

Effectiveness and cost-effectiveness of a web-based cardiac rehabilitation programme for people with chronic stable angina

Williams, Nefyn H; Collins, Brendan; Comerford, Terence J; Dodd, Susanna; Fisher, Michael; Hardwick, Ben; Hennessy, Sophie; Jolly, Kate; Jones, Ian; Lane, Deirdre; Lip, Gregory Y H; Morgan, Erica; Ralph, Penelope; Thijssen, Dick; Singh, Sally J

DOI:

[10.1136/bmjopen-2024-084509](https://doi.org/10.1136/bmjopen-2024-084509)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Williams, NH, Collins, B, Comerford, TJ, Dodd, S, Fisher, M, Hardwick, B, Hennessy, S, Jolly, K, Jones, I, Lane, D, Lip, GYH, Morgan, E, Ralph, P, Thijssen, D & Singh, SJ 2024, 'Effectiveness and cost-effectiveness of a web-based cardiac rehabilitation programme for people with chronic stable angina: protocol for the ACTIVATE (Angina Controlled Trial Investigating the Value of the 'Activate your heart' Therapeutic E-intervention) randomised controlled trial', *BMJ open*, vol. 14, no. 3, e084509. <https://doi.org/10.1136/bmjopen-2024-084509>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.





When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

BMJ Open Effectiveness and cost-effectiveness of a web-based cardiac rehabilitation programme for people with chronic stable angina: protocol for the ACTIVATE (Angina Controlled Trial Investigating the Value of the 'Activate your heart' Therapeutic E-intervention) randomised controlled trial

Nefyn H Williams ¹, Brendan Collins,² Terence J Comerford,³ Susanna Dodd,⁴ Michael Fisher,⁵ Ben Hardwick,⁶ Sophie Hennessy,⁶ Kate Jolly ⁷, Ian Jones,⁸ Deirdre Lane ⁹, Gregory Y H Lip ¹⁰, Erica Morgan,³ Penelope Ralph,¹ Dick Thijssen,¹¹ Sally J Singh¹²

To cite: Williams NH, Collins B, Comerford TJ, *et al.* Effectiveness and cost-effectiveness of a web-based cardiac rehabilitation programme for people with chronic stable angina: protocol for the ACTIVATE (Angina Controlled Trial Investigating the Value of the 'Activate your heart' Therapeutic E-intervention) randomised controlled trial. *BMJ Open* 2024;**14**:e084509. doi:10.1136/bmjopen-2024-084509

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2024-084509>).

Received 20 January 2024
Accepted 21 February 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Professor Nefyn H Williams;
nefyn.williams@liverpool.ac.uk

ABSTRACT

Introduction Chronic stable angina is common and disabling. Cardiac rehabilitation is routinely offered to people following myocardial infarction or revascularisation procedures and has the potential to help people with chronic stable angina. However, there is insufficient evidence of effectiveness and cost-effectiveness for its routine use in this patient group. The objectives of this study are to compare the effectiveness and cost-effectiveness of the 'Activate Your Heart' cardiac rehabilitation programme for people with chronic stable angina compared with usual care.

Methods and analysis ACTIVATE is a multicentre, parallel-group, two-arm, superiority, pragmatic randomised controlled trial, with recruitment from primary and secondary care centres in England and Wales and a target sample size of 518 (1:1 allocation; allocation sequence by minimisation programme with built-in random element). The study uses secure web-based allocation concealment. The two treatments will be optimal usual care (control) and optimal usual care plus the 'Activate Your Heart' web-based cardiac rehabilitation programme (intervention). Outcome assessment and statistical analysis will be performed blinded; participants will be unblinded. Outcomes will be measured at baseline and at 6 and 12 months' follow-up. Primary outcome will be the UK version of Seattle Angina Questionnaire (SAQ-UK), physical limitations domain at 12 months' follow-up. Secondary outcomes will be the remaining two domains of SAQ-UK, dyspnoea, anxiety and depression, health utility, self-efficacy, physical activity and the incremental shuttle walk test. All safety events will be recorded, and serious adverse events assessed to determine whether they are related to the intervention and expected. Concurrent economic

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Pragmatic randomised controlled trial of an established cardiac rehabilitation programme for individuals with chronic stable angina, with unblinded participants and rehabilitation providers.
- ⇒ Concurrent economic evaluation with a health service perspective.
- ⇒ Embedded process evaluation to determine the mechanisms and processes that explain the implementation and impacts of the enhanced rehabilitation programme.
- ⇒ The web-based intervention may not be acceptable to some people, but a paper version is available.

evaluation will be cost-utility analysis from health service perspective. An embedded process evaluation will determine the mechanisms and processes that explain the implementation and impacts of the cardiac rehabilitation programme.

Ethics and dissemination North of Scotland National Health Service Research Ethics Committee approval, reference 21/NS/0115. Participants will provide written informed consent. Results will be disseminated by peer-reviewed publication.

Trial registration number ISRCTN10054455.

