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Understanding the mechanisms of a combined physical and psychological intervention for people with neurogenic claudication: protocol for a causal mediation analysis of the BOOST trial

Christine Comer ,[1,2] Hopin Lee,[3,4] Esther Williamson ,[4] Sarah Lamb[4,5]

Correspondence to
Dr Christine Comer;
c.comer@leeds.ac.uk

ABSTRACT

Introduction Conservative treatments such as exercise are recommended for the management of people with neurogenic claudication from spinal stenosis. However, the effectiveness and mechanisms of effect are unknown. This protocol outlines an a priori plan for a secondary analysis of a multicentre randomised controlled trial of a physiotherapist-delivered, combined physical and psychological intervention (Better Outcomes for Older people with Spinal Trouble (BOOST) programme).

Methods and analyses We will use causal mediation analysis to estimate the mechanistic effects of the BOOST programme on the primary outcome of disability (measured by the Oswestry Disability Index). The primary mechanism of interest is walking capacity, and secondary mediators include fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and/or symptom severity. All mediators will be measured at 6 months and the outcome will be measured at 12 months from randomisation. Patient characteristics and possible confounders of the mediator-outcome effect will be measured at baseline. Sensitivity analyses will be conducted to evaluate the robustness of the estimated effects to varying levels of residual confounding.

Ethics and dissemination Ethical approval was given on 3 March 2016 (National Research Ethics Committee number: 16/LO/0349). The results of this analysis will be disseminated in peer-reviewed journals and at relevant scientific conferences.

Trial registration number ISRCTN12698674.

Strengths and limitations of this study

► Causal mediation analysis of clinical trials can explain how an effective intervention works, or why an ineffective intervention does not work.
► This protocol describes a planned analysis of the underlying causal mechanisms of the Better Outcomes for Older people with Spinal Trouble rehabilitation programme; a combined physical and psychological intervention for people with neurogenic claudication symptoms.
► We propose an exploratory analysis of several potential causal pathways based on theoretical mechanisms of action, acknowledging the risks associated with multiple testing.
► The proposed models will estimate the extent to which candidate mediators (walking capacity, fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and symptom severity) mediate effects on disability measured by the Oswestry Disability index.

INTRODUCTION

Neurogenic claudication (NC) is a leading cause of disability and lost independence in older adults.[1–3] NC is the term used to describe the typical symptoms associated with lumbar spinal stenosis (LSS).[4] These symptoms are provoked by walking, and include pain, aching, paraesthesia and fatigue, which radiate from the spine into the buttocks and legs.[5] NC often leads to reduced mobility[6] contributing to disability, frailty and falls,[7–12] increased risks of comorbidity, social isolation and loss of independence.[13 14] The symptoms are thought to arise because of reduced space and subsequent compromise of the neural and vascular elements in the lumbar spine[4] resulting from degenerative changes in the ageing spine.[15]

LSS has become the most common reason for spinal surgery in people over 65 years of age.[16] Because of the risks, costs and unclear benefits associated with surgical treatment,[16–18] it is widely accepted that non-surgical treatment should be first-line care.[19 20] Advice, exercise and self-management strategies are often used in clinical practice[21–23] but there is limited robust evidence to demonstrate their efficacy and effectiveness.[17]

The Better Outcomes for Older people with Spinal Trouble (BOOST) trial is a large multicentre randomised controlled trial (RCT) testing the effectiveness of a 12-week

combined physical and psychological intervention delivered by physiotherapists in a group setting. The primary focus of this randomised trial is to estimate the effect of the BOOST intervention on patient-reported disability. There is, however, growing recognition of the importance of evaluating hypothesised treatment mechanisms in randomised trials.[24] Doing so can explain how an effective intervention works, or why an ineffective intervention does not work.

Objectives

We present an a priori protocol for a secondary analysis of the BOOST trial to evaluate the effects on the primary mediator of a change in walking capacity, and to explore alternative mediators of changes in fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and symptom severity. The aim of this planned analysis is to contribute to our understanding of treatment mechanisms and provide valuable information to guide future intervention development and implementation.

