PROTOCOL

FULL TITLE:

Personalised Exercise-Rehabilitation FOR people with Multiple long-term conditions (PERFORM)

Randomised Controlled Trial with Prospective Cohort Study and social media SWAT

VERSION NUMBER 1.0

VERSION DATE 07/08/2024

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SPONSOR: University of Leicester

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TRIAL REGISTRATION: ISRCTN number: TBC

FUNDER(S) – NIHR

This protocol has regard for the HRA guidance

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given. Any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator: _____

Chief Investigator Signature: _____

Date:_____

Principal Investigator Name:

Principal Investigator Signature:_____

Date:_____

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Funder(s)	NIHR PGfAR NIHR202020
Funder start and end date(s)	January 2022 to March 2027
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NIHR Portfolio adopted	Yes

Contents

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the study. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
BACPR	British Association for Cardiovascular Prevention and Rehabilitation
BTS	British Thoracic Society
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CR	Cardiac Rehabilitation
CRF	Case Report Form
CTU	Clinical Trials Unit
DSMC	Data Safety and Monitoring Committee
EOI	Expression of Interest
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
LCTU	Leicester Clinical Trials Unit
LTC	Long Term Condition
NHS	National Health Service
NHS R&D	National Health Service Research & Development
PAG	Patient Advisory Group
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PMG	Programme Management Group
PPI	Patient and Public Involvement
PR	Pulmonary Rehabilitation
PSC	Programme Steering Committee
QALY	Quality Adjusted Year Life
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SDV	Source Data Verification
SoMe	Social Media
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WP	Work Package

KEY WORDS

Multimorbidity, multiple long-term conditions, rehabilitation, randomised controlled trial, cohort study, SWAT – study within a trial

TRIAL SUMMARY

Trial Title	Personalised Exercise-Rehabilitation FOR people with Multiple long-term conditions (multi-morbidity) PERFORM A comprehensive cohort study design (randomised controlled trial [RCT] and prospective cohort study [PCS]) with a nested study within a trial (SWAT) and internal 6-month pilot phase.
Trial Design	RCT: Eligible participants will be randomised 1:1 to intervention group (PERFORM rehabilitation programme + usual care) or control group (usual care alone). A 6-month internal pilot phase will be used to demonstrate acceptability and feasibility of randomisation and recruitment commensurate with timely completion. A process and economic evaluation will also be conducted. PCS: Eligible participants with indication for cardiopulmonary rehabilitation will be allocated to intervention group (PERFORM rehabilitation programme + usual care) and observationally compared to a contemporaneous control group (cardiac rehabilitation (CR) or pulmonary rehabilitation (PR) + usual care). Social Media SWAT: A cluster randomised study within a trial. Sites (and all participants within site) will be randomly allocated 1:1 to a social media (SoMe) intervention or not (control).
Trial Participants	RCT: people with two or more long term conditions (LTCs) at least one of which has evidence of benefit from an exercise-based intervention and are not eligible for referral to a standard CR or PR programme. Cohort: people with two or more (LTCs) at least one of which has evidence of benefit from an exercise-based intervention and eligible for referral to a CR or PR programme. Social Media SWAT: All RCT and cohort patients
Planned Sample Size	RCT: Sample size of 604 participants with 1:1 PERFORM intervention (N=302) to control group (N=302) randomisation to be recruited across 20 sites.

	Cohort: Sample size of 604 PERFORM intervention (N=302) patients and control CR/PR (N=302) patients. SWAT: 20 sites (SoMe intervention: 10 sites & control: 10 sites)
Follow up duration	RCT & PCS: baseline (pre-randomisation) and 3 and 12-months post randomisation SWAT: 3 and 12-months post randomisation
Planned Trial Period	Start date: Sept 2024 End Date: 30/03/2028 (from NIHR grant application)
Overarching aims	1. To assess the clinical effectiveness and cost-effectiveness of the addition of PERFORM intervention plus usual care compared to usual care alone in people with multiple LTCs not eligible for referral to a standard CR or PR programme in a RCT. 2. To assess the clinical effectiveness and cost-effectiveness of the addition of the PERFORM intervention to usual care compared to standard CR or PR in people with multiple LTCs in a PCS. 3. To refine programme theory and identify barriers and facilitators to future wide scale implementation and develop an implementation toolkit (RCT and PCS). 4. To assess the effectiveness of a social media intervention to reduce trial attrition. (SWAT)