INTRODUCTION

Angina is chest pain usually caused by atherosclerosis of the coronary arteries, which restricts blood flow to the myocardium, especially when oxygen demand is increased

during exercise. Angina is defined as stable if chest pain occurs predictably on physical exertion, or with emotion, and settles promptly with rest or after taking sublingual nitrate medication. Affected individuals have an increased risk of acute coronary events such as myocardial infarction (MI).¹ Management consists of behaviour change advice to reduce risk factor profile, drug treatment and revascularisation procedures.^{2,3}

Cardiac rehabilitation is routinely offered to patients following MI, or revascularisation procedures, and consists of co-ordinated activities to improve the underlying cause and restore optimal functioning and slow, or reverse, disease progression.⁴ The most prevalent components of cardiac rehabilitation are behaviour change and exercise training, but comprehensive cardiac rehabilitation programmes also include education, interventions to improve mental health, involvement of friends and family members and the development of long-term strategies beyond participation in the cardiac rehabilitation programme. Despite international guidance,^{2,5} such programmes are not offered routinely to people with chronic stable angina.⁶ In the UK, the National Institute for Health and Care Excellence (NICE) does not support cardiac rehabilitation in this group until stronger evidence of effectiveness and cost-effectiveness is available.³ Although there is a good evidence for the effectiveness of cardiac rehabilitation for heart failure,⁷ or following MI or revascularisation procedures,⁸ rates of uptake and long-term adherence are low, especially in women, ethnic minority groups, and in areas of high deprivation.⁶

A systematic review of exercise-based cardiac rehabilitation for adults with stable angina,⁹ identified seven randomised controlled trials (RCTs) (n=581) with high risk of bias. It found low-quality evidence that cardiac rehabilitation resulted in a small improvement in exercise capacity compared with usual care with standard mean difference 0.45 (95% CI 0.2 to 0.7), and uncertainty about the effect on all-cause mortality, acute MI, cardiovascular-related hospital admissions, quality of life and cardiac rehabilitation-related adverse events. These RCTs were small in size and recruited mainly white middle-aged men. More evidence is needed from under-represented groups including women, older age groups, ethnic minorities and those with comorbid conditions. Web-based programmes might increase the reach of cardiac rehabilitation, and there has been one small RCT (n=94) of such a programme ('Activate Your Heart'), which demonstrated that it was possible to provide cardiac rehabilitation to people with chronic stable angina.¹⁰ Trial methods were feasible in terms of recruitment, retention and outcome measurement. After 6 months, there were statistically significant lower levels of angina frequency, but a larger RCT is needed to test longer-term effectiveness and cost-effectiveness.

'Activate Your Heart' has the potential to improve physical and mental health with minimal risk. There may be a risk of injury or provoking an episode of angina when exercising,

however, the physical activity goals are carefully graded and the programme has an excellent safety record.¹⁰

Aims and objectives

We aim to assess whether a web-based cardiac rehabilitation programme can improve the health of people with chronic stable angina, whether it is good value for money and delivered as intended.

The primary objective is to determine the effectiveness of the 'Activate Your Heart' web-based cardiac rehabilitation programme (or a paper version for those who prefer or who do not have internet access or device), for people with chronic stable angina compared with usual care in terms of angina-related health status, at 12 months' follow-up.

Secondary objectives:

- ▶ To estimate the cost-effectiveness of the cardiac rehabilitation programme for people with chronic stable angina compared with usual care in a cost-utility analysis with a health service perspective.
- ▶ To investigate the mechanisms and processes that explain the implementation and impacts of the cardiac rehabilitation programme in the intervention group and usual care in the control group.
- ▶ To identify the barriers and facilitators of uptake and completion of the rehabilitation programme with a focus on equity.

METHODS AND ANALYSIS

Trial design

ACTIVATE is a multisite, parallel-group, two-armed, superiority RCT with 1:1 allocation, stratified by gender and recruitment site (figure 1). A pragmatic RCT of effectiveness compared with usual care, with blinded outcome assessment and statistical analysis; unblinded participants and rehabilitation providers. An internal pilot phase will assess feasibility. There will be a concurrent economic evaluation with a health service perspective. An embedded process evaluation will use mixed methods to examine the mechanisms and processes that explain the implementation and impacts of the enhanced rehabilitation programme, including an examination of barriers leading to health inequities. The Health Inequalities Assessment Toolkit (www.hiat.org.uk) informed trial design. The RCT was registered on 16 September 2021 (ISRCTN10054455). Trial registration data can be found in online supplemental appendix 1.

Trial setting and selection of sites/clinicians

Participants will be recruited from primary and secondary care in areas of England and Wales with high disease burden and socioeconomic deprivation. Many of these areas include high proportions of ethnic minority groups. The web-based rehabilitation intervention (or paper version) will be delivered in the community.

Trial population

Inclusion criteria

- ▶ Adults with chronic stable angina with at least two out of three of the following features: constricting central

