]

#### Fowkes 2008a

Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**(2):197-208. [DOI: [10.1001/jama.300.2.197](https://doi.org/10.1001/jama.300.2.197)]

#### Fowkes 2008b

Fowkes F, Leng GC. Bypass surgery for chronic lower limb ischaemia. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No: CD002000. [DOI: [10.1002/14651858.CD002000.pub2](https://doi.org/10.1002/14651858.CD002000.pub2)]

#### Fowkes 2013

Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg MA, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**(9901):1329-40.

**Gardner 2008**

Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *Journal of Vascular Surgery* 2008;**47**(1):117-22.

**Gorely 2012**

Gorely T, Crank H, Humphreys L, Nawaz S, Tew GA. "Standing still in the street": experiences, knowledge and beliefs of patients with intermittent claudication - a qualitative study. *Journal of Vascular Nursing* 2012;**30**(1):11-20.

**GRADEpro GDT [Computer program]**

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime). Available from [gradepro.org](http://gradepro.org).

**Hageman 2018**

Hageman D, Fokkenrood HJ, Gommans LN, Van den Houten MM, Tejjink JA. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No: CD005263. [DOI: [10.1002/14651858.CD005263.pub4](https://doi.org/10.1002/14651858.CD005263.pub4)]

**Harwood 2015**

Harwood AE, Cayton T, Sarvanandan R, Lane R, Chetter IC. A review of the potential local mechanisms by which exercise improve functional outcomes in intermittent claudication. *Annals of Vascular Surgery* 2015;**30**:312-20.

**Harwood 2016**

Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication. *Annals of Vascular Surgery* 2016;**34**:280-9.

**Harwood 2017**

Harwood AE, Smith GE, Broadbent E, Cayton T, Carradice D, Chetter IC. Access to supervised exercise services for peripheral vascular disease patients. *Bulletin of the Royal College of Surgeons of England* 2017;**99**(6):207-11.

**Harwood 2018**

Harwood AE, Hitchman L, Ingle L, Doherty P, Chetter IC. Preferred exercise modalities in patients with intermittent claudication. *Journal of Vascular Nursing* 2018;**36**(2):81-4.

**Higgins 2017**

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from [training.cochrane.org/handbook](http://training.cochrane.org/handbook).

**Higgins 2019**

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from [training.cochrane.org/handbook](http://training.cochrane.org/handbook).

**Hirsch 2006**

Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): Executive Summary. A Collaborative Report From the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Journal of the American College of Cardiology* 2006;**47**(6):1239-312. [DOI: [10.1016/j.jacc.2005.10.009](https://doi.org/10.1016/j.jacc.2005.10.009)]

**Hooi 2004**

Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, Van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *Journal of Clinical Epidemiology* 2004;**57**(3):294-300.

**Hutchins 2012**

Hutchins SW, Lawrence G, Blair S, Aksenov A, Jones R. Use of a three-curved rocker sole shoe modification to improve intermittent claudication calf pain: a pilot study. *Journal of Vascular Nursing* 2012;**30**(1):11-20.

**Johnson 2007**

Johnson M. Transcutaneous electrical nerve stimulation: mechanisms, clinical application and evidence. *Reviews in Pain* 2007;**1**(1):7-11.

**Kalodiki 2007**

Kalodiki E, Giannoukas AD. Intermittent pneumatic compression (IPC) in the treatment of peripheral arterial occlusive disease (PAOD) - a useful tool or just another device? *European Journal of Vascular and Endovascular Surgery* 2007;**33**:309-10.

**Labrunee 2015**

Labrunee M, Boned A, Granger R, Bousquet M, Jordan C, et al. Improved walking claudication distance with transcutaneous electrical nerve stimulation. *Vascular Rehabilitation* 2015;**11**:941-50.

**Lane 2017**

Lane R, Harwood AE, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No: CD000990. [DOI: [10.1002/14651858.CD000990.pub4](https://doi.org/10.1002/14651858.CD000990.pub4)]

**Laukkanen 2015**

Laukkanen T, Khan H, Zaccardi F, Laukkanen JA. Association between sauna bathing and fatal cardiovascular and all-cause mortality events. *JAMA Internal Medicine* 2015;**145**(4):542-48.

**Liberati 2009**

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**:e1000100.

**Lombardini 2009**

Lombardini R, Marchesi S, Collebrusco L, Vaudo G, Pasqualini L, Ciuffetti G, et al. The use of osteopathic manipulative treatment as adjuvant therapy in patients with peripheral arterial disease. *Manual Therapy* 2009;**14**(4):439-43. [DOI: 10.1016/j.math.2008.08.002 ]

**Mahoney 2010**

Mahoney EM, Wang K, Keo HH, Duval S, Smolderen DJ, Cohen DJ, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circulation: Cardiovascular Quality and Outcomes* 2010;**3**(6):642-51.