Primary Outcome	
RCT/PCS	Generic HRQoL (EQ-5D-5L index score) at 3-months follow up
SWAT	Proportion of RCT patients with completed primary outcome at 12-months follow up
Secondary Outcomes	
RCT/PCS	Following secondary outcomes at 3 and 12-month follow up; • EQ-5D-5L VAS • Incremental shuttle walk test (ISWT) • Endurance shuttle walk test (ESWT); • 4 Metre Gait Speed (4MGS) • Patient Health Questionnaire-9 (PHQ9) • Generalised Anxiety Disorder Assessment-7 (GAD-7) • World Health Organisation Disability Assessment Schedule (WHODAS) • Frailty Fried Exhaustion and Weight Loss • Montreal Cognitive Assessment (MOCA) • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) • Brief Pain Inventory (BPI) • International Physical Activity Questionnaire (IPAQ) • Dysponoea-12 • Medical Outcome Study Sleep Scale (MOS) • Multimorbidity Treatment Burden Questionnaire (MTBQ) • ICEpop CAPability Measures for Adults (ICECAP-A) • Exercise Adherence Rating Scale (EARS) • Hospitalisations and overnight hospital admissions • All-cause mortality • Adverse events (e.g. musculoskeletal injuries from exercise training), • Social and healthcare utilisation (including medication) and primary care contacts
SWAT	Proportion of RCT patients with completed primary outcome at 3-months follow up Proportion of RCT patients with completed ISWT at 3-months follow up Proportion of RCT patients with completed ISWT at 12-months follow up For those on PERFORM intervention: Proportion of PERFORM intervention patients completing ≥60% of intervention sessions

FUNDING AND SUPPORT IN KIND

FUNDER(S)

NIHR PGfAR NIHR202020

ROLE OF TRIAL SPONSOR

The Sponsor of this research is the University of Leicester. The University of Leicester is registered as a research sponsor with the Department of Health and routinely takes responsibility as sponsor for research activities within the NHS.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Programme Management Group (PMG)

Monthly trial management meetings will take place, comprising the Chief Investigators, co-applicants, members of Leicester Clinical Trials Unit (LCTU) and a Patient Advisory Group (PAG) representative. These operational meetings will provide continuous monitoring of key milestones and provide a vehicle to highlight issues, and discuss and agree resolutions. In addition to these monthly meetings, the CIs/members of the research team will meet regularly with the LCTU hub to discuss the day to day running of the programme (these will be virtual). The PMG will report to the Programme Steering Committee (PSC).

Public Advisory Group (PAG)

The PAG, consisting of Patient and Public Involvement (PPI) representatives, will have 11 meetings as part of the larger PERFORM programme grant, each in Glasgow and Leicester to advise on overarching trial set-up, patient-facing materials and the topic guide for the semi-structured interviews and provide input to all WPs (plus 5 PAG evaluation/study meetings). The PAG would meet approximately every 6 months of the PERFORM programme grant timelines to provide input to all WPs, advise on trial conduct and dissemination of results. The PAG will report to the PMG (which will carry on after WP3 completion).

The PAG will evolve through the lifetime of the project and recruit new members (trial participants) to support PAG activities and dissemination events having first-hand experience of the intervention.

