Identifying the most clinically- and cost-effective exercise prescription for patients with intermittent claudication (MAXIMISE): a component network meta-analysis to answer a James Lind Alliance priority research question.

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Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	5.0	18.01.2023	Sean Pymer	No changes made.

Glossary

IC	Intermittent claudication
QoL	Quality of life
SEP	Supervised exercise programme
RCT	Randomised controlled trial
NICE	National institute of health and care excellence
PAD	Peripheral arterial disease
MWD	Maximum walking distance
FITT principle	Frequency, intensity, time and type of exercise
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
TIDieR	Template for intervention description and replication
GRADE	Grading of recommendations assessment, development and evaluations
CNMA	Component network meta-analysis

Detailed research plan

Full title of project

Identifying the most clinically- and cost-effective exercise prescription for patients with intermittent claudication (MAXIMISE): a component network meta-analysis to answer a James Lind Alliance priority research question.

Summary of Research (abstract)

Research question: What is the most clinically and cost-effective exercise prescription for patients with intermittent claudication?

Background: Intermittent claudication (IC) is an ischaemic, ambulatory, lower-limb muscle pain, relieved by rest. It leads to reductions in walking ability and quality of life (QoL), imposing significant burden on patients and healthcare systems. Supervised exercise programmes (SEP) are recommended as the first-line treatment for IC as they are efficacious for improving walking distance and QoL. However, there are numerous SEP prescriptions and current guidance does not define the optimal one (i.e., most clinically and cost-effective), as the clinical and economic evidence on different SEP prescriptions is limited. This leads to suboptimal provision and outcomes for patients.

Further evidence is needed to identify the optimal SEP prescription for patients with IC, leading to the development of comprehensive guidelines.

Aim: To identify the most clinically and cost-effective SEP prescription for improving walking distance and QoL in patients with IC.

Objective: To conduct a component network meta-analysis comparing all possible SEP combinations to identify the most clinically and cost-effective exercise prescription for patients with IC.

Methods: We will perform a component network meta-analysis including all randomised controlled trials (RCT) that compare a SEP with a control group for the treatment of IC. RCTs will be grouped based on certain common prescription components (e.g. the number of sessions performed each week). Different combinations of these components will then be compared to identify which is most effective.
We anticipate that prescription combinations will include at least:

1. Frequency (e.g. once per week vs. twice per week vs. three times per week)
2. Intensity (e.g. pain-free vs. moderate pain vs. maximal pain exercise or low-intensity exercise vs. moderate-intensity exercise vs. high-intensity exercise)
3. Time (e.g. 30 minutes vs. 45 minutes vs. 60 minutes)
4. Type (e.g. walking vs. lower-limb cycling vs. upper-limb cycling vs. circuit-based exercise).

The primary outcomes are maximum walking distance, measured via standardised treadmill tests, and QoL.

We will then develop an economic model to evaluate the cost-effectiveness of different combinations of exercise prescription for patients with IC. The model will link measures of clinical effectiveness of SEPs, collected as outcomes of the network meta-analysis, to short and long-term healthcare costs and patients' health outcomes.

Timelines for delivery: Study duration: 22 months:

- Months 1-2 – Protocol development and registration
- Months 2-11 – Data collection (screening and data extraction)
- Months 11-18 – Data analysis
- Months 18-22 – Dissemination (planning and outputs)

Anticipated impact and dissemination: Study results will lead to the development of comprehensive SEP guidelines, which should also stimulate updates to National Institute for Health and Care Excellence [NICE] (and other relevant international) guidelines. This will result in changes to clinical practice both in the NHS and internationally.

Results will be published via Cochrane and shared with key supporting stakeholders at a dissemination event, which should maximise impact. Key stakeholders include patients, the Vascular Society for Great Britain and Ireland, Cochrane, the Vascular Clinical Reference Group and the Circulation Foundation.

Background and Rationale

Background

Peripheral arterial disease (PAD) is an atherosclerotic disease in which the arteries to the lower limbs become narrowed or occluded, reducing blood supply (1). PAD is a common and age dependant disease, estimated to effect 237 million people worldwide (2). In the UK, it can be estimated that 7.4% of the population aged over 25 (3.5 million people) suffer with PAD (2). This rises to approximately 20% for the population aged over 60 (3). Clearly, as such a high proportion of the population is living with PAD, the associated healthcare burden is significant, especially when patients with PAD report greater healthcare resource use than patients without PAD (4).

In addition, due to population ageing, compounded by an expected increase in the prevalence of diabetes (5), the number of people living with PAD, and the consequential healthcare burden, is set to increase.

The classic symptom of PAD is intermittent claudication (IC), a reproducible ischaemic leg muscle pain that is precipitated by exertion, usually walking, and relieved by rest (6). The impact of IC on patients is profound, causing reductions in walking ability, functional capacity, balance and quality of life (QoL) (6, 7, 8, 9). PAD is associated with a markedly increased mortality risk, which can be up to 15 times higher than for those without PAD and is predominantly due to coexisting atherosclerotic cardiovascular complications (10, 11). Cardiovascular risk reduction is vital for all patients with PAD, including smoking cessation, diet, exercise and appropriate pharmacotherapy (3, 12). For symptomatic benefit, supervised exercise programmes (SEP) have irrefutable, high-quality evidence demonstrating that they are efficacious for improving maximum walking distance (MWD) (13). SEPs are therefore recommended as the first-line treatment for all patients with IC in both national (national institute for health and care excellence [NICE; CG147] (3), and international guidelines (the European Society of Cardiology and the American Heart Association) (12, 14).