**McDermott 2013**

McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L et al. Home-based walking exercise intervention in peripheral artery disease. *JAMA* 2013;**310**(1):57-65.

**Neff 2016**

Neff D, Kuhlenhoelter AM, Lin C, Wong BJ, Motaganahallii RL, Roseguini BT. Thermotherapy reduces blood pressure and circulating endothelin-1 concentration and enhances leg blood flow in patients with symptomatic peripheral artery disease. *Translational Physiology* 2016;**311**(2):R392-400.

**NICE 2012**

National Institute for Health and Care Excellence (NICE). Clinical Guideline 147 Lower limb peripheral arterial disease: diagnosis and management. nice.org.uk/guidance/cg147 (accessed 11 March 2015).

**NICE 2015**

National Institute for Health and Care Excellence (NICE). Type 2 diabetes: the management of type 2 diabetes. nice.org.uk/guidance/ng28 (accessed 12 December 2019).

**Pande 2011**

Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. *Circulation* 2011;**124**(1):17-23. [DOI: 10.1161/CIRCULATIONAHA.110.003954]

**Parmenter 2011**

Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis* 2011;**218**(1):1-12.

**Parmenter 2013**

Parmenter BJ, Raymond J, Dinnen PJ, Lusby RJ, Fiatarone Singh MA. Preliminary evidence that low ankle-brachial index is associated with reduced bilateral hip extensor strength and

functional mobility in peripheral arterial disease. *Journal of Vascular Surgery* 2013;**57**(4):963-73.

**Parmenter 2015**

Parmenter BJ, Dieberg G, Phipps G, Smart NA. Exercise training for health-related quality of life in peripheral artery disease: a systematic review and meta-analysis. *Vascular Medicine* 2015;**20**(1):30-40.

**Pellinger 2019**

Pellinger TK, Neighbors CB, Simmons GH. Acute lower leg heating increases exercise capacity in patients with peripheral artery disease. *Journal of Cardiovascular Nursing* 2019;**34**(2):130-3.

**Poole 1999**

Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *American Journal of Epidemiology* 1999;**150**(5):469-75.

**Review Manager 2020 [Computer program]**

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

**Rooke 2011**

Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. ACCF/AHA Focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;**124**:2020-45.

**Salamon 2004**

Salamon E, Zhu W, Stefano GB. Nitric oxide as a possible mechanism for understanding the therapeutic effects of osteopathic manipulative medicine (Review). *International Journal of Molecular Medicine* 2004;**14**:443-9.

**Seenan 2016**

Seenan C, McSwiggan S, Roche PA, Tan C, Mercer T, Belch JJ. Transcutaneous electrical nerve stimulation improves walking performance in patients with intermittent claudication. *Journal of Cardiovascular Nursing* 2016;**4**:323-30.

**Smolderen 2008**

Smolderen KG, Aquarius AE, de Vries J, Smith OR, Hamming JF, Denollet J. Depressive symptoms in peripheral arterial disease: a follow-up study on prevalence, stability and risk factors. *Journal of Affective Disorders* 2008;**110**:27-35.

**Song 2019**

Song P, Rudan D, Zhu Y, Fowkes FJ, Rahimi K, Fowkes FG. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Global Health* 2019;**7**(8):e1020-30.

**Tew 2015**

Tew G, Humphreys L, Crank H, Hewitt C, Nawaz S, Al-Jundi W, et al. The development and pilot randomised controlled trial of a group education programme for promoting walking in

people with intermittent claudication. *Vascular Medicine* 2015;**20**(4):348-57. [DOI: [10.1177/1358863X15577857](https://doi.org/10.1177/1358863X15577857)]

**Tew 2017**

Tew GA, Shalan A, Jordan AR, Cook L, Coleman ES, Fairhurst C. Unloading shoes for intermittent claudication: a randomised crossover trial. *BMC Cardiovascular Disorders* 2017;**17**(1):283.

**Thomas 2017**

Thomas KN, Van Rij AM, Lucas SJ, Cotter JD. Lower-limb hot-water immersion acutely induces beneficial haemodynamic and cardiovascular responses in peripheral arterial disease and healthy, elderly controls. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 2017;**312**(3):R281-91.

**Treat-Jacobson 2019**

Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH. Optimal exercise programs for patients with peripheral artery disease. *Circulation* 2019;**139**:e10-33.

**Whooley 2009**

Whooley MA. To screen or not to screen? Depression in patients with cardiovascular disease. *Journal of the American College of Cardiology* 2009;**54**:891-3.