METHODS AND ANALYSES

Design

This study is a causal mediation analysis of the National Institute of Health Research (NIHR) funded BOOST trial. The BOOST trial is a high-quality multicentred RCT. It aims to evaluate the clinical-effectiveness and cost-effectiveness of a physiotherapist-delivered, combined physical and psychological intervention for community-dwelling older adults with symptoms of NC, compared with a control treatment of best practice (standardised advice and education). BOOST trial details are published separately in the trial protocol.[25]

Patient and public involvement

Patient and public involvement has been embedded in the BOOST trial and is described fully in the trial protocol.[25]

Participants

In total, 438 participants with symptoms of NC from across 15 primary-care and secondary-care centres in the UK have been randomised to the trial intervention or control treatment at a 2:1 ratio. We recruited participants over the age of 65 years from spinal clinics within primary and secondary care centres (n=394) and via a primary care survey of community-dwelling older adults (n=44). They were eligible for the study if they presented with symptoms consistent with NC (back and/or leg pain or symptoms aggravated by standing or walking and eased by sitting or bending) and were able to participate safely in the group rehabilitation programme.

BOOST trial intervention

A detailed description of the BOOST intervention and its development have been published elsewhere.[26] In summary, the BOOST intervention combines physical and psychological components in a programme delivered to small groups of participants over 12 sessions. The physical component comprises a 60 min exercise programme at each session, including exercises for strength, balance and flexibility and a walking circuit. The level of exercise difficulty is individually tailored, and is progressed over the 12-week programme by increasing the number of repetitions, sets and increasing weights and/ or speed. The psychological component consists of a series of 30 min discussions at each of the 12 sessions. Early sessions are aimed at facilitating self-efficacy and safety, including addressing unhelpful pain behaviour and fear-related avoidance of movement; providing simple concepts of exercise physiology relevant to improving mobility; and introducing basic behavioural techniques of pacing and graded activity. Subsequent sessions use peer-support to encourage exercise adherence, identify facilitators and barriers, and reinforce long-term exercise adherence through peer discussion about exercise confidence and motivation, access to local activities, and advice on coping with acute symptom flare-ups. Over the 12-week supervised programme, session frequency reduces from two times weekly to once weekly and then to once fortnightly. Concurrently, home exercise programmes are introduced with the aim of encouraging participants to increase their level of independent, unsupervised exercise and physical activity at home.

We developed the intervention collaboratively with clinical experts and patients to address some of the unique challenges of managing back problems in older people. These include age-related physical changes of reduced muscle strength and fitness, in addition to psychological factors such as depression[27] and unhelpful behaviours and beliefs about ageing and exercise which are known to negatively impact on outcomes and act as barriers to accessing and engaging with treatment.[28–31]

Control intervention

The control intervention consists of a 1 hour individual session with a physiotherapist for assessment, advice and education about NC and being physically active, advice on exercises including flexion-based exercises, use of medications and when to seek more advice. The advice and education are reinforced in a leaflet and a further two review appointments are available if required.

Outcomes

The Oswestry Disability Index (ODI)[32] is the primary outcome measure for the BOOST trial. The ODI (also known as the Oswestry Low Back Pain Disability Questionnaire) is the most widely used measure in low back pain research and is considered the 'gold standard' of low back functional outcome tools. It is commonly used to provide a patient-reported measure of walking limitation and other functional limitations in LSS trials, alongside objective measures of walking ability.[33]

The ODI comprises a series of questions about how pain impacts on the patient's ability to carry out a range of daily functions. For each question, possible answers are scored on a scale of 0–5. These scores are summed

and expressed as a percentage of the maximum possible score for disability, with higher scores representing worse disability. In the BOOST trial, ODI scores are measured for each participant at baseline, and at 6 and 12 months after randomisation.

Important secondary outcome measures for the BOOST trial focus on walking capacity, and on fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and symptom severity: the 6-minute walk test provides an objective measure of walking capacity and entails a timed measure of walking distance which is easily performed in the clinical setting.[34] The Short Physical Performance Battery (SPPB) provides an objective measure of physical performance which incorporates a balance test, a functional lower limb strength test of five timed chair stands, and a timed walking test over 8 feet. This is similarly easy to complete in a clinic.[35] Outcome questionnaires completed by participants provide a subjective evaluation of relevant constructs. These include physical activity measured by a modified version of the Rapid Assessment Disuse Index (RADI)[36]; severity of stenotic symptoms measured by the Swiss Spinal Stenosis (SSS) symptom severity subscale[37]; walking self-efficacy measured by a single item from the Modified Gait Efficacy Scale (GES)[38] and fear of movement measured by the physical activity subscale of the Fear Avoidance Beliefs Questionnaire (FABQ).[39] These outcomes are all measured at baseline, and at 6 and 12 months following randomisation.

