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Identifying the most clinically effective exercise prescription for people with intermittent claudication (MAXIMISE): a component network meta-analysis with concurrent cost-effectiveness analysis (Protocol).
Cochrane Database of Systematic Reviews 2024, Issue 3. Art. No.: CD015940.
DOI: 10.1002/14651858.CD015940.

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[Intervention Protocol]

Identifying the most clinically effective exercise prescription for people with intermittent claudication (MAXIMISE): a component network meta-analysis with concurrent cost-effectiveness analysis

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Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 3, 2024.

Citation: Pymer S, Harwood AE, Prosser J, Ravindhran B, Fenton C, Hewitt C, Huang C, Long J, Soares MO, Sayers R, Hatfield J, Gordon H, Pittack S, Reeve J, Duarte A, Chetter I. Identifying the most clinically effective exercise prescription for people with intermittent claudication (MAXIMISE): a component network meta-analysis with concurrent cost-effectiveness analysis (Protocol). *Cochrane Database of Systematic Reviews* 2024, Issue 3. Art. No.: CD015940. DOI: 10.1002/14651858.CD015940.

ABSTRACT

Objectives

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

- To conduct a component network meta-analysis (CNMA) comparing different SEP combinations to identify the most clinically effective exercise prescription for people with IC.
- To conduct an economic evaluation comparing different SEP combinations for people with IC to identify which are cost-effective.

BACKGROUND

Description of the condition

Peripheral arterial disease (PAD) is an atherosclerotic cardiovascular disease in which the arteries that supply the lower limbs become narrowed or occluded, reducing blood supply (Hiatt 2001). Global estimates suggest that in 2015, 236 million people were living with PAD, increasing from 202 million in 2010 (Fowkes 2013; Song 2019). The major risk factors for PAD include smoking and diabetes (Peach 2012). However, PAD is also an age-dependent disease, estimated to affect 5% of the population aged 45 to 49 years, rising to 16% in those aged 80 to 84 years (Song 2019).

The spectrum for PAD ranges from asymptomatic disease to critical limb-threatening ischaemia. In between these extremes is the classic symptom of PAD, which is intermittent claudication (IC). IC is a reproducible ischaemic leg muscle pain that is precipitated by exertion, usually walking, and relieved by rest (Meru 2006). The site of pain is commonly the calf, but the thighs or buttocks (or both) can also be affected, depending on the location of the flow-limiting disease (Morley 2018).

IC impacts upon walking ability, functional capacity, balance and quality of life (QoL) (Criqui 2015; Gohil 2013; Meru 2006; Pell 1995). Furthermore, the presence of PAD is associated with up to a 15-fold increased risk of mortality, usually secondary to cardiovascular causes (Criqui 1992). For people with IC, symptomology is often stable, with disease progression occurring in 10% to 20% of cases, leading to critical limb-threatening ischaemia in 5% to 10% of cases over five years (Norgren 2007). Therefore, the primary treatment goals are to provide symptomatic relief via improvements in maximum walking distance (MWD) and QoL, and reduce the risk of cardiovascular events, via reductions in cardiovascular risk factors (Gerhard-Herman 2017; Iso 2015; Ratchford 2017). Randomised controlled trials (RCT) including people with IC often use treadmill walking tests to establish MWD before and after therapeutic interventions. MWD is defined as the point at which a person with IC can no longer walk on the treadmill due to reaching maximally tolerated claudication pain (Hiatt 2014).

However, there is variability in the treadmill tests employed, with regards to the nature (constant load and graded) and protocol employed (Birkett 2021). The most widely used protocol is that of Gardner-Skinner, which is a graded test starting at 2 miles per hour and 0% incline, increasing by 2% every two minutes (Gardner 1991). This protocol also benefits from excellent reliability, which is much better than for constant-load tests (Gardner 1991).

With regards to QoL, several different tools are used which are both generic and disease specific (Harwood 2017). The most commonly used and recommended generic questionnaire to capture changes in QoL in people with IC is the 36-item Short Form (SF-36) (Chetter 1997; Harwood 2017). The most commonly used disease-specific questionnaire is the Walking Impairment Questionnaire, though other questionnaires include the Intermittent Claudication Questionnaire and the Vascular Quality of Life Questionnaire. Importantly, these questionnaires, along with MWD, are responsive to change following an intervention (Chetter 1997; Chong 2002; Hiatt 2001; Morgan 2001; Nicolaï 2009).