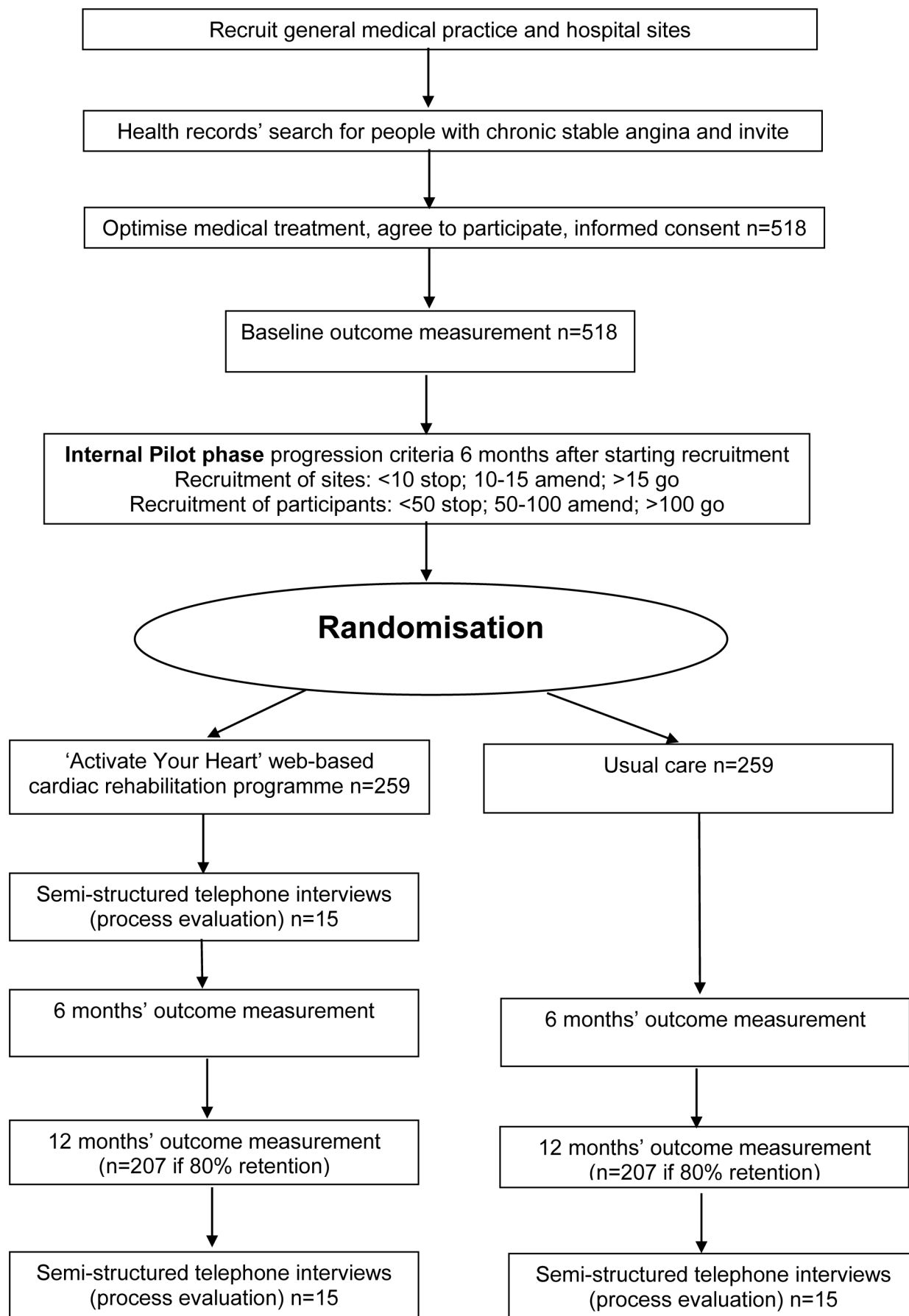


Figure 1 ACTIVATE participant flow chart.

chest pain, precipitated by exertion or emotional stress, relieved by rest or glyceryl trinitrate spray.

- ▶ Evidence of myocardial ischaemia from either a medical history of acute coronary syndrome, MI or revascularisation procedure at least 12 months previously; or from imaging studies such as invasive coronary angiography, CT angiography or myocardial perfusion testing.
- ▶ Revascularisation procedures not planned and managed with medical treatments only, including people with previous MI, or previous revascularisation procedure who may have attended cardiac rehabilitation in the past.

Exclusion criteria

- ▶ History of MI, revascularisation or cardiac rehabilitation participation within the last 12 months.
- ▶ Significant comorbidities (as deemed by the person confirming eligibility) that would limit participation in the exercise-based rehabilitation programme.
- ▶ Refractory angina on maximal medical therapy.

Trial treatment/interventions

We plan to compare web-based cardiac rehabilitation in addition to optimal usual care (intervention) with optimal usual care alone.

Optimal usual care

Usual care will be optimised in all participants. All participants will be seen by their general practitioner or cardiology team, using a protocol informed by NICE guidance³ to ensure that all are receiving optimal care. Considering the pragmatic nature of the proposed RCT, no restrictions will be placed on usual care. NICE guidance³ recommends that patients with chronic stable angina receive adequate information and support, lifestyle advice about smoking, exercise, diet and weight control. Episodes of angina should be treated with short-acting nitrate medication. Antianginal drug treatment to prevent episodes of angina consists of a beta-blocker or calcium channel blocker in the first instance; second-line drugs (such as ivabradine, ranolazine) will be used as needed. In addition, drugs for secondary prevention of cardiovascular disease such as MI or stroke, include aspirin, ACE inhibitor (especially if diabetes is present), statins in line with NICE guidance (and treatment targets) on lipid modification¹¹ and antihypertensives in line with NICE guidance (and treatment targets) on hypertension.¹²

Concomitant medication will be recorded as part of the health economic data collection. There are no restrictions on any medications. Participants will not have participated in a cardiac rehabilitation programme over the previous 12 months, but other schemes such as smoking cessation, exercise referral and weight management schemes may be available and accessible to participants. Where participants have engaged in one or more of these it will be recorded.

Cardiac rehabilitation intervention

Usual care will be optimised as described above. In addition, participants in the intervention arm will be given access to 'Activate Your Heart' (www.activateyourheart.org.uk), which is an online interactive, secure and password-protected website designed for participants to use at home. The programme was coproduced with health-care professionals, patients/members of the public and software designers. The programme aims to deliver the five core components described by the British Association for Cardiovascular Prevention and Rehabilitation: health behaviour change and education, lifestyle risk factor management, medical risk factor management, psychosocial health and long-term management.⁴ The programme uses the following behaviour change techniques: goal setting, self-monitoring, feedback on behaviour, graded tasks, social reward, providing information about health consequences and reducing negative emotions. The programme is tailored to individual need, organised in four stages, which can be completed in 8 weeks, but access to the site and its features continues for 12 months. Before beginning the programme, each participant sees a member of cardiac rehabilitation staff who provides training on the website either face-to-face, or remotely by telephone or video consultation. The participant will complete an online registration form, which records their medical history and cardiac risk factors. A paper-based manual is available for participants who are unable or unwilling to use the online rehabilitation system.¹³ The website generates a tailored plan from this information, consisting of individualised goals for exercise, diet (eating more fruit and vegetables and reducing salt), emotions (managing stress, anxiety and low mood) and smoking. Adherence to these goals is regularly assessed by a short set of questions and feedback on performance. As the participant progresses through the programme, goals become increasingly difficult. Each participant records details of their daily exercise in an online diary, and regular feedback is given. Smokers are provided with feedback about the amount of money they are saving. The programme also contains written information about the health consequences of heart disease and risk factors (exercise, diet, sexual activity, driving, returning to work, hobbies, holidays, benefits, smoking, anxiety and mood). In addition, the programme reduces negative emotions by providing advice about stress reduction and anxiety management skills. There is access to an online discussion forum, and 'ask the expert' email facility. Cardiac rehabilitation staff can monitor participants' progress and respond to questions posted via email. After 12 weeks, the cardiac rehabilitation staff member will see the participant again to discuss progress and local exercise opportunities. Cardiac rehabilitation staff will report any safety events that they become aware of.