Causal mediation analysis: rationale

We will test the mechanisms of the BOOST intervention for patients with NC by estimating the extent to which different potential mediators explain the effect of the BOOST intervention on participants' ODI outcome scores. This will be achieved by deconstructing the total effect of the BOOST treatment into indirect and direct effects. The indirect effect is the path through which the intervention affects the outcome via a selected mediator. The direct effect is the remaining total effect that is not encompassed by the indirect effect.

Walking capacity has been selected as the primary mediator for our causal mediation analysis model. Walking limitation is a hallmark of disability in LSS[40] and a serious concern for people with LSS who often seek healthcare because of reduced mobility.[41–43] The BOOST intervention incorporates both physical and cognitive behavioural components aimed at reducing disability, and increased walking is a key target.

The BOOST intervention is underpinned by a strong theoretical premise for addressing age-related decline in mobility. Exercise components of the intervention aim to improve physical function by targeting reduced muscle strength, balance and sensory impairments.[44–53] While cognitive behavioural approaches have not been well investigated in people with LSS,[54] this is an important component of the BOOST intervention based on evidence that addressing unhelpful beliefs and behaviours can

mediate changes in both disability and symptom severity in low back pain populations.[55–60] In addition, self-efficacy is likely to play a role in mediating disability, physical function and activity in older adults with chronic musculoskeletal conditions.[61–63] Alternative mediators that we will include in our causal mediation models, therefore, include physical function (SPPB), physical activity (RADI), fear-avoidance behaviour (FABQ) and walking self-efficacy (GES).

Our final alternative mediator is symptom severity (SSS). Little is known about how exercise affects NC symptom severity.[64] In theory, better muscular strength, control and endurance and increased flexibility are likely not only to enhance physical ability,[65 66] but also to reduce pain by altering the loading of the musculoskeletal system and changing central pain processes and immune system responses.[67–69] Neuroischaemic lower limb symptoms such as paraesthesia, numbness, sensory and balance changes might also be improved through reduced nerve root ischaemia and venous pooling as a result of exercise.[4 70]

To understand the mechanisms of the BOOST intervention, we plan to test our primary hypothesis that changes in disability will be mediated primarily by changes in walking capacity, and that various mechanisms might explain these changes in walking capacity: We hypothesise that the progressive exercise component of the BOOST intervention will exert its effect on walking capacity via initial changes in physical function and physical activity levels during treatment. We further hypothesise that the cognitive behavioural components of the intervention will exert effects on walking capacity through reductions in fear-avoidance behaviour and increased self-efficacy. There is also the potential for both the exercise and the cognitive behavioural components of the intervention to reduce symptom severity, resulting in increased walking capacity.

Our secondary hypothesis is that the causal effects of the BOOST intervention on disability will be explained through changes in fear-avoidance behaviour, self-efficacy, physical function, physical activity and/or symptom severity (SSS) without exerting any effects on walking capacity.

If the BOOST intervention is found to be effective, causal mediation analysis will explain how the intervention works. Conversely, if the intervention is not found to be effective, causal mediation analysis will identify where the hypothesised mechanism broke down.[71]

Causal mediation analysis: models

The decision-making process that will guide our analyses is laid out in figure 1. Table 1 provides an overview of the planned mediation models contingent on whether or not the BOOST intervention is effective:

► If the intervention is effective, our primary objective is to estimate the extent to which the joint effects of walking capacity, fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and symptom severity mediate this effect.
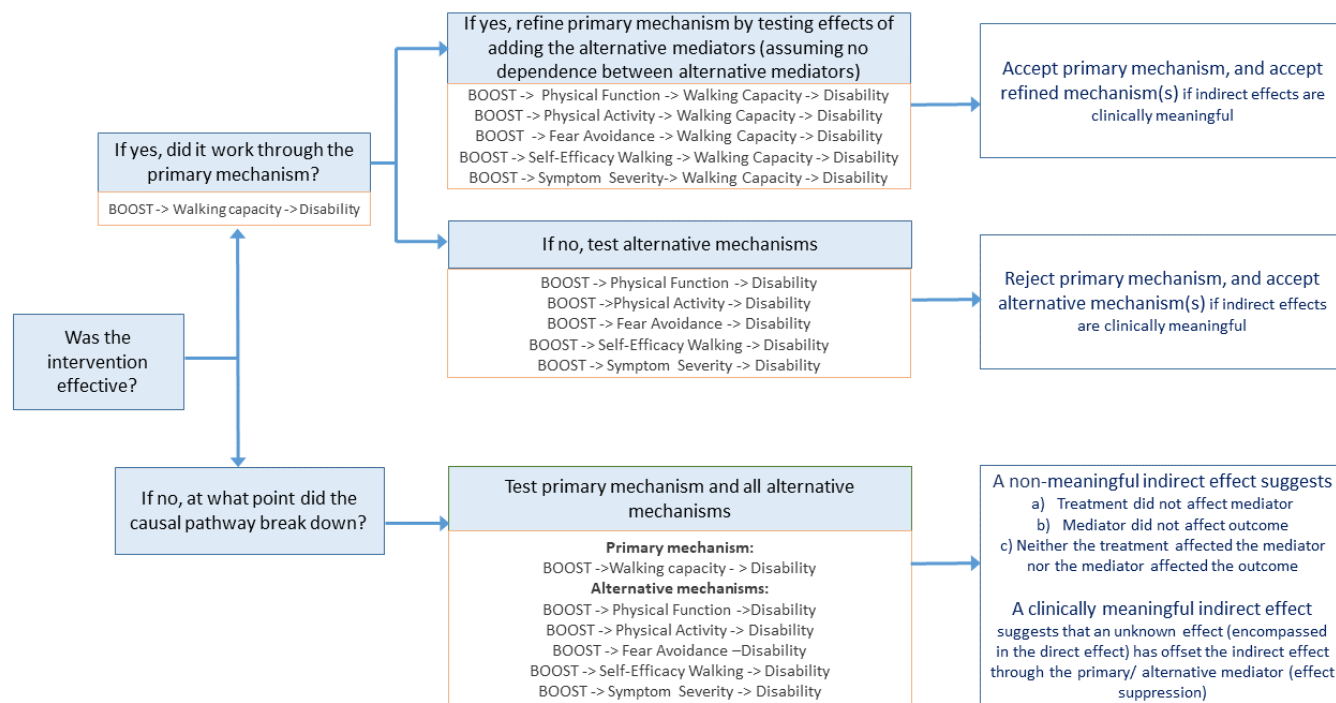
Figure 1 Mediation protocol decision process.

Our secondary objective will be to further refine this model through the candidate primary mediator, walking capacity; and via five secondary mediators (fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and symptom severity). If the indirect effect through the primary mediator is significant, we will consider sequentially ordered multiple mediator models through secondary mediators. The serial multiple mediator models accounting for potential confounders are presented in the directed acyclic graphics in figure 2.

► If the intervention is not effective, our primary objective is to determine where the causal paths break down. All potential mediators (walking capacity, fear avoidance, self-efficacy, physical function, physical activity and symptom severity) will be evaluated.

Statistical analysis

We will use a model-based inference approach for causal mediation analysis.[72] All analyses will be conducted in R (The R Foundation for Statistical Computing) using the 'medflex' and 'mediation' packages.[73 74]

To estimate a joint indirect effect, we will consider a natural indirect effect of the intervention on the outcome that is exerted through a vector of all six mediators (walking capacity, fear-avoidance behaviour, walking self-efficacy, physical function, physical activity and symptom severity). The advantage of this approach is that we can consider all possible mechanisms simultaneously and relax the assumption of omitting confounders of the mediator-outcome effect that is affected by randomisation. We will use the imputation-based approach outlined

by Steen[75 76] to fit a natural effect model with robust standard errors based on the sandwich-estimator—the recommended approach when the ordering of multiple mediators is unknown.