Description of the intervention

Due to the increased risk of cardiovascular events, all people with IC should receive aggressive risk factor management which consists of smoking cessation, diet, weight management and exercise, statin therapy, antiplatelet therapy, and the prevention or diagnosis (or both) and management of diabetes and hypertension (Aboyans 2017; NICE 2012). Although exercise is mentioned as part of this risk factor management, details are lacking. Additionally, 'exercise' is recommended across the whole PAD spectrum and indeed for all cardiovascular diseases. More specifically, for symptomatic relief for people with IC, supervised exercise programmes (SEP) are recommended as the first-line treatment and this is supported by high-quality evidence (Hageman 2018). A SEP is defined as any exercise programme that is performed under supervision, with prescribed components of **F**requency (number of sessions per week), **I**ntensity (how hard exercise is performed), **T**ime (how long each session is and how long the programme is) and **T**ype (the mode of exercise used) (FITT principle) of exercise.

One Cochrane review, including 21 studies and 1400 participants, compared SEPs to home-based exercise therapy and basic walking advice (Hageman 2018). SEPs were superior for improving both pain-free exercise and MWD when compared to both home-based exercise therapy and walking advice. The superiority for improvements in MWD translated to 120 m compared to home-based exercise therapy and 210 m compared to walking advice. Further evidence also suggests that SEPs are equivalent to more invasive treatments for improving MWD and QoL (Murphy 2015).

Generally, recommendations for SEPs are that they are performed two or three times per week, for at least three months (Aboyans 2017; Gerhard-Herman 2017; NICE 2012).

How the intervention might work

Despite the significant improvements in MWD provided by SEPs, the exact mechanisms of action for this remain poorly understood. However, it is likely that these mechanisms are complex and multifactorial. The purported mechanisms include enlargement of existing collateral vessels and angiogenesis, enhanced vasodilation of the microcirculation, improved bioenergetics of the skeletal muscle, haemorheology, changes in cardiorespiratory physiology and changes in muscle conditioning (Conte 2015; Harwood 2016).

Further benefits of SEP include reductions in cardiovascular risk factors such as blood cholesterol levels, and resting and exercising blood pressure (Jansen 2019; Slysz 2021), which may influence the mortality benefit associated with SEP completion (Sakamoto 2009).

Why it is important to do this review

Within individual trials of SEPs, the reported exercise prescription component is widely variable with regards to the FITT principle of exercise. Within the Hageman 2018 Cochrane review, SEP frequency included once, twice and three times per week; intensity was reported as 'varying'; session duration (time) varied from 30 to 70 minutes; programme durations (time) included six weeks, three months, six months and 12 months; and the types of exercise included treadmill walking and circuit-based training (Hageman 2018).

This leads to a significant deficit and limitation of guideline details. For example, in the UK, the National Institute for Health

and Care Excellence (NICE) guidelines state, "consider providing a supervised exercise programme for people with intermittent claudication which involves two hours of exercise per week for a three-month period, encouraging people to exercise to the point of maximal pain" (NICE 2012, which was last updated in December 2020). The European guidelines provide a similarly vague statement of "most studies use programmes of at least 3 months, with a minimum of 3 h/week, with walking to the maximal or submaximal distance" (Aboyans 2017). The American guidelines provide a little more detail, stating that exercise should be performed for 30 to 45 minutes per session, three times per week for 12 weeks, involving interval walking performed to moderate-to-maximal claudication pain (Gerhard-Herman 2017).

These guidelines have more-recently been complemented by a detailed document developed by this review team, which specifies the mode of delivery, the setting, the materials and the FITT exercise prescription required to implement a SEP for people with IC (Harwood 2020). A similar document was also produced by Exercise and Sports Science Australia (Askew 2014). However, both the guidelines and these complementary documents base their FITT exercise prescription components on individual randomised controlled trials (RCTs), summaries of evidence and meta-analyses that do not necessarily make direct comparisons between the different components, hence the disparities in their recommendations. This means that these documents base their recommendations on the best available evidence, rather than the best possible evidence.

Therefore, there remains a need to develop the best possible evidence for SEP prescription, by comparing all possible combinations of each component of the FITT principle to identify which is the most clinically effective. This will allow for the identification of the optimal SEP prescription (i.e. the one that produces the greatest improvement in MWD and QoL), which may or may not have been observed within the evidence. Identification of this prescription should then lead to the development of best evidence guidelines, altering clinical practice. Further, the significance of this need was recently highlighted by the James Lind Alliance Priority Setting Partnership where patients and healthcare professionals ranked the research question 'what is the optimal exercise prescription for patients with poor circulation to the legs?', as the second most important for people with PAD (Pymer 2022).

