ACTIVATE

Cardiac rehabilitation for people with chronic stable angina: a randomised controlled trial

Acronym: Angina Controlled Trial Investigating the Value of the 'Activate your heart' Therapeutic E-intervention (ACTIVATE)

ACTIVATE Protocol
8.0, 24/06/2025

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ISRCTN: 10054455

Research Ethics Ref: 21/NS/0116

Sponsor Ref: UoL001635

Funder Ref: NIHR: 131015

FUNDED BY
NIHR | National Institute for Health and Care Research

This study is funded by the NIHR Health Technology Assessment Programme (NIHR131015). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:** _____

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I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

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Karen Jennings-Wilding
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I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:** _____

Dr Susanna Dodd
Senior Statistician

General Information

This document describes the ACTIVATE trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Prof Nefyn Williams via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 13.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

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The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File

1 Table of Contents

Protocol Approval 2
1 Table of Contents 6
2 Protocol Overview 12
2.1 Schematic of Study Design 14
3 Roles and Responsibilities 15
Sponsor 15
Funder 15
3.1 Protocol Contributors 16
4 INTRODUCTION 17
4.1 Background 17
4.2 Rationale 17
4.3 Risk and Benefits 18
4.4 Objectives 18
5 STUDY DESIGN 20
5.1 Blinding 20
5.2 Who is blinded 20
5.3 Study Setting 20
6 ELIGIBILITY CRITERIA 22
6.1 Inclusion Criteria 22
6.2 Exclusion Criteria 22
6.3 Co-enrolment Guidelines 22
7 TRIAL TREATMENT/INTERVENTIONS 23
7.1 Introduction 23
7.2 Intervention Description 23
7.3 Assessment of Compliance 24
7.4 Concomitant Medications/Treatments and Specific Restrictions 24
7.5 Unblinding 24
8 OUTCOMES 25
Primary Outcome 25
Secondary Outcome(s) 25
9 PARTICIPANT TIMELINES AND ASSESSMENTS 27
9.1 Participant Identification and Screening 27
9.2 Informed Consent 27
Prospective Informed Consent Process 27
Language Considerations 28
9.3 Eligibility Assessment and Confirmation 28
9.4 Baseline Assessments 28
9.5 Randomisation / Registration 28
Randomisation System Failure 29
9.6 Intervention 29
9.7 Schedule for Assessments and Follow-up 29
9.8 Health Economic Evaluation 32
Health economic outcomes: 33
9.9 Process Evaluation 33
9.10 Process Evaluation Sub-study 34
9.11 Intervention Discontinuation and Participant Discontinuation/Withdrawal 34
Premature Discontinuation of Trial Intervention 34
Participant Withdrawal from Follow Up 35
Participant Transfer 35
Loss to Follow-up 35
9.12 End of Trial 35
Study Discontinuation 36
10 SAFETY REPORTING 37
10.1 Terms and Definitions 37

10.2 Assessment of Seriousness 38
10.3 Severity of Adverse Events....38
10.4 Assessment of “Causality” - Relationship to Trial Treatment/Intervention....38
10.5 Assessment of “Expectedness” 39
10.5.1 Reference Safety Information / Information used to Assess Expectedness....39
10.6 Time Period for Active Monitoring of Safety Events 39
10.7 Notes on Safety Event Recording....40
Notification of Deaths....40
10.8 Reporting Procedures....40
Flowchart for Site Reporting Requirements of Adverse Events....41
Reporting Safety Events to the LCTC....41
Follow-up After Adverse Events 41
10.9 Investigator Reporting Responsibilities....42
10.10 LCTC Responsibilities....43
Safety Reports....43
Urgent Safety Measures (USMs)....43
10.11 Contact Details and Out-of-hours Medical Cover 44
11 STATISTICAL CONSIDERATIONS 45
11.1 Sample Size....45
11.2 Method of Randomisation....45
Concealment and Implementation of Allocation Sequence 45
11.3 Blinding Considerations 45
11.4 Interim Analyses 45
11.5 Analysis Plan 46
12 DATA MANAGEMENT AND TRIAL MONITORING....47
12.1 Source Documents 47
12.2 Data Collection Methods....47
12.3 Monitoring 47
Central Monitoring 47
Clinical Site Monitoring 48
12.4 Risk Assessment 48
12.5 Confidentiality 48
12.6 Quality Assurance and Control 48
12.7 Records Retention 49
13 REGULATORY AND ETHICAL CONSIDERATIONS 50
13.1 Statement of Compliance 50
13.2 Ethical Considerations 50
13.3 Approvals....50
13.4 Protocol Deviation and Serious Breaches 51
Non-Serious breaches....51
Serious breaches....51
14 INDEMNITY....52
15 PUBLICATION AND DISSEMINATION 53
15.1 Publication Policy....53
Authorship....53
15.2 Dissemination to Key Stakeholders 53
15.3 Data Sharing....53
16 CHRONOLOGY OF PROTOCOL AMENDMENTS....54
16.1 Version 7.1 03/03/2025....54
• Change from 2 patient interviews for the intervention arm to 1 interview. 54
• Increase in timeframe allowed for the patient interview to allow this to be conducted at any point between 12 weeks in the trial and the 12-month follow-up point. 54
• Addition of a brief survey to be emailed to those who consented to be interviewed. 54
• Addition of sub-study....54
Information on study discontinuation and revised timelines have been added 54
Information on study discontinuation and revised timelines have been added 54
Grammatical errors and spelling mistakes have been corrected throughout 54
16.2 Version 7.0 31/10/2024 (this version was never implemented)....54

Amendment to the Process Evaluation section to allow for patient surveys and focus groups to take place. Information on staff and participant interviews has also been included 54
Information on study discontinuation and revised timelines have been added 54
Grammatical errors and spelling mistakes have been corrected throughout 55
16.3 Version 6.0 14/06/2024....55
Amendment to the trial protocol to allow for recruitment if technical issues arise with ActivPAL. Amendment to allow the interviewing of recruiting staff to take place. Amendment to allow for telephone follow ups to take place if pre-approved by the CI....55
16.4 Version 5.0 04/05/2023....55
Amendment to the trial protocol to remove named geographical areas of recruiting sites as sites outside of area are now taking part. Changes have been made to make the protocol applicable for recruitment in secondary care sites. Clarification on the collection of demographic data is also made throughout....55
16.5 Version 4.0 (20/02/2023) 55
Amendment to inclusion criteria: Evidence of myocardial ischaemia from either a past medical history of Acute Coronary Syndrome (ACS), Myocardial Infarction (MI) or revascularisation procedure at least 12 months in the past; or from imaging studies such as invasive coronary angiography, computerised tomography (CT) angiography, or myocardial perfusion testing....55
16.6 Version 3.0 (07/11/2022) 56
Additional information has also been added to the protocol to instruct sites to contact LCTC if the Incremental Shuttle Walking Test cannot be completed. 56
16.7 Version 2.0 (10/12/2021) 56
16.8 Version 1.0 (30/07/2021) 57
17 REFERENCES....58
18 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL....60

Glossary

AE	Adverse Event
BAME	Black, Asian and Minority Ethnic
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
EU	European Union
EUCTD	European Clinical Trials Directive
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NIHR CRN	National Institute for Health Research Clinical Research Network
NRES	National Research Ethics Service
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RACPC	Rapid Access Chest Pain Clinic
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