To consider the mediators independently, we will construct single mediator models for the ODI outcome. For each single mediator model (primary mediator model of walking capacity, and secondary mediator models of fear avoidance, self-efficacy, physical function, physical activity and symptom severity), we will estimate the intervention-mediator effect, the mediator-outcome effect, the average causal mediation effect (ACME), average direct effect (ADE) and the average total effect (ATE). We will also estimate the proportion mediated in each single mediator model. The ACME is the average intervention effect through the mediator; ADE is the average intervention effect that works through all other mechanisms excluding the selected mediator; and the ATE is the average effect of the intervention on the outcome. The ATE is the sum of the ACME and ADE on the additive scale. The proportion mediated is the fraction of the ATE that is explained by the ACME.

We will fit two regression models: the mediator model and the outcome model. The mediator model will use linear regression with treatment allocation as the independent variable, and the mediator as the dependent variable, with the baseline level of the mediator as a covariate. The outcome model for disability will also use linear regression. Each outcome model will be constructed with the mediator as the independent variable, the outcome

Table 1 Overview of mediator models

Model	Treatment	Alternative mediators at 6 months (M2)	Primary mediator at 6 months (M1)	Outcome at 12 months
If the total effect of the intervention on disability outcome (ODI) is significant				
1.0	BOOST		Walking capacity	Disability (ODI)
If the indirect effect through walking capacity is significant from model 1.0				
1.1	BOOST	Physical function (SPPB)	Walking capacity	Disability (ODI)
1.2	BOOST	Physical activity (RADI)	Walking capacity	Disability (ODI)
1.3	BOOST	Fear avoidance (FABQ)	Walking capacity	Disability (ODI)
1.4	BOOST	Self-efficacy walking (SE-W)	Walking capacity	Disability (ODI)
1.5	BOOST	Symptom severity (SSS)	Walking capacity	Disability (ODI)
If the indirect effect through walking capacity is not significant from model 1.0				
1.6	BOOST	Physical function (SPPB)		Disability (ODI)
1.7	BOOST	Physical activity (RADI)		Disability (ODI)
1.8	BOOST	Fear avoidance (FABQ)		Disability (ODI)
1.9	BOOST	Self-efficacy walking (SE-W)		Disability (ODI)
1.10	BOOST	Symptom severity (SSS)		Disability (ODI)
If the total effect of the intervention on disability outcome (ODI) is not significant				
2.0	BOOST		Walking capacity	Disability (ODI)
2.1	BOOST	Physical function (SPPB)		Disability (ODI)
2.2	BOOST	Physical activity (RADI)		Disability (ODI)
2.3	BOOST	Fear avoidance (FABQ)		Disability (ODI)
2.4	BOOST	Self-efficacy walking (SE-W)		Disability (ODI)
2.5	BOOST	Symptom severity (SSS)		Disability (ODI)

Multiple mediator models will only be tested if there is a significant relationship between M1 and M2. If the relationship is non-significant, then the alternative mediators will be tested in separate single mediator models. Significance levels are set a priori at p<0.05.

BOOST, Better Outcomes for Older people with Spinal Trouble; FABQ, Fear Avoidance Beliefs Questionnaire; M1, 12-month measure; M2, 6-month measures; ODI, Oswestry Disability Index; RADI, Rapid Assessment Disuse Index; SPPB, Short Physical Performance Battery; SSS, Swiss Spinal Stenosis Symptom Severity Scale.

as the dependent variable and treatment allocation, baseline values of the mediator and outcome variable in addition to the set of observed pre-treatment confounders as covariates. Because the mediators are not randomised, it is possible for the mediator-outcome effects to be confounded. To address this problem, we will adjust for the effects of pre-treatment confounders based on theorised causal relationships with the mediators and outcome variables from expert clinical knowledge and available evidence. These potential confounders include age, body mass index, sex, number of comorbidities, in addition to baseline measures of disability, physical function, walking capacity, self-efficacy, physical activity, symptom severity and fear-avoidance behaviour, and also baseline frailty (frailty index/grip strength); use of walking aids; general pain (Nordic pain Q); exercise self-efficacy; and attitudes to ageing. We will also conduct a sensitivity analysis to determine the robustness of the estimated ACME and ADE to possible unmeasured confounding.[77] We will also include an interaction term (treatment allocation X mediator) in the outcome models to allow for an intervention-mediator interaction effect on the outcome and to increase model flexibility.[78]

Using mediator and outcome regression models, we will simulate potential values of the mediator for each participant under each level of the intervention; then simulate potential outcome values for each participant under all combinations of the intervention and simulated mediator values. From these observed and simulated potential values of the mediator and outcome, we will calculate point estimates for the ACME, ADE and ATE and their 95% CIs using 1000 bootstrapped simulations with the percentile method.