OBJECTIVES

- To conduct a component network meta-analysis (CNMA) comparing different SEP combinations to identify the most clinically effective exercise prescription for people with IC.
- To conduct an economic evaluation comparing different SEP combinations for people with IC to identify which are cost-effective.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-group RCTs, where individuals are allocated to one of two or more groups and exclude all other study designs including; cluster-RCTs, single-arm studies, quasi-randomised trials and observational studies. We will include cross-over trials, but, due to the likelihood of a carry-over effect, include only data from the first period in the analysis. Therefore, such trials will be treated as parallel-group trials.

There will be no exclusions based on publication status, date or language.

Types of participants

The eligible population will be people aged 18 years or older with a diagnosis of IC secondary to atherosclerotic disease. We will not apply haemodynamic or imaging criteria for inclusion as these may not be reported within individual trials. A statement made by the study authors noting that participants were required to have IC to be included will be sufficient. Trials including other PAD subgroups (e.g. asymptomatic) will be included only if the data for the IC subgroup can be obtained. Additionally, trials including participants with atypical IC will be included, if sufficient detail is provided to confirm that the symptoms are secondary to PAD (e.g. ischaemic leg symptoms affecting the buttocks or thighs, but not the calves) (McDermott 2021).

Types of interventions

Interventions

We will include all SEPs, as long as they are actively supervised, regardless of the FITT components and classify SEPs based on their respective FITT principle components. This will allow for comparison between different combinations, to identify which is most effective. We anticipate that classifications will be based on the following components and levels.

- Frequency of exercise:
  - once per week
  - twice per week
  - three times per week
  - more than three times per week
- Intensity of exercise:
  - pain-free exercise
  - exercising to moderate pain
  - exercising to maximal pain
  - low-intensity exercise
  - moderate-intensity exercise
  - high-intensity exercise
- Time (length) of exercise sessions:
  - less than 30 minutes
  - 30 to 45 minutes
  - 46 to 60 minutes
  - greater than 60 minutes
- Length of programmes:
  - less than six weeks
  - six weeks
  - greater than six weeks to less than 12 weeks
  - 12 weeks
  - greater than 12 weeks to less than 26 weeks
  - 26 weeks
  - greater than 26 weeks to less than 52 weeks
  - 52 weeks
  - greater than 52 weeks

- Type of exercise
  - treadmill walking
  - overground walking
  - lower-limb cycling
  - upper-limb cycling
  - circuit-based exercise

Whilst each component will remain the same, levels will be guided by the data and may alter from the above.

At least one of the FITT components must be reported within individual SEPs for them to be considered for inclusion.

Comparators

We have previously defined non-exercise controls, exercise advice and home-based exercise programmes (Pymer 2018). These definitions are as follows.

- Non-exercise controls: receiving no exercise-specific advice or being told to maintain usual physical activity levels.
- Exercise advice: encouragement to exercise/walk more at home without receiving specific recommendations for an exercise regimen (e.g. frequency, intensity, etc.).
- Home-based exercise programmes: includes structured verbal or written advice to increase physical activity at home by guiding participants in terms of FITT components rather than basic advice to 'go home and walk'.

We will combine these three groups in the network as a single comparator group in order to maximise the data available. Although these groups are usually distinct, evidence suggests that they are all inferior to SEPs, with no difference between them in terms of improvements in MWD (Hageman 2018; Pymer 2021).

When trials compare two (or more) different types of SEP (e.g. pain-free walking versus maximal pain walking), we will include these regardless of whether a comparator group is also included as an indirect comparison can be made via the CNMA.

Types of outcome measures

Primary outcomes

- Maximum walking distance (MWD) established via treadmill walking tests
- Quality of life (QoL) established via validated questionnaires
  - Note: we will analyse each QoL tool/domain separately, meaning we will combine or analyse (or both) only studies reporting the same QoL tool/domain for each analysis. For example, for the SF-36, we will analyse each of the eight domains separately, rather than as a single metric. This means that if a study reports only one of the eight domains, it will only be included in the analysis of that respective domain.

Secondary outcomes

We will consider a range of secondary outcomes, including, but not limited to, the following.

- Pain-free walking distance established via treadmill walking tests
- Corridor walking tests (e.g. six-minute walk test)
- Ankle-brachial pressure index
- Measures of physical function (e.g. short physical performance battery)
- Daily physical activity (e.g. daily steps)
- Satisfaction, acceptability, compliance and ability to work

For satisfaction, acceptability, compliance and ability to work, it is anticipated that these outcomes will be sparsely reported and versatile. They will therefore be evaluated separately and presented descriptively, rather than being subject to formal statistical analyses. For all outcomes, these will be measured at the end of treatment (e.g. following the SEP), or as close to this time point as possible, rather than at a specific point in time (e.g. 12 weeks). This is because the maximum effect for each SEP is likely to be immediately upon completion.