However, the reported exercise prescription component of SEPs is widely variable leading to significant deficit and limitation of guideline detail regarding the frequency, intensity, time and type [FITT principle] of exercise. For example, NICE guidelines simply 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’ (3). 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’ (12). The American guidelines provide a little more detail, stating that exercise should be performed for 30-45 minutes per session, three times per week for 12 weeks, involving interval walking performed to moderate-to-maximal claudication pain (14).

These guidelines have recently been complemented by a detailed document developed by members of the current research team, which outline the mode of delivery, the setting, the materials and the FITT exercise prescription required to implement a SEP for patients with IC (15). A similar document has also been produced by Exercise and Sports Science Australia (16). However, both the guidelines and these complementary documents base their FITT exercise prescription components on individual randomised controlled trials (RCT), summaries of evidence and meta-analyses that do not necessarily make direct comparisons between the different components. This means that these documents base their recommendations on the best available evidence, rather than the best possible evidence.

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 and cost-effective. This will allow for the identification and creation of the optimal SEP prescription. It will then lead to the development of best evidence guidelines, and will inform updates of existing guideline documents, including NICE CG147 (3). Consequently, this will alter current clinical practice both in the NHS and internationally.

Review of existing evidence
In order to inform this application, the citations from existing guidelines were reviewed and a scoping literature review was undertaken to identify what is already known as well as any possible overlap. We searched the MEDLINE, CINAHL and Cochrane CENTRAL databases using terms such as 'intermittent claudication' AND 'exercise prescription'. We did not find any network meta-analyses that identify the optimal exercise prescription for patients with IC. However, we did identify some publications that may appear to overlap the proposed project. First, three reviews published in 1995, 2004 and 2014 stated similar aims of identifying the most effective components of exercise rehabilitation programmes for patients with IC. However, they all suffered serious limitations in that they included both randomised and non-randomised trials, a mixture of home-based and supervised exercise programmes, used inappropriate outcome measures or grouped different iterations for each exercise component together, when they should be separated. Furthermore, the statistical analyses applied within these studies are not reflective of modern methods (17, 18, 19).

Other reviews only considered individual components of the exercise prescription e.g., exercise intensity (20, 21, 22). They also did not include all possible iterations and combinations of these components.

Overall, in light of the existing evidence, there remains an urgent need to identify the most clinically and cost-effective exercise prescription combination for patients with IC via a comprehensive component network meta-analysis (CNMA) with full economic evaluation.

Evidence explaining why this research is needed now
This research was recently highlighted by the James Lind Alliance priority setting partnership for PAD involving clinicians and patients as being of the upmost, immediate importance (23).

SEPs are irrefutably efficacious for providing a benefit to patients with IC, with increasing evidence demonstrating that they are equivalent to more invasive treatments (24). However, the lack of an optimal exercise prescription and comprehensive guidelines limits the delivery of SEPs in the UK, leading to suboptimal provision (25). The limited guidance currently available precludes implementation for centres without a SEP, as it is impossible to identify the best way to prescribe it. It is also difficult for these centres to build an effective business case for SEP delivery, given the limited information on the resources and facilities required. Finally, where SEP is available, we have demonstrated significant variability in its delivery (25), again likely due to the limited guidance available. This results in a suboptimal prescription, which fails to maximise the benefits available to patients. Indeed, a lack of improvement in symptoms is cited as a key reason for SEP discontinuation (26).

This limited effectiveness, via suboptimal provision and delivery, has economic consequences for healthcare providers as patients either do not receive their first-line treatment or receive a suboptimal version of it. This leads to resource waste and increased costs for further follow-up and more invasive intervention.

Clearly, this research is needed now to identify the optimal exercise prescription for patients with IC, to inform the development of comprehensive guidelines. In turn, these guidelines will increase the number of available SEP centres, whilst maximising the individual patient

benefit, leading to greater access, effectiveness and CE of first-line treatment for these patients.

Aim and objective

Aim:
To identify the most clinically and cost-effective SEP prescription for patients with IC.

Objective:
To conduct a network meta-analysis and economic evaluation comparing different SEP combinations to identify the most clinically and cost-effective exercise prescription for patients with IC.

Research plan / methods

Design
The study design is a CNMA which will be performed with guidance from the Cochrane handbook and other relevant sources (27, 28). The analysis will include all RCTs including patients with IC that compare a SEP to a control group. Control groups will receive best medical therapy ± exercise advice as exercise advice is often given as part of routine care. Should insufficient data be available for analysis, we will also include studies that compare a SEP to a home-based exercise programme.
We will combine RCTs based on their common components of the FITT principle (i.e. number of exercise sessions per week). We will then compare each combination of these components to identify which is most effective.

Target population:
The target population will be patients with IC.