Outcomes

Participants will complete outcome measures at baseline, 6 and 12 months, administered by practice staff blinded

Table 1 ACTIVATE outcome measures

Patient completed measure—primary	Description	Range
UK version of Seattle Angina Questionnaire (SAQ-UK) Physical Limitation domain ¹⁵	Measures how daily activities are limited by angina over the past 4 weeks. Items are weighted equally, summed and transformed to a 0–100 score. Higher score indicates better functioning.	(0–100)
Patient completed measures—secondary		
SAQ-UK Angina Frequency and Perception and Treatment Satisfaction domains ¹⁵	Remaining two domains of SAQ-UK. Items are weighted equally, summed and transformed to a 0–100 score. Higher scores represent higher levels of health or satisfaction with treatment.	(0–100)
MRC dyspnoea scale ¹⁶	Five item questionnaire that assesses the degree of shortness of breath with common activities. One point is assigned to each activity associated with dyspnoea. Higher scores indicates more limitation due to dyspnoea.	(0–5)
Hospital Anxiety and Depression Scale ¹⁷	Measures anxiety (seven items) and depression (seven items) in patients with physical health problems. Two subscales with higher scores indicating greater anxiety or depression.	(0–21)
General Self-Efficacy scale ¹⁸	Measures optimistic self-belief to cope with a variety of difficult demands in life. Higher score indicates greater self-efficacy.	(10–40)
International Physical Activity Questionnaire ²⁰	This questionnaire supplements the accelerometer data by providing self-reported duration (minutes) and frequency (days) of physical activity in the previous 7 days in the domains: job related, transportation, housework, recreation and sitting.	Minutes of light, moderate and vigorous physical activity
Patient Completed Economic Measures		
EQ-5D-5L ²²	Health utility index with five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and five levels to give health states converted to a utility weight. Also Visual Analogue Score (VAS) for health state today	Health utility weight from 0 (death) to 1.0 (perfect health) also with negative values VAS (0–100)
Client Service Receipt Inventory ²³	Collects information about health service use, including medication, smoking cessation, diet management, weight control programmes and exercise referral schemes.	According to activity
Objective measures of physical activity and function		
Physical activity measured with the ActivPAL accelerometer ¹⁹	The ActivPAL device is a small, slim monitor worn on the thigh. It provides accelerometer-derived information about thigh position and acceleration to determine body posture (sitting, lying or upright), stepping and stepping speed (cadence), from which energy expenditure can be inferred. It will be worn for 7 days to measure step count, energy expenditure, duration of sedentary, light, moderate and vigorous physical activity. Participants will be asked to keep a wear diary documenting working hours, sleep, removal reasons and any other comments.	Step count, energy expenditure, duration of sedentary, light, moderate and vigorous physical activity
Incremental Shuttle Walk Test ²¹	Progressive walking test that requires the participant to walk up and down a 10m course, at a speed dictated by an audio signal. The time between signals is reduced every minute and there are 12 levels. The test ends when the participant either (a) is too breathless to maintain the required speed or (b) fails to complete a shuttle in the time allowed or (c) reaches 85% of the predicted maximal heart rate.	Metres walked

EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; MRC, Medical Research Council.

to participant allocation, which are from the standardised outcome measurement for patients with coronary artery disease, agreed by the International Consortium for Health Outcomes Measurement¹⁴ (tables 1 and 2). The primary outcome will be the UK Version of Seattle Angina

Questionnaire (SAQ-UK) Physical Limitation domain¹⁵ assessed at 12 months' follow-up. Participants completed secondary outcomes will include the remaining two domains of the SAQ-UK,¹⁵ Medical Research Council (MRC) dyspnoea scale,¹⁶ Hospital Anxiety and Depression

Table 2 ACTIVATE protocol schedule of forms and procedures

Procedures	Screening	Baseline/randomisation	7 days postrandomisation*	Trial intervention†	26 weeks postrandomisation	27 weeks postrandomisation*	52 weeks postrandomisation	53 weeks postrandomisation*
Eligibility screening and consent								
Assessment of eligibility	X							
Informed consent	X							
Confirm consent		X		X	X		X	
Randomisation		X						
Vital signs, height, weight, serum cholesterol	X							
Outcome measurement								
Seattle Angina Questionnaire		X			X		X	
MRC dyspnoea scale		X			X		X	
Hospital Anxiety and Depression Scale		X			X		X	
General Self-Efficacy scale		X			X		X	
EQ-5D-5L		X			X		X	
Client Service Receipt Inventory		X			X		X	
Physical activity measured with ActivPal accelerometer		X	X*		X	X*	X	X*
International Physical Activity Questionnaire			X			X		X
Incremental shuttle walk test		X			X		X	
Safety event reporting								
Monitoring of adverse events			X	X	X	X	X	X
Monitoring of serious adverse events			X	X	X	X	X	X

*Removal of ActivPal after 7 days.