Studies will not be excluded based on the reporting of certain outcomes. This means that studies not reporting any of the primary or secondary outcomes will still be included.

Search methods for identification of studies

Electronic searches

An experienced information specialist (CF) familiar with vascular vocabulary will design and run searches. They will develop comprehensive search strategies, designed to identify all RCTs that are relevant to the concepts of the study. Term sets will be developed for each concept employed by the search, using a combination of controlled vocabulary and free-text terms. We will search the biomedical databases of Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library), MEDLINE (via Ovid), Embase (via Ovid) and CINAHL (via EBSCO). We will search trial registers (ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/clinical-trials-registry-platform)), and the Web of Science Core Collection (via Clarivate). We will use validated filters for RCTs where available, and run searches without restrictions on date, language or publication status.

Searching other resources

We will consult existing Cochrane reviews for other potentially relevant studies that may have been missed (Hageman 2018; Jansen 2020; Lane 2017), and will handsearch the reference lists of included trials.

Data collection and analysis

Selection of studies

We will import titles and abstracts into Covidence, which will automatically deduplicate the results. Two review authors will independently screen these against the inclusion criteria for potential eligibility. We will obtain the full-text articles and two review authors will independently determine final inclusion. We will resolve disagreements at either stage by consensus, or via inclusion of a third review author. We will list any studies excluded at the full-text stage in the 'Characteristics of excluded studies' table. We will prepare a PRISMA flow chart to report the number of studies screened; the number of duplicates removed; the number of full texts reviewed; and the number of full texts included, excluded (with reasons), awaiting classification or ongoing. If any

full texts are not obtainable via conventional methods, we will contact the study authors to request the full text.

Where studies have multiple publications, we will collate the reports so that each study, rather than each report, is the unit of interest for the review, and such studies have a single identifier with multiple references.

Data extraction and management

We will develop a standardised data extraction form, which will be piloted on 10 studies and then refined by two review authors. This will ensure that all relevant information is captured on the form before it is applied. Two review authors will independently perform data extraction using this form. Where there are any discrepancies, we will return to the original source, extract the correct data and input them into the final form. Data extraction will include the following.

- Study characteristics (country, design, setting, dates and appropriate information to assess the risk of bias)
- Participant inclusion/exclusion criteria
- Sample size (total and per arm) and description (e.g. age)
- Description of the intervention and control conditions (with a focus on the FITT components, guided by the 12-item template for intervention description and replication (TIDieR) checklist) (Hoffmann 2014)
- Outcome measures and length of follow-up
- Main findings related to the outcome measures
- Funding sources and declarations of interest

We will enter the data into the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors will independently assess the methodological quality of each RCT using the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We will assess the effect of assignment to the intervention for each of the outcomes specified in the summary of findings table. As a maximum, we will assess risk of bias for the outcomes of MWD, QoL, pain-free walking distance, corridor walking tests and ankle-brachial pressure index. We will resolve any disagreements between review authors by consensus or by discussion with a third review author.

We will assess risk of bias using the Cochrane RoB 2 tool, which uses signalling questions to judge risk of bias as 'low risk', 'high risk' or 'some concerns' across five domains of randomisation, deviation from intended interventions, missing outcome data, outcome measurement and result reporting (Sterne 2019).

We will use the Excel tool to manage and record the assessments (www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2), which will be summarised, with justifications, for each outcome across all domains in the risk of bias table. We will use the least favourable assessment across all domains for the overall risk of bias for each trial, with the overall risk also used for GRADE assessments.

Measures of treatment effect

For primary outcomes, we will use the estimated mean difference (MD) and its standard error from each RCT for the CNMA. For RCTs with reported postintervention and baseline values, we will use the adjusted MD and its standard deviation (SD), while for RCTs with reported postintervention values only, we will use unadjusted MD and its SD. For RCTs reporting change from baseline, we will seek to convert it to a postintervention value (adjusted or unadjusted). Otherwise, we will use the reported change in MD instead. We will express dichotomous secondary outcomes as risk ratios (RR) with 95% confidence intervals (CI). We will express continuous secondary outcomes as MDs with 95% CIs. If the outcome is measured in different units across trials, we will express it as the standardised mean difference (SMD) with 95% CI.