Health technologies being assessed
The health technology under assessment is a SEP. The term 'SEP' is widely used in the literature. It is used to describe any exercise programme that is performed under supervision for the treatment of IC and programmes are prescribed based on the FITT principle.
SEPs are well established in the management of IC and are recommended as the first line treatment nationally and internationally (3, 12).
However, the guidance for SEP implementation is limited. This contributes to a lack of availability across the UK as well as distinct variation in the delivery of programmes (25). Further assessment of SEPs is required to understand the best way to prescribe this health technology to support the development of comprehensive guidelines. These guidelines will increase the accessibility of SEPs and allow for universal implementation, maximising patient benefit.

Search strategy
Searches will be designed and run by an experienced information specialist familiar with Vascular vocabulary. They will develop comprehensive search strategies, designed to identify all RCTs that are relevant to the concepts of the network meta-analysis. 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 Embase, Medline, CINAHL as well as Cochrane CENTRAL. Trial registers ClinicalTrials.gov and ICTRP will be searched as well as Web of Science Core Collection. Validated filters for randomised controlled trails will be employed where available, and searches will be run without restrictions on date or language.

Review strategy
We plan to include all RCTs that meet the inclusion criteria outlined below. Titles and abstracts will be imported into the Covidence systematic review management software, which will automatically de-duplicate the results. Two members of the research team will independently screen these against the inclusion criteria for potential eligibility. Full texts of any studies that are deemed eligible by both researchers at this screening stage will then be independently reviewed to determine final inclusion. Any disagreements between researchers at either stage will be resolved by consensus, or via inclusion of a third researcher. A Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow chart will be used to present the number of studies screened, the number of duplicates removed, the number of full texts reviewed, the number of full texts excluded (with reasons), and the number of studies included. If any full texts are not obtainable via conventional methods, the authors will be approached to request the full text.

Inclusion / exclusion criteria
Patients – All RCTs of patients aged ≥18 years with a diagnosis of IC will be included. We will not apply haemodynamic or imaging criteria for inclusion as this may not be reported in individual studies. A statement made by the authors noting that patients were required to have IC to be included will be sufficient.

Interventions – All SEPs will be included, as long as they are actively supervised, regardless of the duration, frequency and/or intensity. RCTs will be grouped based on certain common components. This will allow for comparison between different combinations, to identify which is most effective. We anticipate that combinations will include at least:

1. Frequency of exercise (e.g. once, twice or three times per week)
2. Intensity of exercise (e.g. pain-free, moderate pain or maximal pain / low-intensity, moderate-intensity or high-intensity exercise)
3. Duration (time) of exercise (e.g. 30 minutes, 45 minutes or 60 minutes)
4. Type of exercise (e.g. walking, lower-limb cycling, upper-limb cycling or circuit-based exercise).

As grouping will be based on such components, at least one of these must be reported by individual studies to be considered for inclusion.

Comparators –

We have previously defined non-exercise controls, exercise advice and home-based exercise programmes (29). These definitions are as follows:

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

The comparator groups will therefore consist of the following defined groups:

1. Treatment as usual (which will consist of patients who receive exercise advice or are non-exercise controls, as defined above)
2. Home-based exercise programmes

These two groups will be distinct in the network and not combined.

When trials compare two (or more) different types of SEP (e.g., pain-free walking vs maximal pain walking), these will be included, as long as a relevant comparator group (as defined above) is also included.

Outcomes – Studies will not be excluded based on the reporting of certain outcomes. However, the primary outcomes will be MWD, established via treadmill walking tests, and QoL established via validated questionnaires A search of the COMET database reveals that there is no published core outcome set for patients with IC to inform this decision. However, we have selected MWD as one of our primary outcomes as it is almost always reported within RCT's of exercise interventions for patients with IC. It is also the primary outcome in a number of Cochrane reviews and is considered important by vascular clinicians (13, 30). Perhaps most importantly, MWD was identified as the most important outcome by our patient and public involvement group during the focus group meeting held to inform this application. This group also stated that QoL goes hand in hand with MWD, which is why this has also been added as an additional primary outcome. A routine functional measure, such as daily physical activity, has not been selected as a primary outcome as a previous review conducted by our group identified that this is a seldom and heterogeneously reported outcome (31).

All secondary outcomes will be considered but will include at least:

- Pain-free walking distance
- Corridor walking tests (e.g., six-minute walk test)
- Ankle-brachial pressure index
- Measures of physical function (e.g., short physical performance battery and timed up-and-go)
- Daily physical activity
- Satisfaction, acceptability, compliance and ability to work
- Cost effectiveness

Setting
There will be no exclusions based on the setting in which a SEP is delivered, as long as it is supervised. Settings will include primary and secondary care and community centres.

Data collection / extraction
A standardised data extraction form will be developed with the whole research team at a management group meeting. This will then be piloted and refined by two members of the research team. This will ensure that all relevant information is captured by the form before it is applied. Data extraction will be independently performed by two review authors using this form. Where any discrepancies are identified, the original source will be reviewed, and the correct data will be extracted and inputted into the final form. Data extraction will include study characteristics (country, design and appropriate information to assess the quality of the study), sample size and description, a description of the intervention and control conditions, outcome measures, length of follow-up and main findings related to outcome measures. Intervention details to be extracted will be guided by the 12-item template for intervention description and replication (TIDieR) checklist (32). TIDieR is a checklist that should be used by authors to ensure their intervention is reported sufficiently to allow replication. It involves complete reporting of the intervention based on the why (rationale), what (materials and procedures), who and how (delivery), where (location), when and how much (dose), tailoring and modification (personalisation) and fidelity (delivery as intended). By evaluating studies based on this checklist, we will ensure complete extraction of the intervention details. Application of this checklist will also allow us to evaluate and comment upon the completeness of intervention reporting for each RCT.