†If randomised to intervention arm, participants will be invited to meet with member of cardiac rehabilitation staff who will train the participant on how to use the intervention. EQ-5D-5L, EuroQol-5 Dimensions-5 Levels.

Scale¹⁷ and General Self-Efficacy Scale.¹⁸ Physical activity will be measured where possible with the ActivPAL accelerometer¹⁹ for 7 days, supplemented by the International Physical Activity Questionnaire.²⁰ Cardiovascular fitness will be measured with the Incremental Shuttle Walk Test.²¹ Economic measures will be EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)²² and Client Service Receipt Inventory (CSRI)²³ as well as intervention costs. Baseline assessments will also include height, weight, blood pressure and serum cholesterol within the last 12 months.

Qualitative interviews will take place with a selection of participants at the end of the 12-week cardiac rehabilitation programme among those receiving the intervention, and between months 11 and 12 with the same sample of participants in the intervention group and an additional sample from the control group. These will gather data on trial participation and intervention design (see the 'Process evaluation' section).

Routinely collected demographic, clinical and recruitment data will include the number of participants who are eligible, willing to be randomised, withdraw after randomisation, complete outcome measurements, reasons for non-completion, age and gender.

Sample size

In order to detect the minimum clinically important difference of 8 points for the SAQ-UK physical limitation domain, assuming an SD of 25,¹⁵ with 90% power at the 5% significance level, 207 participants per group will be required (calculated using nQuery 8). In order to allow for up to 20% loss to follow-up, we aim to recruit 259 participants per group (518 in total). This sample size will give >99% power for secondary outcomes.

Recruitment and randomisation

Screening and consent

Written informed consent will be sought from potential participants who will be approached by the study team and invited to consider participation, following a search of their health record for eligibility. Where possible, potential participants will be introduced to the study during a face-to-face appointment with clinical staff. Potential participants can also be approached by a member of the local research team by written invitation and followed up by a phone call or text message after a week if there has been no response. Potential participants will be invited to attend a screening appointment. If they are eligible, and interested in the trial, the trial team researchers would then recruit participants following the trial's informed consent process. These assessments will be recorded in a screening log, including any reasons for ineligibility. Copies of the participant information sheet and informed consent form can be found in online supplemental appendix 2.

Randomisation procedures

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally

by the clinical trials unit to receive either usual care or tailored cardiac rehabilitation programme ('Activate Your Heart') plus usual care. Randomisation will have an allocation ratio of 1:1 and use a minimisation programme with a built-in random element, stratified by site and gender. Randomisation should occur no more than 2 weeks after confirming eligibility, obtaining informed consent and completing baseline assessments. Following allocation, participants will be notified of their allocation as soon as possible and then receive their randomised treatment allocation.

Blinding

This is a pragmatic trial comparing the 'Activate Your Heart' cardiac rehabilitation intervention with usual care, so it will not be possible to blind participants or their rehabilitation providers to treatment group allocation. However, collection of outcome measures and data analysis will be performed blind to treatment allocation. We will include a perception of allocation form for the person collecting the outcome measures to complete, to monitor the level of blinding achieved for these researchers.

Statistical analysis

Final analysis will take place once all participants have been followed up for 12 months, and the database has been locked. Analyses will be by 'intention to treat' for the primary and secondary outcomes on all randomised participants, in the group to which they were allocated, and for whom the outcomes of interest have been observed or measured. A full and detailed statistical analysis plan (SAP) will be finalised prior to any comparative analysis of the groups; the main features of the SAP are described briefly here.

Baseline

Demographic and clinical characteristics will be summarised separately using descriptive statistics for each randomised group to allow assessment of whether balance was achieved between randomised groups. This will include gender, ethnicity, socioeconomic status and other relevant PROGRESS-Plus characteristics.²⁴ No statistical testing of differences between groups will be performed.

Analysis of effectiveness

Primary and secondary outcomes at baseline, 6 months' and 12 months' follow-up will be summarised for each treatment group using descriptive statistics at each time point. If normally distributed, the difference between group means (with 95% CIs) will be reported from an analysis of covariance (ANCOVA) adjusted for baseline score and stratification factors.

Missing data and withdrawals

Predictors of missing data will be investigated using regression models (including age, living arrangements and comorbidities) and any significant predictors will be considered for inclusion in the models. In addition,

given the two assessment points at 6 and 12 months, a sensitivity analysis will be conducted using a joint modelling approach to check whether there is any difference in outcome, using longitudinal outcome rather than the outcome at 6 months or 12 months alone, between the randomised arms, adjusted for dropouts or missing values.

Instrumental variable regression

The causal impact of engagement with the intervention will be assessed in an instrumental variable regression model, using the number of stages completed in the rehabilitation programme, and the number of times that the programme is accessed, as measures of intervention use.

Mediation analyses

The hypothesised mechanism of change for the rehabilitation intervention is that participants' primary outcome (physical limitation) is mediated by self-efficacy and physical activity. If the rehabilitation intervention has a significant effect on the primary outcome ($p < 0.05$) in ANCOVA, causal mediation analysis will be used to determine whether these potential mediators predict change in SAQ-UK Physical Limitation domain at 12 months.