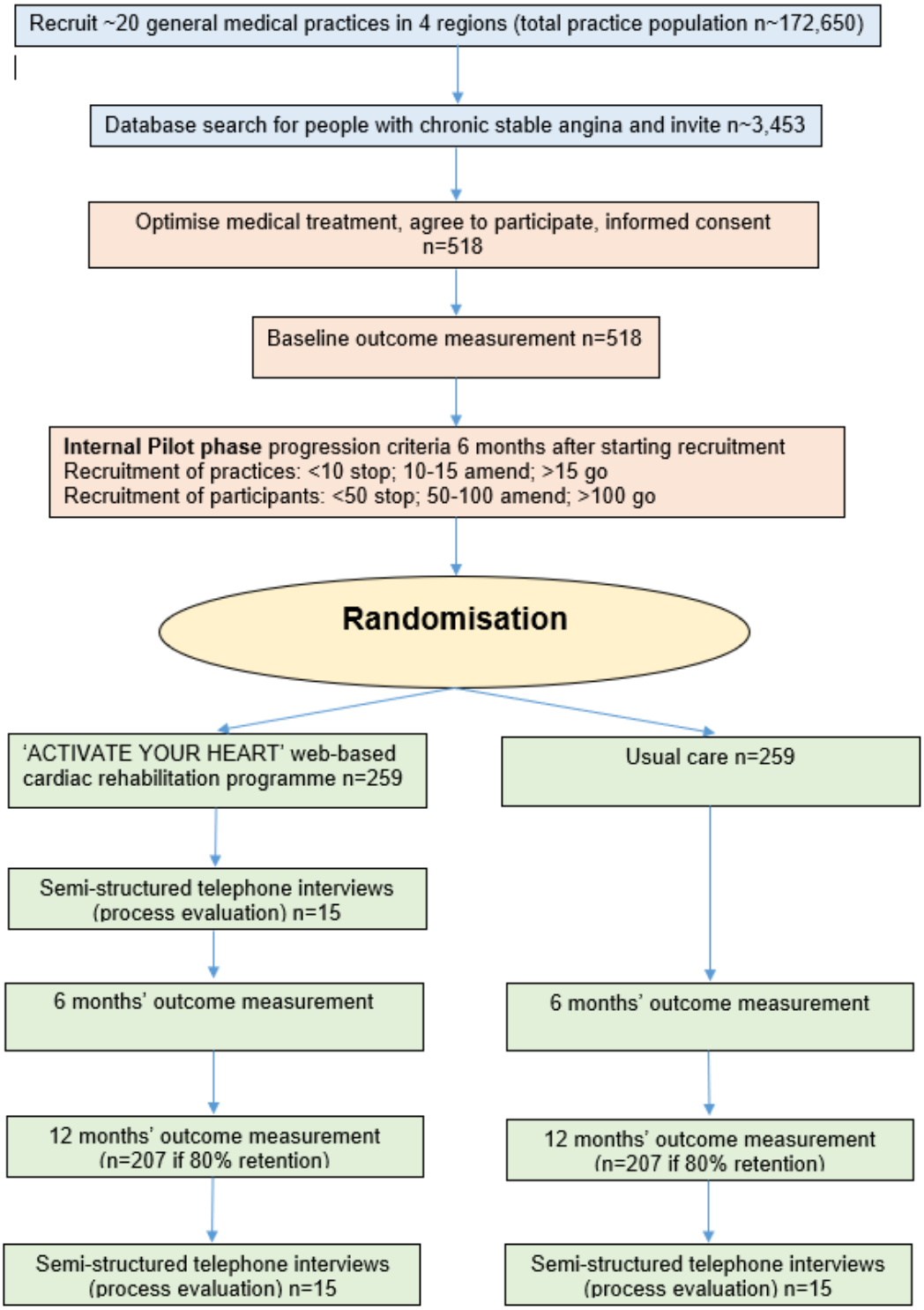
2 Protocol Overview

Full Title:	Cardiac rehabilitation for people with chronic stable angina: a randomised controlled trial
Acronym:	Angina Controlled Trial Investigating the Value of the 'Activate your heart' Therapeutic E-intervention (ACTIVATE)
Phase:	Phase III
Target Population:	Adult patients (age ≥18 years) with a diagnosis of chronic stable angina (including underserved groups: women; BAME groups; low socio-economic status; people with comorbid conditions).
Sample size:	Original target: 259 patients per group (518 in total) Final recruitment figure: 101
Inclusion Criteria:	• Adults with chronic stable angina with at least 2 out of 3 of the following features: constricting central chest pain, precipitated by exertion or emotional stress, relieved by rest or glyceryl trinitrate spray. • Evidence of myocardial ischaemia from either a past medical history of Acute Coronary Syndrome (ACS), Myocardial Infarction (MI) or revascularisation procedure at least 12 months in the past; or from imaging studies such as invasive coronary angiography, computerised tomography (CT) angiography, or myocardial perfusion testing. Revascularisation procedures not planned and treated 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 myocardial infarction (MI) within the last 12 months on electronic health record search. • History of revascularisation procedure within the last 12 months or planned at the time of study consent. • Participation in cardiac rehabilitation programme within the last 12 months or planned at time of study recruitment. • Significant co-morbidities (as deemed by person confirming eligibility) that would limit participation in the exercise-based rehabilitation programme. • Refractory angina on maximal medical therapy.

Study Centres and Distribution:	The population recruited will be from four regions: Liverpool, Lancashire, Leicester and North Wales, which are all areas of high disease burden with socio-economic deprivation. Some of these areas include high proportions of BAME groups and areas with low research activity in this field. Most participants will be identified by searching the computerised medical record databases of general medical practices for diagnostic Read codes. In addition, newly diagnosed patients will be identified from secondary care cardiology services.
Patient Study Duration:	Duration of follow-up: 12 months following randomisation in both arms
Study Duration	From: 01/02/2021 to 01/08/2024 (42 months including pre-award period of 6 months)
Intervention:	**Intervention:** 'ACTIVATE YOUR HEART' web based cardiac rehabilitation programme in addition to usual care
	Control: Usual care

Objectives:		
Primary:	To determine the effectiveness of the cardiac rehabilitation programme compared with usual care in terms of angina-related health status.	
Secondary:	To estimate the cost-effectiveness of the cardiac rehabilitation programme in a cost utility analysis with a health service perspective. To describe the implementation 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.	

2.1 Schematic of Study Design



3 Roles and Responsibilities

Sponsor

The Sponsor is legally responsible for the study. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.

Funder

This study is funded by NIHR HTA NIHR131015

Chief Investigator: Prof Nefyn Williams is the Chief Investigator for the trial and together with the co-lead investigator, Professor Sally Singh, is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of eCRFs/CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: (LCTC) at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, safety reporting, data management, randomisation, statistical analysis, participating site coordination and IMP management.

Oversight Committees

ACTIVATE trial is subject to oversight from the following committees:

Trial Management Group (TMG)
A TMG consisting of individuals responsible for the day-to-day running of the trial will be established and will be responsible for overseeing the progress of the trial throughout all of its phases and will meet regularly every one to two months. The TMG will include the chief investigator, the co-lead investigator, other co-investigators, trial manager, trial statistician, two PPI representatives and other members of the Liverpool Clinical Trials Centre. The group will ensure that the protocol is adhered to, will take appropriate action to safeguard participants and ensure the overall quality of the study.

Trial Steering Committee (TSC)
A TSC meeting will be held every 6 months to provide overall supervision of the trial and ensure that the trial is conducted to the rigorous standards set out in the guidelines for good clinical practice. The TSC will consist of an independent chair, an independent statistician, other independent members who are experts in cardiac rehabilitation, two patient representatives, chief investigator, co-lead investigator, study manager, members observing from the University of Liverpool as the sponsoring organisation, and representatives from the clinical research networks. It will consider trial progress and adherence to the protocol and will provide advice to the trial team. The TSC will make recommendations to the TMG and will report to the sponsor and the funder.

Independent Data and Safety Monitoring Committee (IDSMC)
An IDMSC will consist of an independent chair, an independent statistician and other independent experts in cardiac rehabilitation. The IDSMC will consider trial progress, recruitment and retention. It will oversee patient safety, data monitoring, quality assurance, trial conduct and any new information relevant to the trial. The IDMSC will report to the TSC.

3.1 Protocol Contributors

Name	Affiliations	Contribution to protocol
Nefyn Williams	University of Liverpool	Chief Investigator
Sally Singh	University of Leicester	Co-lead Investigator
Katie Neville	University of Liverpool	Head of Quality Assurance & Regulatory Affairs
Susanna Dodd	University of Liverpool	Senior Statistician
Ben Hardwick	University of Liverpool	Supervising Trials Manager
Clare Jackson	University of Liverpool	Head of Data Management & Monitoring
Kieran Crabtree	University of Liverpool	Trial Co-ordinator Assistant
Gregory Lip	University of Liverpool	Cardiology and trials expertise
Deirdre Lane	University of Liverpool	Qualitative research expert
Rui Duarte	University of Liverpool	Health economist
Kate Jolly	University of Birmingham	Primary care and trials expertise
Sophie Hennessy	University of Liverpool	Trials Manager
Dawn Greene	University of Liverpool	Trial Manager

4 INTRODUCTION

4.1 Background

Angina is chest pain caused by atherosclerosis of coronary arteries, which restricts blood flow to the myocardium, especially on exertion. Current management consists of behaviour change, drug treatment and revascularisation procedures. Cardiac rehabilitation is routinely offered to patients following myocardial infarction or revascularisation procedures, but not for chronic, stable angina. Cardiac rehabilitation consists of lifestyle change, exercise training, education and mental health interventions. The National Institute for Health and Care Excellence will not support cardiac rehabilitation for chronic stable angina until stronger evidence of effectiveness and cost-effectiveness is available.

4.2 Rationale

Angina is a common cardiac condition usually caused by atherosclerosis of coronary arteries, which restricts blood flow to the myocardium, especially when oxygen demand is increased during exercise. Angina is stable if the chest pain symptoms occur predictably on physical exertion, or with emotion, and settle promptly with rest or after taking sublingual nitrate medication. Affected individuals are at increased risk of acute coronary events such as myocardial infarction (MI), although recent evidence has suggested that with modern medical care the magnitude of this risk is quite low, with major adverse coronary event rates less than 2% per year [1]. Management consists of behaviour change advice, drug treatment and revascularisation procedures.

Cardiac rehabilitation is routinely offered to patients following MI or revascularisation procedures, including percutaneous coronary interventions (PCI), and consists of co-ordinated activities to improve the underlying cause and restore optimal functioning and slow, or reverse, disease progression [2]. The most important 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 [3,4], such programmes are not offered routinely to people with chronic stable angina [5]. 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 [6]. Although there is 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 [5].