**Williams 2017**

Williams KJ, Babber A, Ravikumar R, Davies AH. Non-invasive management of peripheral arterial disease. *Advances in Experimental Medicine and Biology* 2017;**906**:387-406. [DOI: [10.1007/5584\\_2016\\_129](https://doi.org/10.1007/5584_2016_129)]

**ADDITIONAL TABLES**

**Table 1. Fontaine classification of peripheral arterial disease (Fontaine 1954)**

Stage	Description
I	Asymptomatic
II	Mild claudication pain
IIa	Claudication distance > 200 metres
IIb	Claudication distance < 200 metres
III	Rest pain (especially at night)
IV	Ulceration and/or gangrene of the limb

**Table 2. Draft 'Summary of findings' table**

**Do non-pharmaceutical, non-invasive alternatives to exercise programmes benefit people with intermittent claudication compared with standard medical care?**

**Patient or population:** people with intermittent claudication

**Settings:** tertiary care, outpatient

**Intervention:** non-pharmaceutical, non-invasive alternatives to exercise programmes<sup>a</sup>

**Comparison:** standard medical care<sup>b</sup>

Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard medical care	Risk with non-pharmaceutical, non-invasive alternatives to exercise programmes				
<b>Changes in MWD (meters)</b>	The mean MWD ranged across control groups from	The mean MWD in the intervention groups was <b>[value] [lower/higher]</b>		[value] ([value])	⊕⊕⊕⊕ <b>very low</b> ⊕⊕⊕⊕	

**Table 2. Draft 'Summary of findings' table** (Continued)

(measured during the 6MWD; follow-up period)	[value][measure]	[(value to value lower/higher)]	[value] ([value])	low ⊕⊕⊕⊕ <b>moderate</b> ⊕⊕⊕⊕ <b>high</b>
<b>Changes in PFWD</b> (meters) (measured during the 6MWD; follow-up period)	The mean PFWD ranged across control groups from [value][measure]	The mean PFWD in the intervention groups was <b>[value] [lower/higher]</b> [(value to value lower/higher)]	[value] ([value])	⊕⊕⊕⊕ <b>very low</b> ⊕⊕⊕⊕ <b>low</b> ⊕⊕⊕⊕ <b>moderate</b> ⊕⊕⊕⊕ <b>high</b>
<b>ABI</b> (follow-up period)	The mean ABI ranged across control groups from [value][measure]	The mean ABI in the intervention groups was <b>[value] [lower/higher]</b> [(value to value lower/higher)]	[value] ([value])	⊕⊕⊕⊕ <b>very low</b> ⊕⊕⊕⊕ <b>low</b> ⊕⊕⊕⊕ <b>moderate</b> ⊕⊕⊕⊕ <b>high</b>
<b>Adherence to treatment</b> (follow-up period)	The mean adherence ranged across control groups from [value][measure]	The mean adherence in the intervention groups was <b>[value] [lower/higher]</b> [(value to value lower/higher)]	[value] ([value])	⊕⊕⊕⊕ <b>very low</b> ⊕⊕⊕⊕ <b>low</b> ⊕⊕⊕⊕ <b>moderate</b> ⊕⊕⊕⊕ <b>high</b>
<b>Changes in QoL</b> (measured using Short Form 36 or EQ-5D-L; follow-up period)	The mean QoL ranged across control groups from [value][measure]	The mean QoL in the intervention groups was <b>[value] [lower/higher]</b> [(value to value lower/higher)]	[value] ([value])	⊕⊕⊕⊕ <b>very low</b> ⊕⊕⊕⊕ <b>low</b> ⊕⊕⊕⊕ <b>moderate</b> ⊕⊕⊕⊕ <b>high</b>
<b>Adverse events due to intervention</b> (follow-up period)	The mean adverse event ranged across control groups from [value][measure]	The mean adverse event in the intervention groups was <b>[value] [lower/higher]</b> [(value to value lower/higher)]	[value] ([value])	⊕⊕⊕⊕ <b>very low</b> ⊕⊕⊕⊕ <b>low</b> ⊕⊕⊕⊕

**Table 2. Draft 'Summary of findings' table** (Continued)

				moderate
				⊕⊕⊕⊕ <b>high</b>
<b>Pain</b> (measured using validated scales; follow-up period)	The mean pain event ranged across control groups from [value][measure]	The mean pain event in the intervention groups was <b>[value] [lower/higher]</b>	[value] ([value])	⊕⊕⊕⊕ <b>very low</b>
				⊕⊕⊕⊕ <b>low</b>
				⊕⊕⊕⊕ <b>moderate</b>
				⊕⊕⊕⊕ <b>high</b>

\***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).