Economic analysis

The economic evaluation aims to estimate the cost-effectiveness of the 'Activate Your Heart' online rehabilitation programme plus optimal usual care when compared with optimal usual care alone. The rehabilitation programme will be fully costed using unit costs from a health service perspective. Unit costs will be obtained from national sources of reference costs and applied to information received from pilot questionnaires, namely salary band of cardiac rehabilitation therapists, time spent with the participant at the initial and final rehabilitation appointments, costs of travel and the costs of registering with the 'Activate Your Heart' online cardiac rehabilitation programme. Participants' health service activity data will be obtained from the CSRI²³ and unit costs from national sources.^{25 26} The costs of service use and the cost of the intervention will be added together for use in a cost-effectiveness analysis. We will account for the likely skewed nature of cost data in any regression carried out, by using Tweedie regression and/or beta distributions. The EQ-5D-5L scores will be converted into a health utility weight using UK norms. The base-case analysis will be conducted using the Van Hout scoring algorithm,²⁷ with sensitivity analysis conducted using the EQ-5D-5L value set for England.²⁸ Utility indices will be used to calculate QALYs over the 12-month trial period, using the area under the curve approach, with regression-based adjustment for baseline EQ-5D utility scores.^{29 30} The health economic results will initially be presented as disaggregated tables of costs alongside the health consequences. In these tables, we will also describe the costs and consequences of the rehabilitation intervention in

the underserved groups recruited, such as women, ethnic minorities and those of low socioeconomic status.

Costs and consequences will then be combined in a cost-utility analysis, to estimate the cost per additional QALY gained associated with each of the compared options. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the obtained results to sample variability and plausible variations in key assumptions and employed analytical methods. Cost-effectiveness acceptability curves will be constructed to show the probability that the intervention is cost-effective at specific thresholds of cost per QALY gained such as NICE threshold range of £20 000–£30 000 per QALY gained.³¹ We will develop a two-stage economic model; a decision tree to reflect the outcomes of the trial (within-trial economic evaluation) and a Markov state transition model to extrapolate the evolution of patient outcome and costs over a lifetime horizon (model-based economic evaluation). Value of information analysis will be conducted after taking into account uncertainty derived from decision-analytical models.

Process evaluation

The concurrent mixed-methods process evaluation will aim to identify and explain the mechanisms and processes that enabled or acted as a barrier to the implementation of the cardiac rehabilitation intervention.^{32 33} The process evaluation will help build a picture of how the intervention was carried out in reality and what factors shaped it. By conducting a process evaluation, it will be possible to identify if observed impacts are solely due to the cardiac rehabilitation programme, or if these impacts are a result of external and internal variables closely linked to the environment and the context in which the intervention takes place. More specifically, the process evaluation will examine the recruitment of sites and rehabilitation teams, recruitment and reach in participants (from the recruitment log), intervention delivery to individuals (coverage, intensity), participation, retention, response of individuals to the rehabilitation intervention (data collected by the 'Activate Your Heart' website), unintended consequences (adverse events and inequities), contextual factors and sustained motivation for behaviour change. The website will be examined for the degree of completion of the programme, the number of occasions that the website was accessed and the extent of the change in behaviour(s) recorded. There will be a particular focus on underserved groups (women, ethnic minorities, low socioeconomic status, other PROGRESS-Plus²⁴ characteristics and those without internet access or device).

Semistructured telephone or video interviews of participants ($n=30$) with purposive sampling to ensure diversity based on age, gender, functional impairment, treatment group, site, ethnicity and mode of delivery. A topic guide will be developed with the assistance of our Public Advisory Group and will ask about the acceptability of the rehabilitation programme and the barriers and facilitators of uptake and completion, such as family support,

health inequities, lack of facilities, lack of transport, etc. However, topic guides will be iterative and informed by earlier interviews and adapted accordingly. There will be a particular focus on the acceptability and barriers to implementation in underserved groups (women, ethnic minority and low socioeconomic status). Interviews will take place at the end of the 12-week cardiac rehabilitation programme among those receiving the intervention, and between months 11 and 12 in both groups. We will interview a minimum of 10 cardiac rehabilitation staff at different time points, to gain insight into the early, medium-term and longer-term delivery of the cardiac rehabilitation programme. All of the interviews will be audio recorded and fully transcribed. Participant contact with the online discussion forum, and the ‘ask the expert’ email facility will also be examined. We will also examine data collected routinely by the website for the purposes of the national audit for cardiac rehabilitation. Qualitative data will be analysed using a thematic analysis approach.³⁴ Quantitative data (recruitment logs, use of the website, recorded change in behaviours, national audit data) will be analysed using descriptive statistics to allow for the exploration of frequency of responses. All data sets will be synthesised in order to describe the complex nature of the enhanced rehabilitation intervention.

Patient and public involvement

There has been patient and public involvement (PPI) at all stages including developing the research question, choosing outcomes relevant to patients, commenting on the burden of the intervention and of trial participation. Two PPI coinvestigators are active members of the trial management group and help to convene a public advisory group which meets throughout the trial to advise on trial procedures, especially patient-facing materials, promotional videos in multiple languages and the dissemination plan. Members of the PPI group recorded voice-overs for the promotional video in different languages.

Ethics and dissemination

NHS research ethics approval was obtained from North of Scotland Research Ethics Committee, reference 21/NS/0116. The current protocol is version 5 (4 May 2023). Participants will provide written informed consent. A trial steering committee is providing overall supervision, and an independent data safety and monitoring committee is responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data.

All safety events will be recorded by researchers when they are made aware of the event by the participant, treating clinician or therapist. Adverse event reports and serious adverse events (SAEs) not related to the intervention will be entered on to the remote data entry system. Each SAE will be assessed by the relevant PI to determine whether it is related to the intervention. A related SAE will be assessed by the CI to determine whether it is expected. If the SAE is related and unexpected it will be

reported to the research ethics committee and sponsor in an expedited manner.

Reporting of the trial will be consistent with the Consolidated Standards for Reporting Trials (CONSORT) 2010 Statement (patient-reported outcomes and non-pharmacological interventions).³⁵ We will submit the final report to a peer-reviewed academic journal, according to our publication strategy and authorship policy. Research data will be available for secondary analysis on reasonable request.