Relative treatment ranking

We will use P scores to rank SEP combinations in a frequentist network meta-analysis (NMA) framework without resampling (Rücker 2015).

Unit of analysis issues

The unit of analysis will be the individual participant. When a trial reports multiple trial arms, we will include only those relevant (e.g. those outlined in the 'types of interventions' and 'comparators' sections under Selection of studies). However, we will list all treatment arms in the 'Characteristics of included studies' table, even if they are not used in the review. It is possible that individually randomised trials have not accounted for a clustering effect, despite it being likely that the same care provider delivered the intervention to multiple participants. However, we will not inflate the variance of the intervention effect as obtaining the required information (e.g. number of participants per care provider) is unlikely.

Dealing with missing data

With regards to the FITT principle, we anticipate that most studies will report these details sufficiently (e.g. exercise frequency is the number of exercise sessions per week). However, should this information not be available, we will contact study authors to request details giving specific deadlines to avoid affecting the review timeline. If this is not successful and the information is not available, for studies with unspecified SEP component(s), we will assign them with a reference category and fit the model. These results will then be compared to the results from completed cases as sensitivity checking. Additionally, we will contact study authors to request any missing outcome data (e.g. SD) or if data are presented in such a way that precludes entry into the analysis (e.g. percentage change from baseline). If median values are presented, we will use these to estimate the sample mean and SD following published recommendations (Cai 2021; McGrath 2020). This will be possible if the following are reported.

- Median
- Sample size
- Minimum and maximum values or
- First and third quartiles

Assessment of heterogeneity

Assessment of transitivity

We will assess the transitivity assumption, to identify the appropriateness of conducting a (C)NMA. The transitivity assumption assumes that within studies contributing to the direct comparisons, the distribution of effect modifiers (e.g. participant or study characteristics) is similar (Ahn 2021; Higgins 2022). If this is not the case, and effect modifiers differ between trials, the resultant indirect comparisons will be inappropriate. We will identify potential effect modifiers (age, disease severity, baseline MWD) and inspect their comparability across direct comparisons and components, to assess the transitivity assumption. We will summarise these effect modifiers grouped by comparison and component in tables presented as an appendix in the full review. We will also assess differences between trials in terms of recruitment criteria, as this may impact on treatment effects. We will include recruitment criteria in the 'Characteristics of included studies' table.

Assessment of statistical coherence

Transitivity can also manifest statistically, and this is referred to as coherence. Coherence suggests that the direct and indirect evidence is in agreement (Higgins 2022). For each NMA, we will examine statistical coherence with a global test using the between-designs Q statistic based on the full design-by-treatment interaction random-effects model (Higgins 2012). If there is evidence of global incoherence, we will evaluate local incoherence using the separating indirect from direct evidence approach (Schwarzer 2015).

Assessment of additivity

Additivity assumes that the effect of a treatment of multiple components is the sum of the effects of those components (Rücker 2020). This means that in comparisons, equal components will cancel out. With regards to SEPs, it is likely that the intervention effect will be a sum of each of the FITT principle components, as these are often used as the minimum to guide exercise prescription (ACSM 2020). If this was not the case, the use of each of these components would not be necessary or recommended.

Regardless, additivity will be tested using a statistical approach based on the Pythagorean theorem, via comparison of Q statistics. This tests whether the standard NMA model is superior to the CNMA model, thus testing the assumption of additivity. This test will be undertaken following completion of data extraction and cleaning.

Assessment of heterogeneity

For assessing heterogeneity/inconsistency in the NMA model, we will report the Q statistic. The Q statistic will be decomposed into heterogeneity (within designs) and inconsistency (between designs) (Rücker 2020). This will be used to assess consistency under the assumption of a full design-by-treatment interaction random-effects model (Higgins 2012).

Assessment of reporting biases

We will attempt to obtain study protocols and review trial registrations in order to assess selective outcome reporting. Additionally, we will search trial registries as part of our electronic search and identify studies that have results available on their respective trial registrations in the absence of a published paper. With the comparator defined in the 'Comparators' section (Types of interventions), for primary outcomes we will assess publication bias using comparison-adjusted funnel plots for NMA (Chaimani 2012).