Plans for missing data

With regards to the FITT principle, we anticipate that most studies will report these details sufficiently (for example, exercise frequency is simply the number of exercise sessions per week). However, should this information not be available, authors will be contacted for the details with specific deadlines given to avoid affecting the study 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.

Risk of bias assessment
The Cochrane risk of bias tool will be used to assess the methodological quality of each included RCT (28). Assessment will be made using the risk of bias tool version 2 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'. Assessment will be made by two independent reviewers and any disagreements will be resolved via consensus or discussion with a third reviewer.

Rating the quality of evidence
The quality of evidence for each outcome will be assessed using the grading of recommendations assessment, development and evaluations (GRADE) approach, following the initial guidelines published in 2014 (33), as well as the advances document published in 2018 (34). 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:

1. Presentation of the direct and indirect effect estimates that contribute to the network meta-analysis along with their 95% confidence intervals
2. Rating of the quality of these direct and indirect estimates, performed separately based on the included trials. For this:
    a. if randomised trials make up the evidence for the effect estimates, the rating starts as high, and is rated down by -1 if there is serious concern or by -2 if there is very serious concern based on the following:
        i. Risk of bias (e.g., failure to conceal allocation or failure to blind)
        ii. Inconsistency (heterogeneity of estimates of effects across trials)
        iii. Indirectness (use of surrogate outcomes, study populations or interventions that differ from those interest). In the case of indirect comparisons, intransitivity is the term used that describes 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.
        iv. Suspicion of publication bias.

   b. N.B. imprecision is no longer considered in the GRADE estimate for the direct and indirect comparisons (34). In addition, the rating should begin with the 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 reviewer can move to steps 3 and 4.
3. The effect estimate of the network meta-analysis is presented with 95% confidence intervals
4. The quality of the network meta-analysis estimate is rated. For this:
   a. If only direct or indirect evidence is available for a comparison, the quality rating for this evidence will be used as the starting point for the network.
   b. If both direct and indirect evidence contributes to the network estimate:
      i. The higher of the two quality ratings should be used as the starting point for the network OR
      ii. 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.
   c. Once the starting point for the network meta-analysis has been established, the quality of the evidence may be rated down based on:
      i. Incoherence (addresses the similarity of the direct and indirect estimates based on their point estimates, confidence intervals and the statistical test of interaction).
      ii. Imprecision (95% confidence intervals that are wide and include or are close to a null effect or range from serious benefit to serious harm).

Data analysis

Included studies will be summarised including the direct comparisons made and population characteristics. SEPs will be firstly grouped into common nodes. We will draw a network diagram with the size of the nodes based on the number of participants assigned to the intervention and the thickness of the lines based on the number of randomised trials contributing to that respective direct comparison.

Previous work in this area suggests that a complex network meta-analysis framework will be required to explore the variability in frequency, intensity, time and type of SEPs. Also differences in recruitment criteria between the RCTs may threaten the transitivity assumption. We will assess whether such differences are sufficiently large to induce intransitivity, prior to undertaking indirect comparisons. Analysis of primary outcomes (MWD and QoL) will be undertaken using the additive and interaction CNMA, which allows interaction terms between components to accommodate their combination effects (27). The additive and interaction CNMA model, in a frequentist framework, will be implemented with the R package netmeta in R language version 4.1 (35). For assessing the heterogeneity/inconsistency in the CNMA model, the between-designs Q statistic will be reported. Heterogeneity will be evaluated to identify whether it is caused by clear differences in the SEPs or by other methodological differences. This will then determine the appropriateness of certain analyses.

For primary outcomes, we will use the estimated mean difference and its standard error from each study for the CNMA. For studies with reported post-intervention and baseline MWD, we will use adjusted mean difference and its SD, while for studies with reported post-intervention MWD only, we will use unadjusted mean difference and its SD. For studies reporting change in MWD from baseline, we will seek to convert it to post-intervention MWD

(adjusted or unadjusted). Otherwise, we will use the reported change in mean difference instead.

A league table of the relative effects between SEP combinations, with associated uncertainty, will be reported. If the assumption of additivity is violated, or available studies are too sparse to support a CNMA, we will first group studies by their common elements (such as frequency, intensity, time and type) and undertake respective, standard network meta-analyses. This will give evidence on marginal optimal SEPs (such as optimal frequency etc.). If a further fall-back is required (e.g. standard network meta-analyses are not possible), this will be discussed within the team and the most appropriate course of action will be taken to maximise the results available from the study.

We will collect and report the correlation between MWD and QoL from available studies, which will be used for cost-effective analyses.

Subgroup / sensitivity analyses and sources 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 (such as 18-55 and above 55) and utilise the CNMA to find the optimal SEP for these groups. Subgroup analyses will also be performed in an attempt to assess the impact of adherence/compliance (such as completed ≥80% vs. <80% of sessions) on clinical outcomes.

We will identify other potential sources of heterogeneity during the data extraction phase and use these to inform further subgroup analyses where appropriate to quantify their impact on clinical effectiveness.