There has been one Cochrane systematic review of exercise-based cardiac rehabilitation for adults with stable angina [9], which identified seven 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% confidence intervals [CI] 0.2 to 0.7), and uncertainty about the effect on all-cause mortality, acute MI, cardiovascular-related hospital admissions, quality of life (QoL) and cardiac rehabilitation-related adverse events. These trials 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 co-morbid conditions. A PubMed search for studies published after the Cochrane review from 01/01/2018 to 30/05/2020, using the search terms cardiac rehabilitation AND angina pectoris, stable [MeSH Terms] did not find any additional studies.

There have been six Cochrane reviews for adults with other types of heart disease. These concluded that exercise-based cardiac rehabilitation for low-risk individuals with cardiac failure, after MI or revascularisation procedures was safe and resulted in reduced hospital admissions (risk ratios 0.69 and 0.75 respectively) and increased QoL [10,11]. Education interventions and psychological interventions on their own improved QoL compared with usual care [12,13]. Home-based or centre-based programmes were equally effective in terms of QoL [14]. Adherence to cardiac rehabilitation was superior in the home settings and healthcare costs were similar. Interventions that promoted uptake of cardiac rehabilitation programmes included: structured contacts with a therapist or nurse, early appointments after discharge, motivational letters, gender-specific programmes and modified programmes for older people [15]. Adherence was improved by self-monitoring, action planning and tailored counselling by cardiac rehabilitation staff. Focus groups of people participating

in a home-based and hospital-based programmes found advantages in both. Participants valued the written manual and individual support from the home programme, and the benefit of group participation and support of others from hospital programme.

A small RCT (n=94) of a web-based cardiac rehabilitation programme ('ActivateYourHeart') demonstrated that it was possible to provide cardiac rehabilitation to people with chronic stable angina [16]. Trial methods were feasible in terms of recruitment rate (15.5%) and retention at 6 months (78%) and outcome measurement. It found statistically significant intervention effects after 6 weeks for increased daily moderate activity of 28.6 minutes (95% CI 6.0 to 51.2), step count, energy expenditure, self-efficacy, emotional QoL, angina frequency, and reduced daily sedentary activity of 31 minutes (95% CI 7 to 55), and body weight of 1.0 Kg (95% CI 0.2 to 1.8) [17]. At 6 months there were statistically significantly lower levels of angina frequency with an effect size 0.63 and increased social QoL with an effect size 0.6. The main barrier to participation was no internet access and BAME groups were underrepresented (only 8% of participants). In terms of fidelity, all participants completed 3 out of 4 stages, but only 40% completed the programme. This RCT was underpowered for all domains of the Seattle Angina Questionnaire [18], which is a core outcome measure for angina [19]; there was no economic evaluation and no process evaluation of the programme implementation. A larger RCT would need to test longer-term effectiveness in terms of angina-related health status and cost-effectiveness.

4.3 Risk and Benefits

4.3.1 Potential Risks

The risks of the online rehabilitation intervention ‘ActivateYourHeart’ are minimal. The programme uses behaviour change techniques such as goal setting, self-monitoring, providing feedback on behaviour, graded tasks, social reward, providing information about health consequences and reducing negative emotions. At the beginning of the programme, each user completes an online form providing information about their medical history and current cardiac risk factors. This information is used to set individualised tailored goals focussing on exercise, diet, emotions and smoking. There may be a risk of injury or provoking an episode of angina when exercising, however the physical activity goals are carefully graded. Programme users can also contact the cardiac rehabilitation nurses for advice and support via an online email link or by joining an online scheduled weekly chat room. Experience from using the ‘ActivateYourHeart’ programme for cardiac rehabilitation has confirmed its excellent safety record.

More detail regarding management of risks associated with this trial are detailed in a separate Risk Assessment maintained in the Trial Master File.

4.3.2 Potential Benefits

Cardiac rehabilitation has the potential to improve angina related health status, mental health, QoL, physical activity levels and physical functioning in people with chronic stable angina.

4.4 Objectives

The aims of the project are to improve the health of people with long-term angina chest pain, that is not getting worse and does not require an operation, but which still limits daily activities. We aim to assess whether a rehabilitation programme is more effective than usual care in improving the health of people with long-standing stable angina, whether the programme is good value for money, and whether it is delivered as intended.

4.4.1 Primary Objective

The primary objective is to determine the effectiveness of the ‘ActivateYourHeart’ 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.

4.4.2 **Secondary Objective(s)**

- 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.

5 STUDY DESIGN

Multisite, pragmatic, parallel-group, two-arm, superiority, randomised controlled trial (RCT), with 1:1 allocation ratio, stratified by gender and recruitment site (GP practice/secondary care site). Blinded outcome assessment; unblinded participants, clinicians and statistical analysis. Internal pilot phase. Concurrent economic evaluation with a health service perspective. Embedded process evaluation using mixed methods that will include an examination of barriers leading to health inequities.

An internal pilot phase will assess recruitment of practices and participants after the first 6 months of recruitment. The internal pilot will include the following progression criteria:

Trial Recruitment	**Red (Stop)**	**Amber (Amend)**	**Green (Go)**
Recruitment rate/site/month	<2	≥2 to <4	≥4
Number of practice sites opened	0-9	10-15	16-20

5.1 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 clinicians to treatment group allocation. Collection of outcome measures will be performed blind to treatment allocation. Statistical analysis will not be blinded. We will include a perception of allocation form for the person collecting the outcome measures to complete, in order to monitor the level of blinding that was achieved for these researchers.

The person collecting the outcome measures will not be informed which group the patient participant has been randomised to.

5.2 Who is blinded

Members of staff collecting outcome measures at follow-up visits will be blinded to treatment allocation.

5.3 Study Setting

Most participants will be recruited from primary care, along with those newly diagnosed from secondary care cardiology services. Participants can also be recruited from secondary care sites via Rapid Access Chest Pain Clinics (RACPC) or as inpatients. The rehabilitation intervention will be delivered in the community or health and leisure services by appropriately qualified staff. The participants will be recruited from areas of high disease burden with socio-economic deprivation. Some of these areas include high proportions of black, Asian and minority ethnic (BAME) groups and areas with low research activity in this field.

5.3.1 Selection of Participating Sites

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in a separate document 'ACTIVATE Site Suitability Assessment' maintained in the Trial Master File (TMF).

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the ACTIVATE trial and will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the CTU. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

5.3.2 **Selection of Principal Investigators**

Principal Investigators will be required to demonstrate equipoise, relevant experience and commitment during early-stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance with the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable co-investigator should be identified at each site to deputise in case of PI absence.

6 ELIGIBILITY CRITERIA

The ACTIVATE trial aims to recruit 518 patients based on sample size calculations described in Section 11.1.1. All patients must provide written, informed consent before any study procedures occur (see Section 9.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below.

6.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

- Adults with chronic stable angina with at least 2 out of 3 of the following features: constricting central chest pain, precipitated by exertion or emotional stress, relieved by rest or glyceryl trinitrate spray.
- Evidence of myocardial ischaemia from either a past medical history of Acute Coronary Syndrome (ACS), Myocardial Infarction (MI) or revascularisation procedure at least 12 months in the past; or from imaging studies such as invasive coronary angiography, computerised tomography (CT) angiography, or myocardial perfusion testing.
- Revascularisation procedures not planned and treated with medical treatments only, including people with previous MI, or previous revascularisation procedure who may have attended cardiac rehabilitation in the past.

6.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

- History of myocardial infarction (MI) within the last 12 months on electronic health record search.
- History of revascularisation procedure within the last 12 months or planned at the time of study recruitment.
- Participation in a cardiac rehabilitation programme within the last 12 months or planned at time of study recruitment.
- Significant co-morbidities (as deemed by person confirming eligibility) that would limit participation in the exercise-based rehabilitation programme.
- Refractory angina on maximal medical therapy.

6.3 Co-enrolment Guidelines

Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the ACTIVATE trial, this must first be discussed with the CTU who will contact the Chief Investigator (Nefyn Williams).

7 TRIAL TREATMENT/INTERVENTIONS

7.1 Introduction

We plan to compare cardiac rehabilitation in addition to usual care (intervention) with usual care alone (standard of care).

7.2 Intervention Description

7.2.1 **Arm A – Intervention**

Usual care will be optimised as described above. In addition, participants in arm B will be given access to 'ActivateYourHeart' (www.activateyourheart.org.uk), which is an online interactive, secure and password-protected website designed for participants to use at home. The programme was co-produced with health care professionals, patients/members of the public and software designers. The programme aims to deliver the seven core components described by the British Association for Cardiovascular Prevention and Rehabilitation (BACPR): health behaviour changes and education, lifestyle risk factor management, cardioprotective therapies, medical risk factor management, psychosocial health, long-term management, audit and evaluation. 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 and is in four stages, which can be completed in 8 weeks, but access to the site and its features continue for 12 months.