Data synthesis

We will summarise studies including the direct comparisons made within individual RCTs and the population characteristics. SEPs will be grouped into common nodes based on having the same combination of components. We will draw a network diagram with the size of the nodes and the thickness of the edges set proportional to the number of participants and the number of trials in the comparison, respectively. For studies with missing information for any of the FITT components, despite attempts to obtain it, we will assign them a reference category for each missing component. For example, we will assign a reference category 'unknown frequency' to studies with missing information on SEP frequency. We will use both the NMA and CNMA for each of the primary outcomes (MWD and QoL), and any relevant secondary outcomes following the steps outlined below. We will start with a standard random-effects NMA (known as a full interaction model) as the first analysis model (Rücker 2020). In this model, each combination of components is treated as a distinct node in the network. Next, we will employ the additive CNMA model, whereby SEPs will be decomposed into their four components (frequency, intensity, time and type). In this additive CNMA model, we assume no interaction between components. With the reported Q statistics for the NMA and additive CNMA models, the additivity assumption will be tested via the likelihood ratio statistics. At the final stage, we will run the interaction CNMA, which allows interaction terms between components to accommodate their combination effects. Currently, we are unable to prespecify interaction terms. This is because the evidence suggests that SEPs, regardless of their FITT combination, are effective for improving MWD, with little evidence to suggest which is the best combination, hence the aim of this study. One study, published in 1995, used simple meta-analysis techniques to identify the most effective SEP components (Gardner 1995). The study found that the components of intermittent walking (type) to near-maximal pain (intensity) for six months (time) were the most effective. However, this was based on each component being an independent predictor for improving MWD, rather than on their interaction effects.

Overall, this means we have limited prior knowledge to inform interaction terms as we are unable to suggest that certain combinations are more effective than others. Therefore, we will identify potential interaction terms after exploring the structure of the NMA and additive CNMA, meaning we will consider the interaction CNMA a 'post-hoc' analysis.

We will compare the reported Q statistics for the NMA model and the interaction CNMA model via the likelihood ratio statistics.

If the assumption of additivity is violated, or available studies are too sparse to support the NMA/CNMA models, we will synthesise the data for each of the four individual FITT components via individual NMAs, in order to evaluate the locally optimal prescription for each component. Taking the frequency component as example: we will first group studies by frequency (e.g. once, twice or three times per week) and undertake a standard NMA for this component. This analysis will give evidence for the optimal SEP

frequency. We will repeat this analysis process for the intensity, time and type components.

If data are still too sparse to allow this, we will narrow the groupings further (e.g. low frequency (once per week), moderate frequency (twice/three times per week) and high frequency (more than three times per week)) before performing standard NMAs.

If a further fall-back is required (e.g. standard NMAs by component are not possible), we will discuss this within the review team and take the most appropriate course of action to maximise the results available from the studies.

The standard NMA and additive and interaction CNMA models, in a frequentist framework, will be implemented with the R package netmeta in R language (using the most recent version at the time of final data analysis) (R).

Cost-effectiveness considerations

The study will include an additional cost-effectiveness analysis from a National Health Service (NHS) and personal social services perspective, in accordance with NICE guidance (NICE 2022). The results of the CNMA will identify the optimal SEP prescription from a clinical outcome perspective. The cost-effectiveness analysis will complement this by identifying which SEP prescription is cost-effective out of the full set of SEP prescriptions for which there is clinical effectiveness based on the results of the CNMA.

Costs and health outcomes (expressed as quality-adjusted life years (QALY)) over a lifetime horizon and discounted at an annual 3.5% rate will be compared between alternative SEPs and comparator groups for the first-line treatment of people with IC. We will include costs relevant to the NHS and personal social services perspective in the analysis. Resource use will be sourced from the literature and unit costs informed by published national sources, such as NHS reference costs and the Personal Social Services Research Unit costs manual (Jones 2022).

We will develop a de novo model to link the measures of clinical effectiveness of SEPs, collected as outcomes of the CNMA, to short- and long-term healthcare cost and patients' health outcomes. A previous Markov model informed NICE recommendations to manage IC with a SEP as first-line treatment (Bermingham 2013; NICE 2012). This model considered the direct impact of exercise on health-related quality of life, as well as indirect impacts on cardiovascular and mortality outcomes of remaining physically active over time (adherence to exercise). We will assess the appropriateness of extending this previous model to 1. allow evaluating alternative SEP prescriptions, and 2. capture the impact of potential avoidance/deferral to subsequent lines of treatment (e.g. angioplasty). We will also examine other model-based cost-effectiveness analyses of SEPs for alternative structural assumptions and evidence sources (e.g. van den Houten 2016). The newly developed model will consider relevant and contemporary evidence, particularly that which may have emerged since the publication of NICE guidance (NICE 2012; which was last updated in December 2020). To identify this evidence, and inform the model, we will conduct targeted literature reviews, and seek clinical, patient and public expert advice. For example, we anticipate being able to incorporate evidence from the OPTIMA (systematic review and integrated report on the quantitative and qualitative evidence base for behaviOur change interventions to promote Physical acTivity in people with InterMittent clAudication) study on short- and long-term adherence to exercise in the model (NIHR130664). Clinical opinion will also be sought to validate the model, and potentially inform model parameters where evidence is scarce.