**ABI:** ankle brachial index; **CI:** confidence interval; **IC:** intermittent claudication; **MWD:** maximum walking distance; **PFWD:** pain-free walking distance; **QoL:** quality of life; **RR:** risk ratio; **SET:** supervised exercise therapy

#### 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

<sup>a</sup>Non-pharmaceutical, non-invasive alternatives to exercise programmes include psychological or structured education programmes and therapeutic interventions (such as electrical stimulation, intermittent pneumatic compression, negative pressure therapy, heat therapy, hydrotherapy, unloading shoes, and osteopathic manipulation).

<sup>b</sup>Standard medical care is defined as best medical therapy plus basic walking advice.

## APPENDICES

### Appendix 1. Medline search strategy

1 Intermittent Claudication/

2 exp Peripheral Vascular Diseases/

3 exp Peripheral Arterial Disease/

4 exp Arterial Occlusive Diseases/

5 exp Leg/bs

6 Iliac Artery/

7 Popliteal Artery/

8 Femoral Artery/

9 Tibial Arteries/

10 (PVD or PAOD or PAD).ti,ab.



- 11 ((arter\* or vascular or vein\* or veno\* or peripher\*) adj3 (occlus\* or steno\* or obstruct\* or lesio\* or block\* or harden\* or stiffen\* or obliter\*)).ti,ab.
- 12 (peripheral adj3 dis\*).ti,ab.
- 13 claudic\*.ti,ab.
- 14 arteriopathic.ti,ab.
- 15 dysvascular\*.ti,ab.
- 16 (leg adj3 (occlus\* or steno\* or obstruct\* or lesio\* or block\* or harden\* or stiffen\* or obliter\*)).ti,ab.
- 17 (limb adj3 (occlus\* or steno\* or obstruct\* or lesio\* or block\* or harden\* or stiffen\* or obliter\*)).ti,ab.
- 18 (lower adj3 extrem\* adj3 (occlus\* or steno\* or obstruct\* or lesio\* or block\* or harden\* or stiffen\* or obliter\*)).ti,ab.
- 19 ((iliac or femoral or popliteal or femoro\* or fempop\* or crural or tibial) adj3 (occlus\* or steno\* or obstruct\* or lesio\* or block\* or harden\* or stiffen\* or obliter\*)).ti,ab.
- 20 or/1-19
- 21 Complementary Therapies/
- 22 Electric Stimulation Therapy/
- 23 Hydrotherapy/
- 24 Intermittent Pneumatic Compression Devices/
- 25 Patient Education as Topic/
- 26 Therapy, Soft Tissue/
- 27 "cognitive behaviour therapy".ti,ab.
- 28 "craniosacral manipulation".ti,ab.
- 29 "educational program\*".ti,ab.
- 30 "electrical muscle stimulation".ti,ab.
- 31 "electrical nerve stimulation".ti,ab.
- 32 "electrical stimulation".ti,ab.
- 33 "full immersion".ti,ab.
- 34 "heat therap\*".ti,ab.
- 35 "hot bath\*".ti,ab.
- 36 "intermittent pneumatic compression".ti,ab.
- 37 "leg shower\*".ti,ab.
- 38 "myofascial release".ti,ab.
- 39 "negative pressure therap\*".ti,ab.
- 40 "neuromuscular electrical stimulation".ti,ab.
- 41 "psychological program\*".ti,ab.
- 42 "rock\* shoes".ti,ab.
- 43 "transcutaneous electrical nerve stimulation".ti,ab.
- 44 "unloading shoes".ti,ab.

- 45 "vacuum therapy".ti,ab.  
46 "water perfused trousers".ti,ab.  
47 CBT.ti,ab.  
48 hydrotherapy.ti,ab.  
49 massage.ti,ab.  
50 NMES.ti,ab.  
51 NPT.ti,ab.  
52 OMT.ti,ab.  
53 osteopath\*.ti,ab.  
54 TENS.ti,ab.  
55 "unloading footwear".ti,ab.  
56 "craniosacral manipulation".ti,ab.  
57 (patient adj3 educat\*).ti,ab.  
58 or/21-57  
59 20 and 58  
60 randomized controlled trial.pt.  
61 controlled clinical trial.pt.  
62 randomized.ab.  
63 placebo.ab.  
64 drug therapy.fs.  
65 randomly.ab.  
66 trial.ab.  
67 groups.ab.  
68 or/60-67  
69 exp animals/ not humans.sh.  
70 68 not 69  
71 59 and 70

## **HISTORY**

Protocol first published: Issue 3, 2021

## **CONTRIBUTIONS OF AUTHORS**

AH: protocol drafting, guarantor of the review

SP: protocol drafting

SI: protocol drafting

BP: protocol drafting

IC: protocol drafting

---

## DECLARATIONS OF INTEREST

AH: none known  
SP: none known  
SI: none known  
BP: none known  
IC: none known

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK

The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

## NOTES

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