Before beginning the programme, each participant sees a member of cardiac rehabilitation staff who provides face-to-face training on the website and a written user manual. In case of COVID-19 restrictions, this could be performed by remote 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. Participants using the paper-based manual will be requested to complete a questionnaire to record how often they used the programme. The website generates a tailored plan from this information, consisting of individualised tailored goals for exercise, diet (eating more fruit and vegetables and reducing salt), emotions (managing stress, anxiety and low mood) and smoking.

Adherence with these goals is regularly assessed by a short set of questions and feedback on performance. As the user progresses through the programme, goals become increasingly difficult. Each user 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 will report any safety events that they become aware of through online discussions forums. Cardiac rehabilitation staff can monitor participants' progress and respond to questions posted via e-mail. After 12 weeks the cardiac rehabilitation staff member will see the participant again for a face-to-face consultation to discuss progress and local exercise opportunities. In case COVID-19 restrictions persist, this could also be performed by remote telephone or video consultation. We will develop a paper-based alternative for people who cannot or are reluctant to use the website. These participants will complete a questionnaire to record how often they access the paper version of the intervention.

7.2.2 **Arm B – Standard of Care**

Usual care will be optimised in all participants. All participants will be seen by their healthcare provider, who will use a protocol informed by NICE guidance [6] 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 guidance [6] 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 consist 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 myocardial infarction or stroke, include aspirin, angiotensin-converting enzyme inhibitor (especially if diabetes is present), statins in line with NICE guidance (and treatment targets) on lipid modification, and anti-hypertensives in line with NICE guidance (and treatment targets) on hypertension.

7.3 Assessment of Compliance

Participants recruited to the intervention arm will complete an online registration form, which records their medical history and cardiac risk factors. The website generates a tailored plan from this information, consisting of individualised tailored goals for exercise, diet (eating more fruit and vegetables and reducing salt), emotions (managing stress, anxiety and low mood) and smoking. Adherence with these goals is regularly assessed by a short set of questions and feedback on performance. As the user progresses through the programme, goals become increasingly difficult. Each user records details of their daily exercise in an online diary, and regular feedback is given. Cardiac rehabilitation staff can monitor participants' progress using the ActivateYourHeart system. Participants use of the rehabilitation programme will be assessed as part of a concurrent process evaluation. For those participants who use the paper-based manual rather than the website, we will examine the manual for degree of completion and provide participants with a questionnaire to complete to record compliance

7.4 Concomitant Medications/Treatments and Specific Restrictions

Concomitant medication will be recorded as part of the health economic data collection. There are no restrictions on any medications. As this is a pragmatic RCT, we will not place restrictions on usual care. 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.

7.5 Unblinding

In the event that the researcher collecting outcome data becomes unblinded to treatment allocation they must notify the LCTC Trial Co-ordinator.

8 OUTCOMES

We will collect the following patient completed outcome measures from the standardised outcome measurement for patients with coronary artery disease, agreed by the International Consortium for Health Outcomes Measurement [19]. The process evaluation outcomes are described in section 9.9.

Primary Outcome

The primary outcome will be the UK Version of Seattle Angina Questionnaire (SAQ-UK) Physical Limitation domain [18] measured at baseline, 6 months and 12 months. The SAQ-UK comprises 14 items that form 3 scales: physical limitations, anginal frequency and perception and treatment satisfaction. Items are weighted equally and summed and transformed to a 0-100 score. The physical limitation domain measures how daily activities are limited by symptoms of angina over the past 4 weeks. It is scored from 0 to 100 with a higher score indicating better functioning. It has been positively correlated with patients' exercise treadmill test duration.

Secondary Outcome(s)

Objectives Effectiveness:	**Outcome Measures**	**Timepoint(s) of evaluation**
UK Version of SAQ-UK Angina Frequency and perception and Treatment Satisfaction domains	These are the remaining two domains of the SAQ-UK, which are all scored from 0 to 100. The angina frequency and perception and treatment satisfaction domains. Items are weighted equally and summed and transformed to a 0-100 score. Higher scores represent higher levels of health or satisfaction with treatment.	Baseline, 6 months and 12 months
MRC dyspnoea scale	This is a five-item questionnaire that assesses a patients' level of shortness of breath with common activities. One point is assigned to each activity associated with dyspnoea. Scores range from 0 to 5, where 0 indicates no dyspnoea with activity and 5 indicates significant limitations due to dyspnoea.	Baseline, 6 months and 12 months
Hospital Anxiety and Depression Scale (HADS)	This scale measures anxiety (7 items) and depression (7 items) in patients with physical health problems. The two sub-scales have a range of 0 to 21 each with higher scores indicating increased anxiety or depression. The HADS was designed for use in the hospital setting but has been used successfully with the general population.	Baseline, 6 months and 12 months
Generalised Self-Efficacy scale	This is a measure to assess optimistic self-beliefs to cope with a variety of difficult demands in life. The scores range from 10 to 40 with higher scores indicating increased self-efficacy.	Baseline, 6 months and 12 months
Physical activity measured with the ActivPAL accelerometer	The ActivPAL device is a small, slim monitor worn on the thigh. It can provide accelerometer-derived information about thigh position and acceleration to determine body posture (sitting, lying or upright) and transition between these postures, 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	Baseline, 6 months and 12 months

	physical activity. Participants will be asked to keep a wear diary documenting working hours, sleep, removal reasons and any other comments. It will be supplemented by the International Physical Activity Questionnaire [20] administered when the ActivPal is removed, which provides self-reported duration (minutes) and frequency (days) of physical activity in the previous 7 days in the domains: job-related, transportation, housework, recreation, sitting.	
International Physical Activity Questionnaire (IPAQ)	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.	7 days, 27 weeks and 53 weeks post randomisation (or at baseline, 6 months and 12 months if ActivPAL not fitted)
Incremental Shuttle Walk Test	This is a progressive walking test that requires the participant to walk up and down a 10 m course identified by two cones inset 0.5 m from either end to avoid the need for abrupt changes in direction. The speed at which the patient walks is dictated by an audio signal. The time between signals is reduced every minute and there are 12 levels. The end of the test is determined by either (a) when the participant 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. Every effort should be made to perform this test at site. If sites are unable to perform the test due to lack of space at site, they must inform the trial management team prior to greenlight.	Baseline, 6 months and 12 months
Health Economics:		
Quality Adjusted Life Years calculated from EQ-5D-5L	This is an index of health-related quality of life, which gives a weight to different health states. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and five levels. Responses to the EQ-5D will be converted into a health utility index using a set of weights to reflect UK population preferences for the particular health state. In line with NICE's position statement, base-case analysis will be conducted using the Van Hout scoring algorithm [21]. Quality adjusted-life years (QALYs) will be calculated from these utility weights using an area under the curve method [22,23].	Baseline, 6 months and 12 months
Health service activity using the Client Service Receipt Inventory (CSRI)	The CSRI will be used to collect retrospective information about participants' use of health services and medication use, including smoking cessation, diet management, weight control programmes and exercise referral schemes.	Baseline, 6 months and 12 months

9 PARTICIPANT TIMELINES AND ASSESSMENTS

9.1 Participant Identification and Screening

A pseudonymised screening log of patients who are assessed for eligibility but not randomised will be maintained as this will provide important information for monitoring purposes.

9.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in CTU coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be re-affirmed throughout the trial and all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent, they do not have to give a reason.

Prospective Informed Consent Process

Written informed consent will be sought from patients who will be approached by the study team and invited to consider participation following a search of the primary care computerised medical record database. Patients in secondary care settings can be identified in RACPC clinics, as inpatients or via a computerised medical record search.

In primary care settings possible patients should be introduced to the study during a GP appointment or by arranging an appointment for medication review and discussing the study. If it is not possible to speak to the patient during a GP appointment, then patients can 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. Patients will be invited to attend a screening appointment. Patients identified in secondary care settings can be approached directly in RACPC clinics or on the wards by members of the research team to discuss the study.

A written information sheet that forms part of the ethically approved Participant Information Sheet and Consent form will be provided. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the patient has fully understood all the information and will ask if they are happy to consent to participation in the trial. Participants will be given as much time as they need to decide whether to take part or not.

Where this is the case, written informed consent will be obtained by means of a dated patient's signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the patient for their information,
- One copy transferred to the CTU via post or secure email.
- One copy filed in the participant's medical records paper/electronic.

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

Language Considerations

Patient information sheets and consent forms will be translated into Bengali, Polish, Punjabi, Urdu and Welsh languages.

9.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until fully informed consent is documented. Eligibility criteria are described in detail in 6.

Eligibility confirmation must be documented in the participant's medical notes and then on the trial's Eligibility eCRF. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation).