For multiple mediator models, we will use an expanded framework.[79] Multiple mediator models will only be constructed if the alternative mediator (fear avoidance, self-efficacy, physical function, physical activity and symptom severity) and primary mediator (walking capacity) are associated.[79] We will use the *multimed* function from the *mediation* package to estimate the ACME and ADE, and the sensitivity parameters.
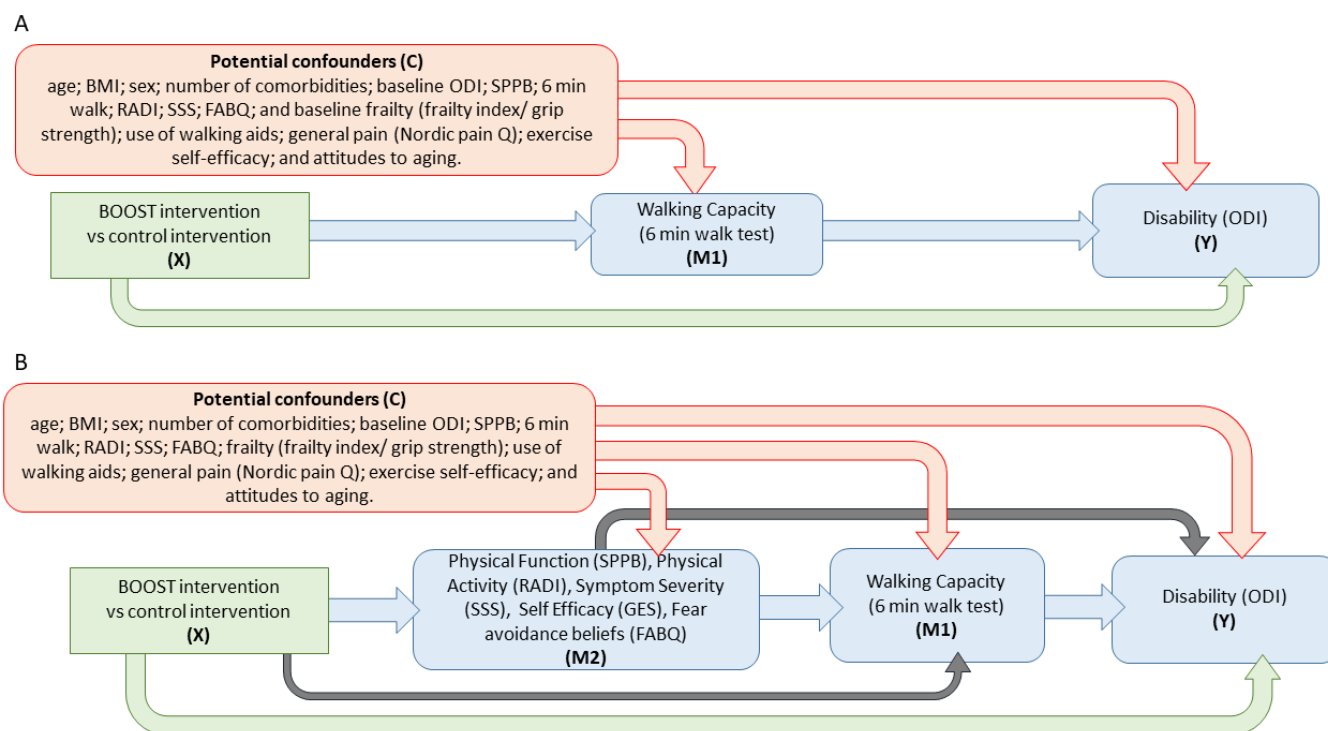
Figure 2 Directed acyclic graphics blue lines represent indirect effects (mechanisms) of interest. Green lines represent direct effects (direct effect of treatment on outcome plus all unspecified indirect effects). Red lines represent possible effects that could induce confounding for indirect and direct effects. (A) A single mediator model where the intervention (X) exerts its effect on the outcome(s) Y, via an indirect path through the primary mediator (M1). (B) A serial multiple mediator model where the intervention (X) exerts its effect on the outcome (Y) via an indirect path through one of five alternative mediators (M2) and the primary mediator (M1), and a direct path (X to Y). BMI, body mass index; BOOST, Better Outcomes for Older people with Spinal Trouble; FABQ, Fear Avoidance Beliefs Questionnaire; GES, Gait Efficacy Scale; M1, 6-month measure; M2, 6-month measures; ODI, Oswestry Disability Index; RADI, Rapid Assessment Disuse Index; SPPB, Short Physical Performance Battery; SSS, Swiss Spinal Stenosis Symptom Severity Scale; Y, 12-month measure.