Further sensitivity analyses will be performed based on the quality of evidence and factors that influence it. For example, we may re-run the analysis after removing RCTs with a high risk of bias or with wide confidence intervals for the intervention effect, because both factors will influence the GRADEing. 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.

Presentation of results and summary of findings tables
Results will be presented using tables and forest plots where appropriate, with effect estimates displayed for both the additive and interaction CNMA models.
Each possible SEP combination will be compared to controls, based on the FITT principle. This means that there will be a number of comparisons made within the analysis. As such, it is likely that tables and forest plots will only be produced for the primary outcomes. However, when it is deemed appropriate, secondary outcomes will also be presented in this way.

Measurement of costs and outcomes
The study will include a CE analysis from an NHS and personal social services perspective, in accordance with NICE guidance (36). Costs and health outcomes (expressed as quality-adjusted life years) 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 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 (3, 37). This model considered the direct impact of exercise on health-related QoL, 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 i) allow evaluating alternative SEP prescriptions, and ii) capture the impact of potential avoidance/deferral to subsequent lines of treatment (e.g., angioplasty). We will also examine other model-based CE analyses of SEPs (e.g., van den Houten et al., 2016) for alternative structural assumptions and evidence sources (38). The newly developed model will consider relevant and contemporary evidence, particularly that which may have emerged since the publication of NICE guidance (3). 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 study on short and long-term adherence to exercise in the model. Clinical opinion will also be sought to validate the model, and potentially inform model parameters where evidence is scarce.

The CE of alternative exercise prescriptions will be expressed as incremental cost-effectiveness ratio and net monetary benefit at the range of cost-effectiveness thresholds considered by NICE (36). Deterministic and probabilistic sensitivity analyses (PSA) will be undertaken to explore uncertainty and determine the drivers of CE. Correlation between the CNMA outcomes will be considered in the PSA. Sources of heterogeneity (guided by the subgroup and sensitivity analyses) will be formally modelled, where evidence allows, with the impact on cost-effectiveness estimates quantified (e.g., via subgroup analysis by age categories). Value of information analysis will be conducted to quantify the potential impacts of decision uncertainty and prioritise further areas of research.

Dissemination, outputs and anticipated impact

Dissemination will be considered throughout the project and will be an agenda item at each team meeting. To maximise impact and ensure that dissemination is timely, we have included a number of key stakeholders as collaborators and co-applicants in the application. These stakeholders will also attend the management group meetings (where necessary) and represent patients, clinicians from both primary and secondary care, professional bodies and charitable organisations.

To broker partnerships, enhance knowledge exchange and mobilise evidence into practice, we have included the chair of the Vascular Clinical Reference Group as a co-applicant, who is involved in the commissioning of clinical services.

Our dissemination plan will include at least the following:

Dissemination event

We will invite all key stakeholders to a single-day event which will involve discussions about the optimal exercise prescription and how this compares to current practice in the UK. This will allow us to identify the support needed to implement this prescription within existing SEPs and the support needed to create new SEP centres. Key stakeholders will include (at least) patients, consultant vascular surgeons, trainee vascular surgeons, general practitioners and exercise professionals as well as organisations such as the Vascular Clinical Reference Group, The Vascular Society of Great Britain and Ireland, Cochrane and the vascular charity, The Circulation Foundation.

It is expected that the Vascular Clinical Reference Group chair (and co-applicant) can extend this by communicating our findings to clinical commissioning groups.

Infographic

We will produce an infographic to aid quick and easy to interpret dissemination. It will highlight the importance of SEPs and outline the optimal exercise prescription. If the management group deem it necessary, separate infographics will be produced for patients/members of the public and healthcare professionals. Members of our research team

have previously produced an infographic that has achieved international coverage in countries such as India, South Africa, Japan, Brazil, Argentina, the USA, Canada and most of Europe. It has also been mentioned by seven news outlets and the majority of Twitter interactions have come from members of the public (73%) suggesting that patients engage with this dissemination method.

Presentations and Publications
We will produce a full report for the NIHR.

We will submit an abstract for oral presentation at relevant (inter)national conferences and have included conference costs for this purpose. We will publish our protocol and full report via the Cochrane open-access pathway, meaning both will be freely available to access immediately. In addition, by publishing via Cochrane, the review will be automatically registered on PROSPERO.

We intend to develop and publish comprehensive SEP guidelines based on the findings. The guidelines will be developed with a multidisciplinary team and will maximise the impact of this project.

Social Media
We will use Twitter and other social media outlets to engage with a wide and diverse audience, posting a summary of the research findings and infographic. The Circulation Foundation will also share relevant links via their Twitter page and website. Our research team will create a list of potential contacts, who are willing to share our outputs with relevant stakeholders.

Public dissemination
We intend to submit a research summary and our infographic to the relevant professional bodies of our research team members, for publication in their magazines (e.g. British Association of Sport and Exercise Science Magazine 'The Sport and Exercise Scientist').

We will also write an article for 'The Conversation'. The Conversation allows academics to work with specialist editors to share their research in a way that is accessible to non-specialists. Both the universities of Hull and York (the lead applicant's institutions) are members of The Conversation.

Finally, we will work with our PPI group to produce an output suitable for members of the public. This will ensure that relevant parties (e.g., patients and carers) are able to access and understand the research that answers the research priority that they ranked as important to them.