9.4 Baseline Assessments

Baseline assessments should be completed as per the Schedule of Assessments (Section 9.7) in order to accurately complete the Baseline eCRF and collect the necessary information for the trial analyses. This includes the following assessments:

- Height and Weight
- Blood pressure
- Serum cholesterol
- Fitting of accelerometer (if there are technical issues with device or software then this can be omitted)
- Primary and secondary outcome measures listed in section 8
- Demographic data as listed in the eCRF

Routinely collected information e.g. medical history / vital signs / relevant blood test results etc. can be transcribed from the patient's medical notes into the eCRF once appropriate consent has been obtained.

The patient can proceed to randomisation once all the baseline assessments have been completed.

9.5 Randomisation / Registration

Participants will be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the CTU to receive either usual care or tailored cardiac rehabilitation programme (ActivateYourHeart). The randomisation will have an allocation ratio of 1:1. Randomisation will use a minimisation program with a built-in random element, stratified by site and gender.

Randomisation should occur no more than 2 weeks after:

a) Eligibility criteria have been fulfilled (and eligibility confirmed)
b) Fully informed written consent has been obtained (and appropriately documented)
c) Baseline assessments have been completed.

A personal login username and password, provided by the LCTC will be required to access the randomisation system. Designated research staff will be issued with their personal login and password upon completion of training in the use of the system. This training will be coordinated by the LCTC.

When the system requirements (i.e. consent and eligibility) are confirmed the participant treatment allocation and a unique study number (randomisation number) will be displayed on a secure webpage. An automated email confirmation will be sent to the authorised randomiser, Principal Investigator (PI), members of the research team and trial coordinator.

Randomisation: web access www.activate-trial.org.uk

If there are any problems with the randomisation systems contact the coordinating CTU on 0151 794 9765 or via email on activate.trial@liverpool.ac.uk

(Note that the coordinating CTU is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Following allocation, participants should be notified of their allocation as soon as possible and then should receive their randomised treatment allocation as described in Section 7.2

Randomisation System Failure

In the event of a randomisation system failure, the centre should contact the coordinating team at the CTU (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem cannot be resolved the coordinating CTU will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a stand-alone PC at CTU.

9.6 Intervention

Once the research team are made aware of the treatment allocation participants who are randomised to ActivateYourHeart will receive details on how to access the system and training on how to use it. Participants will be given these details when they meet with a member of the research team. Paper copies can be provided to patients who are not able to access the system online.

9.7 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Schedule of Assessments:

	Screening	Baseline / Randomisation	7 days post randomisation*	Trial intervention**	26 weeks post randomisation	27 weeks post randomisation*	52 weeks post randomisation	53 weeks post randomisation*
Eligibility screening and consent								
Assessment of eligibility criteria	X							
Written and informed consent	X							
Confirm consent		X		X	X		X	
Randomisation		X						
Vital signs, height, weight and serum cholesterol		X			X		X	
Demographic data		X						
Outcome measurement - patient								
Seattle Angina Questionnaire (SAQ-UK)		X			X		X	
MRC dyspnoea scale		X			X		X	
Hospital Anxiety and Depression Scale (HADS)		X			X		X	
Generalised Self-Efficacy scale		X			X		X	
Physical activity measured with the ActivPAL**** accelerometer		X	X*		X	X*	X	X*
IPAQ*****			X			X		X
Incremental Shuttle Walk Test***		X			X		X	
EQ-5D-5L		X			X		X	
Client Service Receipt Inventory (CSRI)		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.
*** Every effort should be made to perform this test at site. If sites are unable to perform the test due to lack of space at site they must inform the trial management team prior to greenlight.

**** If there are technical issues at site with ActivPAL software downloads or with the devices themselves the ActivPAL can be omitted
***** If the ActivPAL is not fitted the IPAQ can be completed at baseline, 6 months and 12 months

Screening Visit
Potential patients will be invited to attend a screening visit. During the screening visit eligibility criteria will be completed and written and informed consent obtained if patient is eligible and agrees to participate.

Baseline Visit
Prior to randomisation, baseline assessments should be completed, the following activities should occur:

- Vital signs, height, weight and serum cholesterol
- SAQ-UK
- MRC dyspnoea scale
- HADS
- Generalised Self-Efficacy scale
- Physical activity measured with the ActivPAL accelerometer (to be removed after 7 days) (if there are technical issues with device or software then this can be omitted)
- Incremental Shuttle Walk Test
- EQ-5D-5L
- CSRI
- Demographic data collection

Removal of Accelerometer
The following activities should occur 7 days post randomisation:
- ActivPAL accelerometer removed if fitted at previous visit.
- IPAQ

Follow-up Visit 1
The following activities should occur at the 26 weeks post-randomisation follow-up visit:

- Vital signs, weight and serum cholesterol
- SAQ-UK
- MRC dyspnoea scale
- HADS
- Generalised Self-Efficacy scale
- Physical activity measured with the ActivPAL accelerometer (to be removed after 7 days) (if there are technical issues with device or software then this can be omitted)
- Incremental Shuttle Walk Test
- EQ-5D-5L
- CSRI

Follow up visits may take place over the telephone if pre-approved by the Chief Investigator. ISWT and ActivPAL will not be performed at telephone follow ups.

Removal of Accelerometer
The following activities should occur 7 days after follow-up visit 1:
- ActivPAL accelerometer removed if fitted at previous visit.
- IPAQ

Follow-up Visit 2
The following activities should occur at the 52 weeks post randomisation follow-up visit:

- Vital signs, weight and serum cholesterol
- SAQ-UK
- MRC dyspnoea scale
- HADS
- Generalised Self-Efficacy scale

- Physical activity measured with the ActivPAL accelerometer (to be removed after 7 days) (if there are technical issues with device or software then this can be omitted)
- Incremental Shuttle Walk Test
- EQ-5D-5L
- CSRI

Follow up visits may take place over the telephone if pre-approved by the Chief Investigator. ISWT and ActivPAL will not be performed at telephone follow ups.

Removal of Accelerometer

The following activities should occur 7 days after follow-up visit 2:

- ActivPAL accelerometer removed if fitted at previous visit.
- IPAQ

ActivPAL use

If sites are unable to download the ActivPAL software due to local Data Protection restrictions the use of the ActivPAL can be omitted until the software is successfully downloaded. If there are issues with the devices at site and they are unable to be connected or data is unable to be downloaded, the ACTIVATE trial manager must be informed. In these instances, the ActivPAL devices can me omitted from the visit and participants can continue in the trial as normal. The participant number and device serial number must be sent to the ACTIVATE trial manager so the issues can be logged, and replacement devices can be sent if required.

9.8 Health Economic Evaluation

The economic evaluation aims to estimate the cost-effectiveness of the 'ActivateYourHeart' online rehabilitation programme plus usual care when compared to 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 'ActivateYourHeart' online cardiac rehabilitation programme. Participants' health service activity data will be obtained from the CSRI and unit costs from national sources [24, 25]. The costs of service use and the cost of the intervention will be added together for use in a cost-effectiveness analysis. 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 [21], with sensitivity analysis conducted using the EQ-5D-5L value set for England [26]. The utility indices will be used to calculate QALYs over the 12 months trial period, using the area under the curve approach with regression-based adjustment for baseline EQ-5D utility scores [22,23]. 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 socio-economic 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 to £30,000 per QALY gained [27]. We will develop a two-stage economic model; a decision tree to reflect the outcomes of the trial and a Markov state transition model to extrapolate the evolution of patient outcome and costs over a lifetime horizon. Value of information analysis will be conducted after taking into account uncertainty derived from decision-analytic models.

Health economic outcomes:

- Quality Adjusted Life Years calculated from EQ-5D-5L

This is an index of health-related quality of life, which gives a weight to different health states. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and five levels.

Responses to the EQ-5D will be converted into a health utility index using a set of weights to reflect UK population preferences for the particular health state. In line with NICE's position statement, base-case analysis will be conducted using the Van Hout scoring algorithm [21]. QALYs will be calculated from these utility weights using an area under the curve method [22,23].

- Health service activity using the Client Service Receipt Inventory (CSRI)

The CSRI will be used to collect retrospective information about participants' use of health services and medication use, including smoking cessation, diet management, weight control programmes and exercise referral schemes.

9.9 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. The process evaluation will help build a picture of how the intervention was carried out in reality and what factors shaped it. By carrying out 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 that are 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 'ActivateYourHeart' website), unintended consequences (adverse events and inequities), contextual factors and sustained motivation for behaviour change. The website will be examined not only for the degree of completion of the programme, and the number of occasions that the website was accessed, but also for the extent of the change in behaviour recorded. There will be a particular focus on underserved groups (women, BAME, low socio-economic status, other PROGRESS-Plus [28] characteristics and those without internet access or device).