We will assess the proportion of missing mediator and outcome data. We will conduct all analyses on complete cases if the proportion of missing data is <5%. If missing data exceeds 5% we will use multiple imputations by chain equations to impute 10 datasets using the 'mice' package.[80]

To facilitate clinical interpretation, we will calculate how much change in a given mediator would equate to a minimally clinically important difference (MCID) of disability (5 point change in ODI score[81]) by using the regression coefficients from the outcome model, and we will divide the MCID by the mediator coefficient and 95% CI from the outcome regression model.

Clinical implications

We do not currently know whether non-surgical interventions are effective in reducing disability reported by older people with NC symptoms. The BOOST trial will provide important high-quality evidence about the effectiveness of an intervention incorporating components to address both physical and psychological impairments. The targets of this comprehensive intervention include walking capacity, physical function, physical activity, self-efficacy, unhelpful beliefs about activity and symptom severity. We

cannot assume, however, that if the intervention improves any of these variables, the participants will experience benefits in patient-reported outcomes, such as the ODI.

Mediation analysis conducted in parallel to an RCT can address specific questions about the underlying mechanisms of the intervention being tested. This protocol describes the planned causal mediation analysis that we will undertake to evaluate hypothetical mechanisms that underlie the effect of the BOOST rehabilitation programme. This will help us to understand how the BOOST intervention works, or doesn't work.

If the BOOST intervention is found to be effective and this mediation analysis indicates that improvements in ODI scores are mediated by walking capacity, which in turn is mediated by improved self-efficacy, then this provides valuable information for refining the intervention with a greater focus on self-efficacy to optimise treatment effectiveness. If, on the other hand, the BOOST trial is not found to produce a significant improvement in patient-reported disability, then the analysis will help us to understand where the hypothesised causal mechanisms of treatment break down. For example, we may find that although the BOOST intervention improves walking

capacity, this does not translate into an improvement in ODI score and may therefore not be an appropriate treatment target. The causal analysis will, therefore, provide valuable information for designing, refining and implementing an effective intervention.

Because this is an exploratory study, we have selected several mediators based on our current clinical understanding and evidence for exercise and behavioural treatments. Several potential causal pathways will, therefore, be explored, and we acknowledge the risks associated with this multiple testing. If alternative pathways of mediation emerge during the analysis of the trial and associated qualitative data, we will investigate these further. The publication of this protocol does not preclude other analyses if indicated. Future studies may be needed to further explore the inter-relationship of the mediators explored in our analyses.

CONCLUSION

Clinical trials do not address questions around *how* an intervention affects outcomes, and therefore may not identify the most effective treatment targets for a particular patient population. Mediation analysis of clinical trials can estimate how much the total effect of the treatment can be attributed to pre-specified treatment targets. Improving our understanding of these treatment mechanisms can generate evidence that can be used to tailor and refine treatments and optimise clinical effectiveness. In this study, we will estimate the causal mediation effects of a rehabilitation programme incorporating exercise and behavioural components for patients with NC.

Author affiliations
[1]Musculoskeletal and Rehabilitation Services, Leeds Community Healthcare NHS Trust, Leeds, UK
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds Faculty of Medicine and Health, Leeds, UK
[3]School of Medicine and Public Health, University of Newcastle, New South Wales, Australia
[4]The Centre for Rehabilitation Research, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK
[5]College of Medicine and Health, University of Exeter, Exeter, UK

ORCID iDs
Christine Comer http://orcid.org/0000-0001-9847-9408
Esther Williamson http://orcid.org/0000-0003-0638-0406

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