What do you intend to produce from your research?
Deliverables from this project will include:

1. Identification of the most clinically and cost-effective exercise prescription(s) for patients with IC, leading to the development of clinical guidelines for SEPs which will have international impact.
2. An event held with key stakeholders (including patients) to discuss the findings and identify the next steps for implementation
3. A full report for the NIHR
4. A minimum of two peer-reviewed publications
5. A minimum of two conference presentations
6. An infographic to aid dissemination to the public
7. A suite of outputs suitable for members of the public, developed with our PPI group.

How will you inform and engage patients/service users, carers, NHS, social care organisations and the wider population about your work?
We have developed collaborations with key stakeholders for this project.

Patients will be involved throughout the research lifecycle with PPI meetings planned to discuss progress and to encourage input where required. Patients will also be a key part of dissemination plans, to ensure the results are accessible to them.

The PAD SIG and the Circulation Foundation have already agreed their support for this project, and we will be able to share on going progress and results of MAXIMISE through their networks, websites, newsletters and social media communications to ensure that MAXIMISE remains high profile within the vascular community.

We will also engage with all stakeholders via a public dissemination event, which is outlined above. We will continue to work with these stakeholders during and after the development of comprehensive guidelines to aid implementation. This will ensure that each key stakeholder is actively involved in the development and implementation of the results and subsequent guidelines, maximising success.

Although clinicians and healthcare professionals will be involved as key stakeholders, the wider members of this audience will engage with the findings by attending conferences and accessing the final study articles, which will be available open access. Information packs outlining how the results should be implemented into local practice will be shared by the vascular Clinical Reference Group. This will ensure that commissioning teams contract services accordingly to allow for the delivery of the optimal exercise prescription either via existing SEPs, or where required, via the development of new SEP centres. This information pack will also be shared with business managers to support the development of business cases where required.

The management group will contact NICE upon completion of the study, to ensure their involvement in the development of comprehensive guidelines, which can be published as an appendix of CG147. This will ensure that the guidelines are accessible to healthcare professionals and the NHS as a whole, which will again aid implementation.

To enable wider sharing of the results to both patients and other key stakeholders, we intend to maximise the reach of social media. We intend to share the results via the Twitter pages of the Circulation Foundation and other key bodies such as the Vascular Society of Great Britain and Ireland. To increase engagement with social media posts, we intend to use these platforms to share the infographic and other multimedia items.

We will also work with the NIHR press office to maximise the impact of our results.

How will your outputs enter our health and care system or society as a whole?
The results from this study will influence and alter clinical practice. They will enter the health and care system in the UK via influence of NICE CG147 (3). The results will be shared with the previously convened NICE committee, whom we will work with to create an appendix, which can be added to the current guidance, furthering what is available to healthcare professionals and commissioning groups. Fundamentally, this will lead to more effective implementation of SEPs, maximising the benefits for patients with IC. It will also lead to cost savings by ensuring that the existing resources currently assigned to SEPs are utilised to their full potential, whilst also encouraging greater provision and access, reducing the need for further costly follow-up and interventions.

We anticipate that the results will enter the wider vascular society via influence of the European Society of Cardiology and American Heart Association guidelines for the management of PAD. We firmly believe that these results can influence guidelines and clinical practice globally.

What further funding or support will be required if this research is successful (e.g. From NIHR, other Government departments, charity or industry)?
We anticipate that support will be required from key organisational stakeholders following completion of this study. These organisational stakeholders are outlined above and include:

- The Vascular Clinical Reference Group
- The Vascular Society of Great Britain and Ireland
- Cochrane
- The Circulation Foundation
- PAD specialist interest group

We anticipate that we will need the support of these organisations via their participation at our dissemination event and via sharing of our outputs through their relevant media and internal communication streams.

We have included the chair of the Vascular Clinical Reference Group as a co-applicant and have received letters of support from The Vascular Society of Great Britain and Ireland, Cochrane, the PAD specialist interest group, and the Circulation Foundation. These letters have been uploaded to this application.

What are the possible barriers for further research, development, adoption and implementation?
SEPs are not universally available in the UK, which may hinder initial adoption and implementation of the results and therefore their accessibility. However, we anticipate that the findings can be directly implemented into existing NHS SEPs, meaning adoption will be instantaneous for approximately 50% of vascular centres in the UK. For the remaining centres, the results and subsequent guidelines should support the development and implementation of a SEP, where this was previously not possible. However, this may take time, as it will require the development of a comprehensive business case and the establishment of the required staff and facilities.

We believe that adoption and implementation may occur in two phases; an initial instantaneous implementation phase and a gradual adoption phase. When the guidelines have been developed, we intend to establish a working group who can support both of these phases.

What do you think the impact of your research will be and for whom?

Patients / service user
Immediate: There will be an increase in SEP effectiveness, meaning that a larger proportion of patients with access to a SEP will receive a significant improvement in their symptoms, leading to an improvement in QoL, reducing the need for more invasive interventions.

Longer term: There will be an increase SEP availability across the UK, this means that an even greater proportion of patients will be able to attend a SEP, leading to the benefits outlined above.

This also means that patients will be less likely to need further follow-up appointments and inpatient stays, reducing the need for attending hospital appointments in the long term, following completion of the initial SEP.