Semi-structured telephone or video interviews of up to 30 participants will be conducted 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 in particular 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 socio-economic status). Interviews will take place between the end of the 12 week cardiac rehabilitation programme and the end of the 12 month follow-up assessment for those receiving the intervention. For those in the standard of care arm interviews will take place towards the end of the 12 month follow-up assessment. The cardiac rehabilitation staff, recruiting staff and staff completing baseline and follow up assessments involved will also be interviewed throughout the project. For some of the staff in Leicester they will be familiar with the 'ActivateYourHeart' website, but this trial will involve a new patient group with chronic stable angina. Staff in other areas will be less familiar with online rehabilitation programmes. We will aim to recruit a minimum of 10 staff members. All of the interviews will be audio recorded and fully transcribed. Contact with the online discussion forum, and the 'ask the expert' email facility will also be examined. We will also examine routinely collected data that is collected by the website for the purposes of the national audit for cardiac rehabilitation. Qualitative data will be analysed using a thematic analysis approach. Quantitative data (recruitment logs, use of the website, recorded change in behaviours, national audit data) will be analysed using descriptive statistics, which will allow the exploration of frequency of responses. All data sets will be synthesised in order to describe the complex nature of the enhanced rehabilitation intervention.

A brief survey will be emailed to those patients in the intervention arm who consented to be interviewed for the study. (Those patients with no email access will be contacted via telephone.) This will consist of a short set of questions to gain some feedback on their experiences in the trial and will include an option for patients to indicate they are still happy to be interviewed.

9.10 Process Evaluation Sub-study

In order to maximise trial outputs a sub-study is being conducted on patients who did not respond to their initial contact. The sub-study will contain the following:

Patient surveys – The online patient survey will be circulated to all eligible patients who were contacted about the trial but did not respond to the initial mailout. The survey will be sent out via text message to patients via practice systems with two reminder text messages every two weeks. The surveys will consist of a short set of questions and will collect information on why the participants did not respond to the initial mailout inviting them to take part in the study and ascertain their preferred method of contact. Patients will also be asked if they would be happy to be contacted to take part in a focus group to discuss their responses in more detail. All patients who complete the survey will be entered into a prize draw to win one of three £25 vouchers. Responses from the survey will be used to inform discussions at the focus groups.

Patient Focus Groups – After the surveys are completed the patient focus groups will take place. The focus groups will allow us to directly speak to eligible patients to discuss why they didn't respond to the mailout inviting them to take part in the main study, what could have been done differently and to discuss their preferences for Cardiac Rehabilitation and what they would expect or prefer from a Cardiac Rehab programme.

The sub-study will involve sites open to the main trial and sites for the sub-study will be selected based on their capacity and number of eligible patients at site. The site teams will be responsible for sending out the initial patient surveys and referring them to the Process Evaluation team and LCTC for the focus groups.

9.11 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

Premature Discontinuation of Trial Intervention

Participants may discontinue participation for reasons including, but not limited to:

- Participant-led i.e. request by the participant
- Intercurrent illness preventing further participation
- Death
- Clinician-led - participant meets an exclusion criterion (either newly developed or not previously recognised)

Discontinuation from study intervention does not mean discontinuation from the study altogether, and the remaining study procedures, follow up assessment / visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn). Data to be collected at the time of discontinuation will include the following:

- completion of eCRF detailing reason for discontinuation

Participant Withdrawal from Follow Up

Participants are free to withdraw from follow up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study and the CTU should be informed via email and via completion of a Withdrawal eCRF.

If participants express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, or if, for example, data from routine assessments can still be collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the CTU via processes detailed in Section 10 even if a participant has withdrawn from follow up.

Participant Transfer

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via their new healthcare provider.

A copy of the participant eCRFs should be provided to the new site. The participant remains the responsibility of the original site until the new site PI has signed the Transfer CRF.

Loss to Follow-up

A participant will be considered lost to follow up if s/he misses both the 6- and 12-month follow-up visits and is not contactable by the site research team.

If a participant fails to attend/facilitate a required study visit the following actions must be taken:

- Site will attempt to contact the participant and reschedule the missed visit and advise the participant on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed to be lost to follow up, site research staff will make every effort to regain contact with the participant (i.e. telephone calls and, if necessary, a headed letter to last known address). These efforts should be recorded in the patient medical notes.
- If the participant continues to be unreachable, they should be considered withdrawn from the study with a primary reason of lost to follow up and this should be recorded on the withdrawal eCRF.

9.12 End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with CTU processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC
- Trial-related materials reconciled
- All site data entered onto the study database, discrepancies raised, and satisfactory responses received
- Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

Study Discontinuation

~~In the event that the trial is discontinued, all participants will complete their treatments as randomised. No further patients will receive access to ActivateYourHeart~~.

The trial was closed to recruitment on 30th September 2024 with a final recruitment figure of 101 participants randomised by the end of the recruitment period. All participants will complete their treatments as randomised. There were significant delays to recruitment at sites and it was agreed that recruitment could not be completed within a reasonable time frame. It was agreed that the Process Evaluation should be expanded to try and gain as much from the trial as possible.

The new project timelines can be found below as a result of study discontinuation:

Recruitment end: 30/09/2024
12 months follow up: 18/09/2025 (last patient last visit)
9 months data cleaning, site closure, analysis and report writing: 18/06/2026

10 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

All safety events will be recorded by researchers when they are made aware of the event by the patient, carer, the treating clinicians, or therapists, in accordance with the principles of GCP. Safety event reporting information will be included in the training given to the therapy teams delivering the intervention and they will be given copies of the safety event reporting forms and details of how to enter them on to the trial database or send to the LCTC.

AE reports and SAEs not related to the intervention will be entered on to the remote data entry system at follow-up visits. SAE reports related to the intervention will be completed and sent to the LCTC within 24 hours of becoming aware of the event.

Safety events will be captured on two separate forms: Adverse Events form for all non-serious events and SAEs not related to intervention and a Serious Adverse Events (SAE) form for serious events related to intervention. The healthcare professional will complete the SAE form including the seriousness of the event and whether it is related to the trial and return to the LCTC Central Safety Team. The Central Safety Team will liaise with the Chief Investigator (or agreed delegate) to ascertain an assessment of expectedness for related events.

All SAEs, along with the PI's assessment of whether it is related to the intervention and for related events the CI's assessment of whether or not it is expected, will be reported to the REC annually. All SAEs which are assessed as related and unexpected will be reported to the REC and Sponsor in an expedited manner.

10.1 Terms and Definitions

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Related Adverse Event (Related AE)
An AE which resulted from administration of any of the research procedures – i.e. assessed as "probably", "possibly" or "almost certainly" related to the trial procedures (see section 10.4).

Serious Adverse Event (SAE)
An adverse event which meets the definition of "serious" (see section 10.2).

Related Serious Adverse Event (Related SAE)
A SAE which is assessed to be "probably", "possibly" or "almost certainly" related to the trial procedures (see section 10.4).

Related Unexpected Serious Adverse Event (RUSAE)
A Related SAE which is not expected, i.e. not consistent with the known effects of the trial procedures (see section 10.5).

10.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event (whether or not assessed as related to the trial) is assessed as serious if it:

- Results in death;
- Is life-threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of trial participants, or their partners, regardless of time of diagnosis), or
- Is otherwise considered medically significant by the investigator.

10.3 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 1: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.
Life-Threatening	
Death	

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 10.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

10.4 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur at the same time as the intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest that there is a causal relationship (e.g. because the event did not occur at the same time as the intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded, and the REC will be informed of both points of view.

10.5 Assessment of "Expectedness"

The Chief Investigator (or agreed delegate) for the ACTIVATE trial is responsible for determining whether a related safety event is expected or unexpected, however a Chief Investigator will not assess their own patients, these patients will be assessed by the Medical Reviewer. There is no requirement for a reporting investigator to make an assessment of expectedness.

All related safety events will be considered unexpected as there are no expected events as part of the ActivateYourHeart intervention.

10.5.1 Reference Safety Information / Information used to Assess Expectedness

There is a minimal risk that the ActivateYourHeart intervention may lead to accident or injury or an episode of angina. However, the ActivateYourHeart programme generates a tailored plan for each participant so the daily exercise is appropriate for each participant and so we do not expect that participants will become injured or have an episode of angina. Cardiac rehabilitation staff monitor participants' progress and can respond to any queries or concerns.

There are no expected safety events as part of the trial intervention.

10.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the below described "active monitoring" period which are related to the intervention and meet the definition of serious (see section 10.2) and are recorded for this study (see section 10.7) must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 10.8. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be from the period of randomisation until 53 weeks post randomisation.

Pregnant women will be followed up until at least the outcome of the birth (see Section 10.7 for more information on reporting pregnancy).

10.7 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

- Non-injurious falls;
- An exacerbation of a pre-existing illness;
- An increase in frequency or intensity of a pre-existing episodic condition;
- A condition (even though it may have been present prior to the start of the trial) detected after the start of the trial; and
- Continuous persistent disease or symptoms present at baseline that worsens during the trial
- Pregnancy (See below for more details)

Do not record:

- Medical or surgical procedures where the condition which leads to the procedure is the adverse event;
- Pre-existing disease or conditions present before treatment that do not worsen; and
- Overdose of medication without signs or symptoms.

The events above do not need recording as based on discussion with the TMG/CI as the trial is considered low risk this was determined by the TMG and is documented in the TMF.