Trial status

The first participant was recruited in July 2022. At the time of submission this trial had been open in 20 sites, with 10 more sites in preparation and had recruited 68 participants. Updated recruitment information can be found on the trial website (<http://activate-trial.org.uk>).

Author affiliations

¹Department of Primary Care and Mental Health, University of Liverpool, Liverpool, UK

²Department of Public Health Policy and Systems, University of Liverpool, Liverpool, UK

³Patient and Public Involvement, National Institute for Health and Care Research Applied Research Collaboration North West Coast, Liverpool, UK

⁴Department of Health Data Science, University of Liverpool, Liverpool, UK

⁵Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

⁶Liverpool Clinical Trials Centre, University of Liverpool, Liverpool, UK

⁷Institute of Applied Health Research, University of Birmingham, Birmingham, UK

⁸School of Nursing and Allied Health, Liverpool John Moores University, Liverpool, UK

⁹Department of Cardiovascular and Metabolic Medicine, University of Liverpool, Liverpool, UK

¹⁰Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK

¹¹School of Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

¹²Department of Respiratory Sciences, University of Leicester, Leicester, UK

Twitter Nefyn H Williams @NefynWilliams

Acknowledgements The authors would like to thank all of the principal investigators, research nurses, hospital staff, cardiac rehabilitation teams, leisure centre and exercise referral scheme staff: Dr Timothy Smith (Pendle Medical Partnership), Lisa Robson (Pendle View Medical Centre), Dr Tanveer Ahmed Dr Eve Frost (Shifa Surgery), Vishal Mashru (Billesdon Surgery, Croft Medical Centre, South Leicestershire Medical Group), Dr Selena Harris, Maisie Wrightson (Clarence House, Dr Jenny Liddell (Corwen Medical Centre), Dr Joanna Le Noury (Plas Menai Surgery), Dr Helen Alefounder, Dr Jessica Deacon, Lucie Parrie, Chantal Stewart (West End Medical Centre), Dr Nadja Van Ginneken, Theresa Nuttall, Jessica Keane (Brownlow Group), Dr Stephen Forster (Heswall and Pensby Group Practice), Dr David Lewis, Ann Kent, Carol Burgess, Carrie Geldhart (Vauxhall Primary Care Health Centre), Dr Helen Steiner, Stella Oldham (The Village Practice), Dr Rebecca Sinfeld, Hannah McGowan (St George's Medical Centre), Dr Gareth Powell, Michelle Morgan, Shirley Salter (Llan Healthcare), Dr Michael Fisher, Laura Pennington, Anthony Burns, Daniel Evans, Ahmed Elamin (Liverpool University Hospitals NHS Foundation Trust), Professor Sally Singh, George Hudson, Donna Alexander (Leicester Hospitals NHS Trust). Special thanks to the LCTC head of data management and monitoring (Clare Jackson), LCTC information systems team (Sharon Keane, Janet Harrison, Keith Kennedy, Tim Charter), trial co-ordinator assistant (Eleanor MacDonald) and quality assurance managers (Katie Neville, Claire Johnson), and to the North West Coast Clinical Research Network. We very much appreciate the work of the Trial Steering Committee Clare Wilkinson (chair), Robert Copeland (Independent Member) Rod Taylor (Independent Member), Katie Pike (Independent Statistician), Tracy Kitto (Independent Member), Keith Wilson (PPI Representative); Independent Data and Safety Monitoring Committee Umesh Chauhan (chair), Catriona Keerie (Independent Statistician), Ahmet Fuat (Independent Member), Adrian Taylor (Independent

Member); PPI team Terrence Comerford, Ray Martin, Erica Morgan, Hameed Khan, Naheed Tahir, Robert Smart and Lynn Hedgecoe.

Contributors NW is the chief investigator and grant holder, and SJS is the joint lead investigator and they are responsible for study design, conduct and analysis, have overall responsibility for the study and act as guarantors. SH is the trial co-ordinator and BH the senior trial co-ordinator overseeing day-to-day conduct, and providing methodological input. SD will write the statistical analysis plan. BC will write the health economic analysis plan. DL and PR will write the process evaluation analysis plan with NW. EM and TJC are Patient and Public Involvement co-investigators. GYHL, MF, TJ and KJ are coinvestigators responsible for study design, methodological oversight and provide cardiology (GYHL, MF), exercise science (DT), cardiac nursing (IJ) and primary care (NW, KJ) expertise. All authors were involved in drafting, revising and approving this manuscript.

Funding This work was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme, grant number 131015. It was supported by the NIHR Applied Research Collaboration North West Coast, NIHR Clinical Research Network North West Coast and NIHR Leicester Biomedical Research Centre. SJS and GYHL are NIHR Senior investigators. KJ is part funded by the NIHR Applied Research Collaboration West Midlands.

Disclaimer The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

Competing interests NW reports additional grants from NIHR HTA outside the submitted work and deputy chair of the NIHR HTA programme funding committee (commissioned research). DL reports additional grants from the NIHR outside the submitted work and investigator-initiated educational grants from BMS and Pfizer. DL has been a speaker for Bayer, Boehringer Ingelheim, and BMS/Pfizer and has consulted for BMS, and Boehringer Ingelheim; all outside the submitted work. GYHL has been a consultant and speaker for BMS/Pfizer, Medtronic, Boehringer Ingelheim and Daiichi-Sankyo. No fees were directly received personally. BC works part-time for Welsh Government outside of the submitted work. KJ was subcommittee chair of the NIHR Programme Grants for Applied Research until 2023. BH reports additional grants from the NIHR outside the submitted work and investigator-initiated grant from Novartis. All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