Health/social care staff benefits: Improved SEP availability and effectiveness means that theoretically, a greater number of patients can be discharged from vascular services following SEP participation. This means that less follow-up would be required, allowing redistribution of a significant proportion of consultant / clinic time to other key areas of vascular care. In addition, it should also lead to a lesser proportion of patients with IC requiring invasive intervention. This would be associated with a reduction in the amount of inpatient care needed by these patients, facilitating redistribution of multidisciplinary resources to other elements of vascular care.

It is also expected that this would also lead to cost savings that could be redistributed.

Public wellbeing: Greater availability of SEP centres as well as standardised exercise prescription will reduce health inequalities between patients residing in different areas of the UK. This reduction will be gradual but eventually, each vascular centre should be able to offer a SEP and each SEP should provide the same exercise prescription.

Project / research timetable

Please see the uploaded Gantt chart, for a project timeline. The study will last for a total of 22 months, with the following planned milestones:

- Months 1-2 – Protocol development and registration
- Months 2-11 – Data collection (screening and data extraction)
- Months 11-18 – Data analysis
- Months 18-22 – Dissemination (planning and outputs)

Project management

Mrs Judith Long will act in her capacity as project manager for the duration of this study, with appropriate time costed for this purpose in addition to her role as PPI lead. Working closely with the co-applicant leads, Judith will be responsible for set-up and delivery of the study management group, with bi-monthly meetings and input from the co-applicant team. She will also provide general administrative support ensuring the project is managed according to contractual requirements and that progress reports are delivered on time.

A study management group will be formed consisting of all co-applicants to guide the day-to-day running of the study and each member will be jointly responsible for its delivery. Management group meetings will be held bi-monthly throughout the project to ensure progress is appropriately monitored, with input from all co-applicants, including those from different institutions. Our patient co-applicant will also be present at each management group meeting and will be encouraged to actively participate in discussions throughout. She will receive pre- and debrief support before and after each meeting, supported by our PPI lead.
Where required, communication between co-applicants from different institutions will take place via email or ad-hoc virtual meetings.

Due to the nature of the study, a trial steering committee and independent data monitoring committee are not required.

Ethics
Due to the nature of this study, and the use of secondary data analysis, no specific ethical approvals are required.

Project / research expertise
Joint lead applicants
Dr Sean Pymer, Hull York Medical School, 50% FTE, lead applicant: Sean is an accredited clinical exercise physiologist who has vast experience of delivering SEPs for patients with IC. His PhD project focussed on alternative exercise programmes for patients with IC, namely home-based programmes and high-intensity interval training. Sean has also led and co-authored several systematic reviews and meta-analyses, including Cochrane reviews. Sean will take on further responsibilities under the guidance of the co-lead applicant. He will lead the day-to-day running of the study and will be heavily involved in all aspects. He will also chair management group meetings to aid his professional development.

Professor Ian Chetter, Hull York Medical School, 5% FTE, co-lead applicant: Professor Chetter is Chair of Surgery at Hull York Medical School, and an NIHR Senior Investigator. He has over 2 decades of experience in research involving SEPs for patients with IC and over 200 original publications supported by research funding from NIHR (RfPB, EME & HTA), BHF, Circulation Foundation, Royal College of Surgeons of England and British Journal of Surgery. He has expertise in PPI engagement supported by RDS funding. Professor Chetter will provide supervision to Dr's Pymer and Harwood, who are early career researchers. He will also provide oversight at all management group meetings.

Co-applicants
Dr Amy Harwood, Coventry University, 25% FTE: Amy is assistant professor who also has vast experience in the delivery of SEPs for patients with IC. Her PhD project considered optimising the efficacy of SEPs for patients with IC, specifically via identification of the mechanism of action. Amy has also led and co-authored a number of systematic reviews and meta-analyses including the 'exercise for intermittent claudication' Cochrane review, which is the most cited review from the Cochrane vascular group. Amy assisted with designing of the study and writing the application. She will also be involved in all aspects of the study and will be present at all management group meetings.

Professor Rob Sayers, University of Leicester, 2% FTE: Professor Sayers is chair of vascular surgery. He has also authored and supervised several systematic reviews and meta-analyses. Professor Sayers has assisted in the writing of this application and will provide oversight at each management group meeting. He will also aid with dissemination and knowledge exchange in his role as chair of the vascular clinical reference group.

Mrs Candida Fenton, Edinburgh University, 2% FTE: Candida has over 14 years' experience working as Information Specialist in clinical and social sciences. She is currently Information Specialist for Cochrane vascular and is co-author on a number of their reviews. Candida will act as Information Specialist for this study, and will lead with search development and running. She has also written these sections for the application.

Mrs Judith Long (PPI lead), Hull York Medical School, 10% FTE: Judith is project manager for the Academic Vascular Surgical Unit at Hull York Medical School. Judith has vast experience leading PPI projects on both a local and national scale including managing the vascular James Lind Alliance priority setting partnership. Judith also leads all PPI elements within the Academic Vascular Surgical Unit for both funded and unfunded studies. Judith has assisted in the development and writing of this application and has facilitated the calculation of costings. She has also led the PPI work that informed this application and will

continue to lead this work throughout the study as PPI "champion", alongside her role as project manager.