Reporting of Pregnancy:
If pregnancy occurs during either the intervention or follow up period of the trial this must be notified to the LCTC using Safety event CRF within 24 hours of the research team becoming aware. The pregnancy must be followed up by the site research team until birth and reported to LCTC.

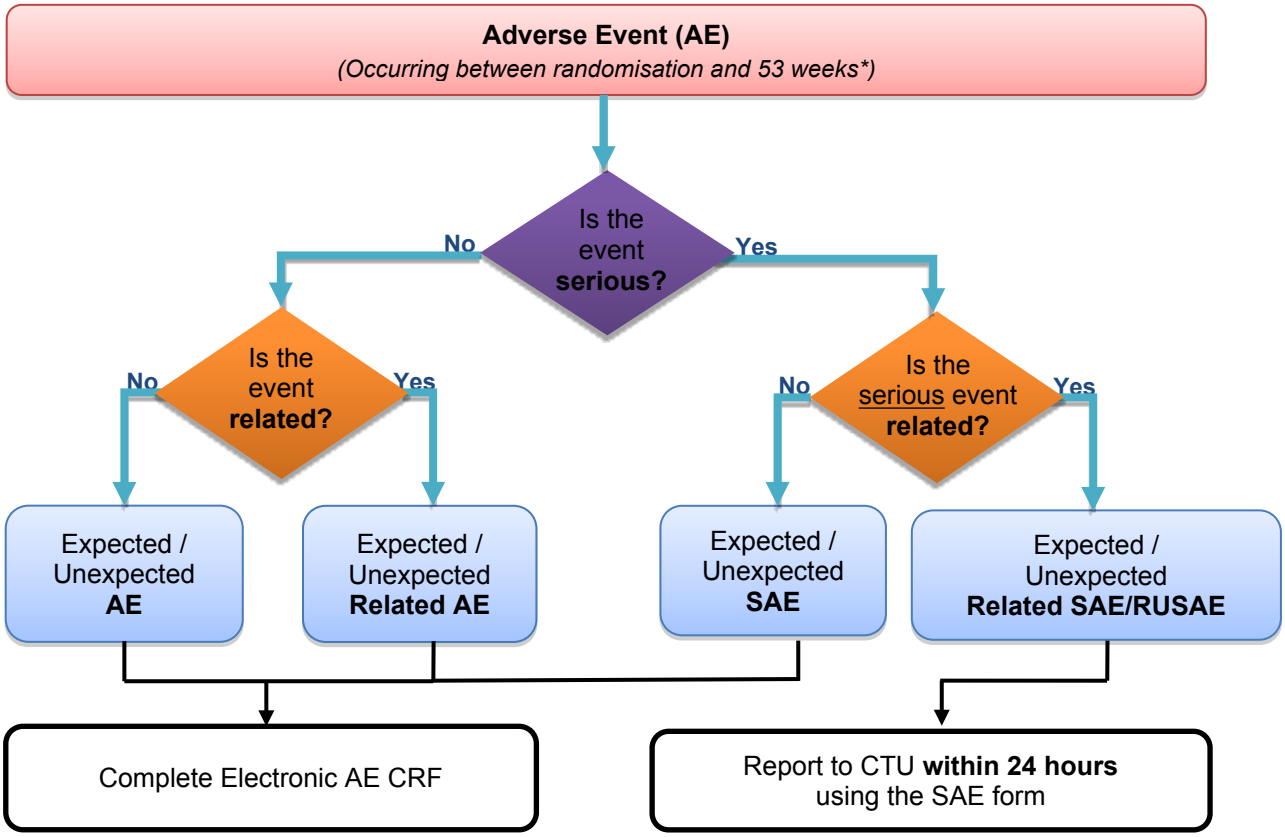
Any pregnancies which result in a safety event assessed as “serious” (e.g. birth defect) must also be reported separately on the appropriate Safety Event CRFs in accordance with processes described in section 10. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

Notification of Deaths
If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate CRF within 24 hours of becoming aware.

10.8 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant’s notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. “serious” events related to the intervention are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events.

Flowchart for Site Reporting Requirements of Adverse Events



*Additionally, any serious and related events beyond this period.

Reporting Safety Events to the LCTC

All safety events (whether or not assessed as serious / related / expected) should be recorded on an Adverse Event Form; multiple events can be recorded on one form.

Safety events which are related to the intervention and assessed as "serious" must **also** be recorded in more detail on SAE Forms; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Each SAE should have a corresponding record on the participant's AE form. Where additional information is received by site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. SAE Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the Chief Investigator or Medical Reviewer and assessed for causality and expectedness.

Follow-up After Adverse Events

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

10.9 Investigator Reporting Responsibilities

The PI in each site is responsible for ensuring that all safety events requiring recording on this study (see above) which the local research team becomes aware of are reported to LCTC. It is the responsibility of the local PI or Co-Investigator as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events.

All safety events must be recorded on an AE form in the trial database by the site **within seven days of the site team becoming aware of the event**.

Safety events which are related and that meet the definition of "serious" must be reported in more detail to the LCTC on an SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware** unless the SAE is specified in the protocol as not requiring immediate reporting (see above) where they will be appropriately processed.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

- Trial randomisation number
- Sponsor trial number
- One identifiable reporter
- Description of event
- Seriousness assessment
- A causality assessment

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy.

REPORTING AN INITIAL OR FOLLOW-UP SAE
The investigator should ensure the actions below are completed for all reportable SAEs:

1) Research sites should telephone the appropriate trial co-ordinator / data manager on telephone number **0151 794 9765** to advise that an SAE report has been submitted as soon as possible.

2) **The SAE form should be transferred securely to lctcsafe@liverpool.ac.uk (within 24 hours) to the CTU**

3) The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
4) The patient must be identified by trial number, age and initials **only**. The patient's name **should not** be used on any correspondence.
5) SAEs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. N.B. Follow-up may continue after completion of protocol treatment if necessary.

- Follow-up information is noted on a new SAE form to be transferred securely to the CTU as soon as more information becomes available
- Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.

6) Extra, annotated information and/or copies of anonymised test results may be provided separately.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

10.10 LCTC Responsibilities

The trial Sponsor, University of Liverpool have delegated to LCTC the duty of onward reporting of safety events to REC. LCTC SOPs will be followed to ensure appropriate reporting as detailed below.

All “serious” safety events will be forwarded to the Chief Investigator or Medical Reviewer by LCTC within 24 hours of receiving the minimum information from site. The CI or Medical Reviewer will review information provided by site and for all events assessed as “related” will provide an assessment of “expectedness”.

Safety events which are assessed as “serious”, “related” and “unexpected” (RUSAEs), will be onward reported by LCTC to the ethics committee **within 15 days** of the LCTC first becoming aware of the event.

Additionally, RUSAEs will be reported to the trial Sponsor(s) and Principal Investigators of participating sites

A list of all safety events recorded for the trial will also be reported annually by LCTC to the ethics committee and Independent Data Safety & Monitoring Committee

Any concerns raised by the TSC/IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported safety events in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of safety event including reporting rates and safety events by site. The LCTC will send Annual Progress Reports (APRs) containing a list of all serious safety events to the IDSMC and REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC.

The LCTC will notify the REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC. If the study is temporarily halted it may not recommence until authorised to do so by the REC. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC), the Sponsor should notify the REC within 15 days of the date of termination by submitting the formal End of Trial Notification.

10.11 Contact Details and Out-of-hours Medical Cover

As this is a low-risk intervention with no reported safety events associated with the intervention, emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for ACTIVATE participants. All participants will be provided with a contact card and copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size

The total sample size is 518 patients, 259 in each arm.

11.1.1 Sample Size Calculation

In order to detect the minimum clinically important difference of 8 points for the SAQ-UK physical limitation domain, assuming a standard deviation of 25 [29], with 90% power at the 5% significance level, 207 patients 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 patients per group (518 in total). This sample size will give >99% power for secondary outcomes.

Due to slow recruitment at sites the final recruitment figure was 101 participants recruited. After meeting with the funder, the TMG and oversite committees it was agreed that recruitment should end on 30th September 2024.

11.1.2 Feasibility of Sample Size

The recruitment rate from the previous 'ActivateYourHeart' RCT for people with angina who were invited to participate was 15% (176). This would mean that in order to recruit our sample size of 518, we would need to invite 3,454 people with angina. The prevalence of angina is 2% in the general population, so we would need a total practice population of 172,700. As the average list size for a general medical practice in the UK is 8,757, we would need to recruit from about 20 practices (five from each of the four regions).

11.2 Method of Randomisation

11.2.1 Allocation Sequence Generation

Patient participants who give their informed consent will complete baseline processes and outcome measures before being individually randomised. The randomisation will be performed by the site team using 24-hour web-based randomisation system to protect against subversion whilst ensuring that the trial maintains good balance to the allocation ratio of 1:1 both within each stratum and across the trial. Randomisation will be requested by and will be archived by secure web access to the remote randomisation centre at the LCTC. This system will be set up, maintained and monitored independently of the trial statistician or other trial staff.

Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after all baseline measurements have been completed.

11.3 Blinding Considerations

Members of the research team conducting the outcome assessments will be blinded to allocations. They can receive notification that a patient was randomised but this will not contain allocation.

11.4 Interim Analyses

There will no formal interim analyses conducted during the course of this trial. Descriptive summaries of the accumulating data on safety will be prepared by the LCTC at regular intervals (at least annually) for review by an IDSMC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further

follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

11.5 **Analysis Plan**

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised below:

Final analysis will take place once all participants have been followed-up for 52 weeks, 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. Demographic and baseline 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, socio-economic status and other relevant PROGRESS-Plus characteristics. No statistical testing of demographic and baseline differences between groups will be performed. 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% confidence intervals) will be reported from an analysis of covariance (ANCOVA) adjusted for baseline score and stratification factors.

Predictors of missing data will be investigated using regression models (including age, living arrangements and co-morbidities) and any significant predictors will be considered for inclusion in the models. In addition, given the two assessment points at 6 and 12 months, we will carry out a sensitivity analysis using a joint modelling approach to check whether there is any difference in outcome (here the longitudinal outcome rather than the outcome at 6 or 12 months alone) between the randomised arms adjusted for dropouts or missing values.

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. 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 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.

Our reporting of the trial findings will be informed by using the CONSORT-Equity 2017 reporting standards [30], which are an extension to the CONSORT (Consolidated Standards of Reporting Trials) statement that aims to improve the reporting of intervention effects in randomised trials where health equity is relevant.

12 DATA MANAGEMENT AND TRIAL MONITORING

For the ACTIVATE trial the responsibilities for Data Management and monitoring are delegated to the CTU. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the CTU throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local CTU processes and in line with all relevant regulatory, ethical and legal obligations.

12.1 Source Documents

The electronic case report form (eCRF) will be considered the source document for data where no prior record exists, and which is recorded directly in the bespoke eCRF. An ACTIVATE source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes ACTIVATE-specific source data.

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

12.2 Data Collection Methods

Data are to be entered into ACTIVATE remote database by members of the research team at site. Training will be provided prior to any data entry. Only serious safety event reports will be completed using a paper CRF.

12.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 3.

Central Monitoring

There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per CTU processes. Any suspect data will be queried within the trial database. Sites will respond to the queries by updating the data within the database in line with the source documentation or by providing an explanation/resolution to the discrepancies.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

12.4 **Risk Assessment**

A risk assessment is performed for each trial coordinated by the LCTC to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial. Monitoring can take the form of on-site visits or central monitoring. A detailed monitoring plan will be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

12.5 **Confidentiality**

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial screening and/or randomisation number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the CTU by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioner's Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

12.6 **Quality Assurance and Control**

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

12.7 Records Retention

The retention period for the ACTIVATE data and information is 10 years from the official End of Trial date.

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File, the applicable participant medical records for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the sponsor.
The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. language translators).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Statement of Compliance

Statement of compliance: The study will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki (2013)
- LCTC SOPs
- The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013)
- UK Policy Framework for Health and Social Care Research 2017.

13.2 Ethical Considerations

Potential ethical issues include informed consent where potential participants will be identified by NHS clinicians providing their usual care and will avoid any coercion. Clinical equipoise exists for this study because there is insufficient evidence that the intervention improves patient outcome, so the trial team believe it is acceptable to randomise patients to the two treatment arms. The cardiac rehabilitation intervention is low risk as it encourages changing harmful behaviours such as smoking, poor diet and physical inactivity. It also promotes positive mental health. The intervention encourages patients to set achievable goals in terms of physical activity and encourages self-monitoring. We will record adverse events and take advice from the IDMSC regarding the frequency of these, especially those related to the study. The control group poses no additional risk to participants as they will receive care as usual, and this usual care will be optimised by their healthcare provider

If COVID-19 restrictions persist, or are reintroduced, we have considered the following mitigating factors. Systems for remote working are now commonplace in primary care, which can be used to identify potential participants and discuss involvement by telephone and video consultation. 'ActivateYourHeart' is designed to be used remotely and has been enthusiastically adopted by cardiac rehabilitation teams throughout the UK to help overcome the current COVID-19 restrictions. The initial and 12-week follow-up assessments by the cardiac rehabilitation therapist could also be performed remotely if necessary. We can also design remote methods of data capture for the 6- and 12-months' follow-up assessments. This means that, even with stringent COVID-19 restrictions, we will be able to recruit participants and successfully perform and evaluate the (online) intervention.

The trial will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion.

13.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and host institution(s) for written approval.
Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

13.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and REC requirements are handled based on their nature and severity.

Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.
The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to REC.

Breaches confirmed as 'serious' will be reported to REC within 7 days by the CTU on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.
Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.
Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

14 **INDEMNITY**

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

15 PUBLICATION AND DISSEMINATION

15.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).
The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.
Any publications arising from this research will be reviewed appropriately prior to publication.

Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, will be included by name at the manuscript head or otherwise listed at the end in a by-line as members of the ACTIVATE Consortium which will also be named at the manuscript head.

15.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the REC. The results of ACTIVATE will be published regardless of the magnitude or direction of effect.

15.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be assessed by the trial Sponsor and Data Controller.

16 CHRONOLOGY OF PROTOCOL AMENDMENTS

16.1 Version 7.1 03/03/2025

Summary of Amendments from Protocol V6.0 to Protocol V7.1		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
9.9	Process Evaluation	• Change from 2 patient interviews for the intervention arm to 1 interview. • Increase in timeframe allowed for the patient interview to allow this to be conducted at any point between 12 weeks in the trial and the 12-month follow-up point. • Addition of a brief survey to be emailed to those who consented to be interviewed. • Addition of sub-study
9.12	End of trial	Information on study discontinuation and revised timelines have been added
11.1.1	Sample Size Calculation	Information on study discontinuation and revised timelines have been added
Throughout	N/A	Grammatical errors and spelling mistakes have been corrected throughout

16.2 Version 7.0 31/10/2024 (this version was never implemented)

Summary of Amendments from Protocol V6.0 to Protocol V7.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
9.9	Process Evaluation	Amendment to the Process Evaluation section to allow for patient surveys and focus groups to take place. Information on staff and participant interviews has also been included
9.12	End of trial	Information on study discontinuation and revised timelines have been added

Summary of Amendments from Protocol V6.0 to Protocol V7.0		
Throughout	N/A	Grammatical errors and spelling mistakes have been corrected throughout

16.3 Version 6.0 14/06/2024

Summary of Amendments from Protocol V5.0 to Protocol V6.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Throughout	Throughout	Amendment to the trial protocol to allow for recruitment if technical issues arise with ActivPAL. Amendment to allow the interviewing of recruiting staff to take place. Amendment to allow for telephone follow ups to take place if pre-approved by the CI.

16.4 Version 5.0 04/05/2023

Summary of Amendments from Protocol V5.0 to Protocol V5.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Throughout	Throughout	Amendment to the trial protocol to remove named geographical areas of recruiting sites as sites outside of area are now taking part. Changes have been made to make the protocol applicable for recruitment in secondary care sites. Clarification on the collection of demographic data is also made throughout.

16.5 Version 4.0 (20/02/2023)

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
6	Eligibility	Amendment to inclusion criteria: Evidence of myocardial ischaemia from either a past medical history of Acute Coronary Syndrome (ACS), Myocardial Infarction (MI) or revascularisation procedure at least 12 months in the past; or

Summary of Amendments from Protocol V3.0 to Protocol V4.0		
		from imaging studies such as invasive coronary angiography, computerised tomography (CT) angiography, or myocardial perfusion testing

16.6 Version 3.0 (07/11/2022)

Summary of Amendments from Protocol V2.0 to Protocol V3.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
8	Outcomes	Additional information has also been added to the protocol to instruct sites to contact LCTC if the Incremental Shuttle Walking Test cannot be completed.
9.2	Informed Consent	Clarification to processes for inviting participants to take part in the study
9.9	Process Evaluation	Timelines for process evaluation interviews have been removed
Throughout	Throughout	References to SAQ-7 removed and replaced with SAQ-UK. The SAQ-7 was submitted with original regulatory applications in error. This was corrected in amendment 6 and reflected in this protocol amendment
Throughout	Throughout	References to Rose Dyspnoea scale removed and replaced with MRC dyspnoea scale. The MRC dyspnoea scale was submitted with the original regulatory applications, the protocol has been amended to change this typographical error

16.7 **Version 2.0 (10/12/2021)**

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Front page	Front page	Insertion of REC reference and ISRCTN number
9.5	Randomisation / Registration	Additional information regarding randomisation allocated and minimisation
11.4	Interim Analyses	Additional information confirming that there will be no interim analyses conducted for this trial, but safety data will be reviewed at regular intervals

16.8 **Version 1.0 (30/07/2021)**

Original Approved version

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18 **DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL**

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or Ethical review are submitted as separate version-controlled documents.