Nefyn H Williams <http://orcid.org/0000-0002-8078-409X>

Kate Jolly <http://orcid.org/0000-0002-6224-2115>

Deirdre Lane <http://orcid.org/0000-0002-5604-9378>

Gregory Y H Lip <http://orcid.org/0000-0002-7566-1626>

REFERENCES

- Eisen A, Bhatt DL, Steg PG, *et al.* Angina and future cardiovascular events in stable patients with coronary artery disease: insights from the reduction of atherothrombosis for continued health (REACH) registry. *J Am Heart Assoc* 2016;5:e004080.
- Knuuti J. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis & management of chronic coronary syndromes of the European society of cardiology. *Russ J Cardiol* 2019;25:119–80.
- National Institute for Health and Clinical Excellence. CG126. stable angina: management. Available: <https://www.nice.org.uk/guidance/cg126/resources/stable-angina-management-pdf-35109453262021> [Accessed 15 Sep 2023].
- British association for cardiovascular prevention and rehabilitation (BACPR) standards and core components for cardiovascular disease prevention and rehabilitation 2023 (4th edition). Available: https://www.bacpr.org/_data/assets/pdf_file/0021/64236/BACPR-Standards-and-Core-Components-2023.pdf [Accessed 15 Sep 2023].
- Fihn SD, Gardin JM, Abrams J, *et al.* 2012 ACC/AHA/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2012;60:e44–164.
- British Heart Foundation. The National audit of cardiac rehabilitation: quality and outcomes report. 2019. Available: <https://www.bhf.org.uk/informationsupport/publications/statistics/national-audit-of-cardiac-rehabilitation-quality-and-outcomes-report-2019> [Accessed 03 Jul 2020].
- Taylor RS, Sagar VA, Davies EJ, *et al.* Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014;2014:CD003331.
- Heran BS, Chen JM, Ebrahim S, *et al.* Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011:CD001800.
- Long L, Anderson L, Dewhurst AM, *et al.* Exercise-based cardiac rehabilitation for adults with stable angina. *Cochrane Database Syst Rev* 2018;2:CD012786.
- Devi R, Powell J, Singh S. A web-based program improves physical activity outcomes in a primary care angina population: randomized controlled trial. *J Med Internet Res* 2014;16:e186.
- National Institute for Health and Clinical Excellence. CG181. Cardiovascular disease: risk assessment and reduction, including lipid modification. Available: <https://www.nice.org.uk/guidance/cg181/resources/cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-pdf-35109807660997> [Accessed 15 Sep 2023].
- National Institute for Health and Clinical Excellence. Cg136. hypertension in adults: diagnosis and management. Available: <https://www.nice.org.uk/guidance/ng136/resources/hypertension-in-adults-diagnosis-and-management-pdf-66141722710213> [Accessed 15 Sep 2023].
- Warschauer M, Matuchniak T. New technology and digital worlds: analyzing evidence of equity in access, use, and outcomes. *Review of Research in Education* 2010;34:179–225.
- McNamara RL, Spatz ES, Kelley TA, *et al.* Standardized outcome measurement for patients with coronary artery disease: consensus from the International consortium for health outcomes measurement (ICHOM). *J Am Heart Assoc* 2015;4:e001767.
- Garratt AM, Hutchinson A, Russell I, *et al.* The UK version of the Seattle angina questionnaire (SAQ-UK): reliability, validity and responsiveness. *J Clin Epidemiol* 2001;54:907–15.
- MRC dyspnoea scale. Available: <https://www.ukri.org/councils/mrc/facilities-and-resources/find-an-mrc-facility-or-resource/mrc-dyspnoea-scale/> [Accessed 08 Apr 2023].
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
- Schwarzer R, Jerusalem M. *Generalized Self-Efficacy scale, Measures in health psychology: a user's portfolio. Causal and control beliefs.* Windsor, UK: NFER-NELSON, 1995.
- Edwardson CL, Winkler EAH, Bodicoat DH, *et al.* Considerations when using the activPAL monitor in field-based research with adult populations. *J Sport Health Sci* 2017;6:162–78.
- Craig CL, Marshall AL, Sjörström M, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
- Singh SJ, Morgan MDL, Scott S, *et al.* Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47:1019–24.
- Group E. EuroQol – a new facility for the measurements of health-related quality of life. *Health Policy* 1990;16:199–208.
- Database of Instruments for Resource Use Measurement. Client service receipt inventory (CSRI). Available: <http://www.dirum.org/instruments/details/44> [Accessed 31 Jan 2019].
- O'Neill J, Tabish H, Welch V, *et al.* Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *J Clin Epidemiol* 2014;67:56–64.

- 25 Department of Health. NHS reference costs 2015 to 2016. Available: <https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016> [Accessed 03 Jul 2020].
- 26 Curtis L, Burns A. Unit costs of health and social care 2019. personal social services research unit (PSSRU). Available: <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/> [Accessed 03 Jul 2020].
- 27 van Hout B, Janssen MF, Feng Y-S, *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value SETS. *Value Health* 2012;15:708–15.
- 28 Devlin NJ, Shah KK, Feng Y, *et al*. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018;27:7–22.
- 29 Glick H, Doshi J, Sonnad S, *et al*. *Economic evaluation in clinical trials*. Oxford: Oxford University Press, 2007.
- 30 Drummond ME, Sculpher MJ, Torrance GW, *et al*. Methods for the economic evaluation of health care programmes. In: *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 2 June 2005.
- 31 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. Available: <http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-themethods-of-technology-appraisal-2013-pdf> [Accessed 03 Jul 2020].
- 32 Oakley A, Strange V, Bonell C, *et al*. Process evaluation in randomised controlled trials of complex interventions. *BMJ* 2006;332:413–6.
- 33 Moore GF, Audrey S, Barker M, *et al*. Process evaluation of complex interventions: medical research council guidance. *BMJ* 2015;350:h1258.
- 34 Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3:77–101.
- 35 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* 2010;8:18.