Dr Chao Huang, Hull York Medical School, 10% FTE: Chao is a medical statistician at Hull York Medical School, who works closely with the Hull Health Trials Unit. Chao has helped with the statistical design of this study and will lead on the conduction, interpretation and presentation of all analyses.

Professor Joanne Reeve, Hill York Medical School, 2% FTE: Professor Reeve is an academic general practitioner, who is professor of primary care at Hull York Medical School. Professor Reeve is internationally recognised for her work and expertise in medical generalism. Professor Reeve has provided feedback on the application and will sit on the management group, attending all management group meetings to provide primary care insight. She will also provide knowledge exchange insight.

Dr Marta Soares, University of York, 3% FTE: Marta is a senior research fellow within the team for economic evaluation and health technology assessment at the University of York. Marta has experience in the development and application of statistical, econometric and decision analysis methods in all components of health technology assessment, including evidence synthesis. Marta has assisted with the design of this study and will assist on the health economics element in an advisory capacity. She will also contribute to management group meetings.

Ms Ana Duarte, University of York, 5-25% FTE: Ana is a research fellow within the team for economic evaluation and health technology assessment at the University of York. Her research focuses on the application of decision analytic models to inform health technology assessment. Ana has led on the health economics design for this study and will lead this analysis, with assistance provided by Dr Soares. Ana will also work closely on the data extraction elements, to ensure all relevant data is extracted.

Professor Catherine Hewitt, University of York, 5% FTE: Professor Hewitt is a professor of trials and statistics and deputy director of the York trials unit. Professor Hewitt manages a vast team, including those within the team for economic evaluation and health technology assessment. Professor Hewitt has provided feedback on this application and will utilise her expertise by providing oversight at management group meetings.

PPI co-applicant

Mrs Sara Pittack, Circulation Foundation, patient expert and PPI co-applicant: Mrs Pittack has lived experience of IC and has a keen interest in the research area. She is an active patient member of the vascular community, serving as the lay member for The Circulation Foundation and participating in the vascular James Lind Alliance priority setting partnership. Mrs Pittack has provided views on the research question and feedback on elements of the application. She will take an active role during management group meetings and will play a key role during the dissemination phase. Mrs Pittack is also a general practice manager, so can also provide some primary care insight.

Success criteria and barriers to proposed work

This study will be successful if we can perform a comprehensive network meta-analysis to identify the optimal exercise prescription for patients with IC, providing the best possible evidence to inform the development of comprehensive guidelines. These guidelines will inform future practice. We anticipate that the main barrier to this study will be a lack of RCT's to support the analysis. However, this is unlikely given the volume of evidence that informed the most recent 'exercise for intermittent claudication' Cochrane review. In addition, we have a contingency plan to allow us to extend the inclusion criteria in such a scenario.

A key benefit of this study is that it uses secondary data, meaning it will not be affected by research capacity difficulties within the NHS in the post COVID-19 era.

Patient and public involvement
Please see the *Patient and Public Involvement* section of the application.

PPI is a central component of the MAXIMISE project. MAXIMISE is underpinned by the vascular JLA priority question that was co-produced by patients and carers with lived experience of PAD. The question "What is the optimal exercise prescription for patients with poor circulation to the legs? How can we improve provision and access to exercise programs?" was deemed to be the second highest priority, as agreed by both patients and healthcare professionals.

We will provide a flexible approach to our PPI collaboration and co-production, creating a supportive environment to ensure that individuals feel confident and able to contribute to discussion and feedback sessions. We also aim to make being part of our PPI activities both an informative and enjoyable process to ensure that patients remain motivated and engaged with the project.

We have already established a local PPI group comprising people with experience of PAD and different types of SEP. We have been able to have discussions with them about the MAXIMISE application for which they worked together to review the plain English summary. The contribution of our PPI group has already provided valuable insight into patient perspectives about the design and delivery of SEPs and what they consider to be important components of interest. This information feeds directly into the study design, and will be crucial during the data extraction and dissemination phases to ensure that we are considering and reviewing all elements of SEPs that are important and relevant to patients.

Our PPI representative will be joining our management group meetings, supported by our dedicated PPI lead, to ensure that the patient perspective is incorporated throughout the project. PPI will be a standalone agenda item for all project meetings. Additionally, our PPI lead is the lay member of the Circulation Foundation, the only UK Vascular Charity. We will be able to utilise this direct link to keep the Circulation Foundation informed of progress.

A public dissemination event will be co-produced with our PPI group to ensure that the results of this project reach as wide an audience as possible. Our PPI representatives will help us develop the material used in our dissemination strategy for public facing outputs. Results will be communicated in an accessible format and through a variety of media channels relevant to the vascular community, building on our existing links with the leading UK vascular societies and charity groups.

We will use NIHR resources to guide us and ensure appropriate payment and recognition of PPI involvement. In order to monitor and evaluate our PPI, we will implement a simple log to document our activities, with outcomes and reflections for each interaction**.** We will review the process and quality of PPI representation to evaluate the impact of PPI on this project, coordinated by the PPI lead. This will be reported using the GRIPP2-SF checklist and shared with the project team and fed back to the NIHR.

By undertaking the MAXIMISE project, we are ensuring that research is focussed on what matters most to people with direct experience of PAD.