We will express the cost-effectiveness of alternative exercise prescriptions as incremental cost-effectiveness ratio and net monetary benefit at the range of cost-effectiveness thresholds considered by NICE (GBP 20,000 to GBP 30,000 per additional QALY) (NICE 2022). We will undertake deterministic and probabilistic sensitivity analyses (PSA) to explore uncertainty and determine the drivers of cost-effectiveness. We will consider correlation between the CNMA outcomes in the PSA. We will formally model sources of heterogeneity (guided by the subgroup and sensitivity analyses), where evidence allows, with the impact on cost-effectiveness estimates quantified (e.g. via subgroup analysis by age categories). We will conduct value of information analysis to quantify the potential impacts of decision uncertainty and prioritise further areas of research.

Subgroup analysis and investigation of heterogeneity

We plan to undertake subgroup analyses to investigate the optimal SEP for different age groups as this is a potential source of heterogeneity. Subject to data availability, we will split the data by age group (e.g. 18 to 55 years and above 55 years) and utilise the CNMA to find the optimal SEP for these groups. We will perform subgroup analyses in an attempt to assess the impact of adherence/compliance (such as completed 80% or greater versus less than 80% of sessions) on clinical outcomes.

Additionally, if appropriate, we will perform subgroup analyses to identify whether grouping the three comparators as a single comparator group impacts on clinical effectiveness. For this, we may rerun the analyses with each group as a distinct comparator.

Sensitivity analysis

We will perform sensitivity analyses based on the certainty of the evidence and factors that influence it. For example, we may rerun the analysis after removing RCTs with a high risk of bias or with wide CIs for the intervention effect, because both factors will influence GRADE. This will allow us to identify if the overall evidence base provides similar or differing findings compared to the higher quality evidence base, informing our recommendations and conclusions.

Summary of findings and assessment of the certainty of the evidence

We will present results using tables and forest plots where appropriate, with effect estimates displayed for both the NMA and CNMA models.

We will compare each possible SEP combination to controls, based on the FITT principle. This means that there will be a number of comparisons made for each outcome. As such, it is likely that tables and forest plots will only be produced for the primary outcomes (i.e. MWD and QoL). However, for secondary outcomes, we will produce tables and forest plots for pain-free walking distance, corridor walking tests and ankle-brachial pressure index, if appropriate. We will not produce tables and forest plots for any other secondary outcomes.

We will assess the certainty of the evidence for each outcome using the GRADE approach, following the initial guidelines published in

2014 (Puhan 2014), as well as the advances document published in 2018 (Brignardello-Petersen 2018). However, this is only applicable to NMA and no system for grading the certainty of the evidence within CNMA has been developed. Therefore, we will apply the GRADE approach only to NMA models, though should a system for CNMA become available in the interim, we will adopt this.

The GRADE approach allows review authors to highlight the degree of confidence or certainty they have in the estimated treatment effects. The degree of confidence can be high (we are very confident that the true effect lies close to that of the estimate of the effect), moderate (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 (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect) or very low (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect).

This approach follows four steps.

- Step 1: presentation of the direct and indirect effect estimates that contribute to the NMA along with their 95% CIs.
- Step 2: rating of the quality of these direct and indirect estimates, performed separately based on the included trials. For this:
  - if RCTs make up the evidence for the effect estimates, the rating starts as high, and is downgraded one level if there is serious concern or two levels if there is very serious concern based on the following:
    - risk of bias (e.g. failure to conceal allocation or failure to blind);
    - inconsistency (heterogeneity of estimates of effects across trials);
    - indirectness (use of surrogate outcomes, study populations or interventions that differ from those of interest). In the case of indirect comparisons, intransitivity is the term used to describe differences in the study characteristics that may modify the treatment effect in the direct comparisons that contribute to the indirect comparison, thus biasing the indirect assessments. If differences are considered large enough to introduce intransitivity, indirect comparisons will be invalidated and not undertaken;
    - suspicion of publication bias.
  - note: imprecision is no longer considered in the GRADE estimate for the direct and indirect comparisons. In addition, GRADE should first be applied to direct evidence. If the certainty of this evidence is high and it contributes as least as much to the network estimate as the indirect evidence, there is no need to rate the indirect evidence and the review authors can move to steps 3 and 4.
- Step 3: the effect estimate of the NMA is presented with 95% CIs
- Step 4: the quality of the NMA estimate is rated. For this:
  - if only direct or indirect evidence is available for a comparison, the certainty rating for this evidence will be used as the starting point for the network;
  - if both direct and indirect evidence contributes to the network estimate:
    - the higher of the two certainty ratings should be used as the starting point for the network *or*
    - identify whether the direct or indirect evidence is making the dominant contribution to the network estimate and use the quality rating for this evidence as the starting point for the network;
  - once the starting point for the NMA has been established, the certainty of the evidence may be downgraded based on:
    - incoherence (addresses the similarity of the direct and indirect estimates based on their point estimates, CIs and the statistical test of interaction);
    - imprecision (95% CIs that are wide and include or are close to a null effect or range from serious benefit to serious harm).

Conduct of the review

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

If a review author is also a contributor to a study that may be of interest to the review, that review author will not be involved in the selection process, data extraction and management process, assessment of risk of bias and assessment of the certainty of the evidence process.

ACKNOWLEDGEMENTS

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Toby Lasserson, Central Editorial Unit.
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Anupa Shah, Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Lisa Wydrzynski, Central Editorial Service.
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service.
- Peer-reviewers (provided comments and recommended an editorial decision): Jo Platt, Cochrane Central Editorial Information Specialist (search review); Sofia Tsokani, Cochrane Central Editorial Team (methods review); Dr Zahid Khan, Bart's Hospital NHS Foundation Trust (clinical/content review); Neal R Barshes, MD, MPH; Associate Professor of Surgery, Baylor College of Medicine (Houston, Texas, USA) (clinical/content review); Wagner Silva-Ribeiro, Care Policy and Evaluation Centre, London School of Economics and Political Science (cost-effectiveness review).

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APPENDICES

Appendix 1. MEDLINE draft search

1 Arterial Occlusive Diseases/

2 Arteriolosclerosis/

3 Arteriosclerosis/

4 Arteriosclerosis Obliterans/

5 Femoral Artery/

6 Iliac Artery/

7 Intermittent Claudication/

8 Ischemia/dt, et, mo, su, th [Drug Therapy, Etiology, Mortality, Surgery, Therapy]

9 Leg/bs [Blood Supply]

10 exp Peripheral Vascular Diseases/

11 Popliteal Artery/

12 Tibial Arteries/

13 arteriosclero*.ti,ab.

14 arteriopathic.ti,ab.

15 claudic*.ti,ab.

16 CLI.ti,ab.

17 dysvascular*.ti,ab.

18 PVD.ti,ab.

19 PAOD.ti,ab.

20 (peripheral adj3 dis*).ti,ab.

21 (("lower extrem*" or arter* or crural or femdist* or femoral or fempop* or iliac or infrainquinal or infrapopliteal or inguinal or "lower limb" or peripher* or popliteal or tibial or vascular or vein* or veno*) adj (block* or harden* or lesio* or obliter* or obstruct* or occlus* or reocclus* or re-occlus* or restenos* or steno* or stiffen*)).ti,ab.

22 or/1-21

23 exp Exercise/

24 exp Exercise Therapy/

25 exp Walking/

26 exp Physical Exertion/

27 Exercis*.ti,ab.

28 physical activit*.ti,ab.

29 treadmill.ti,ab.

30 walk*.ti,ab.

31 (Cycl* adj4 train*).ti,ab.

32 (Lower limb adj4 cycl*).ti,ab.

33 (upper limb adj4 cycl*).ti,ab.

34 "Circuit based exercise".ti,ab.

35 (Circuit adj4 exercise).ti,ab.

36 SEP.ti,ab.

37 or/23-36

38 22 and 37

39 randomized controlled trial.pt.

40 controlled clinical trial.pt.

41 randomized.ab.

42 placebo.ab.

43 drug therapy.fs.

44 randomly.ab.

45 trial.ab.

46 groups.ab.

47 or/39-46

48 exp animals/ not humans.sh.

49 47 not 48

50 38 and 49

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DECLARATIONS OF INTEREST

SP: none.

AH: none.

JP: none.

BR: none.

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RS: none.

JH: none.

HG: none.

SP: none.

JR: none.

AD: none.

IC: none.

SOURCES OF SUPPORT

Internal sources

- None, Other

  No internal sources of support.

External sources

- National Institute for Health Research, Health Technology Assessment Programme (NIHR152587), UK

  This review is funded by the NIHR HTA programme.