Programme Steering Committee (PSC)

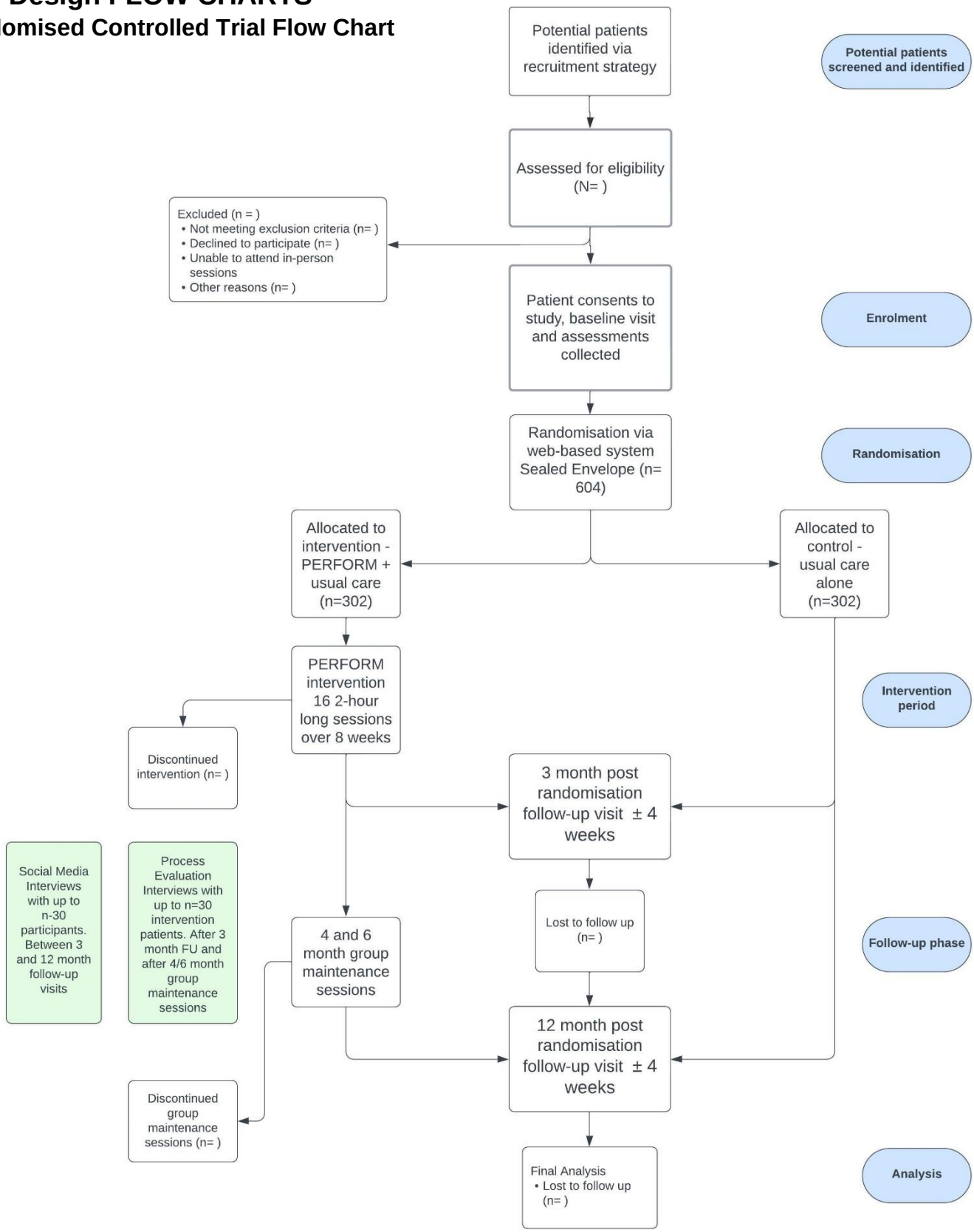
A Programme Steering Committee (PSC) has been established to provide independent expert oversight of the PERFORM research programme and includes Trial Steering Committee (TSC) and Data Safety and Monitoring Committee (DSMC) responsibilities for the RCT, PCS and SWAT. Meetings will normally take place once a year 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; however, the PSC may be convened during the recruitment phase to advise/address any study concerns. The PSC consists of an independent chair, an independent statistician, other independent members who are experts in rehabilitation and multimorbidity, two patient representatives, meetings may also be attended by PERFORM co-chief investigators, study manager, the sponsoring organisation, and representatives from the

clinical research networks. The PSC will make recommendations to the PMG and will report to the sponsor and the funder.

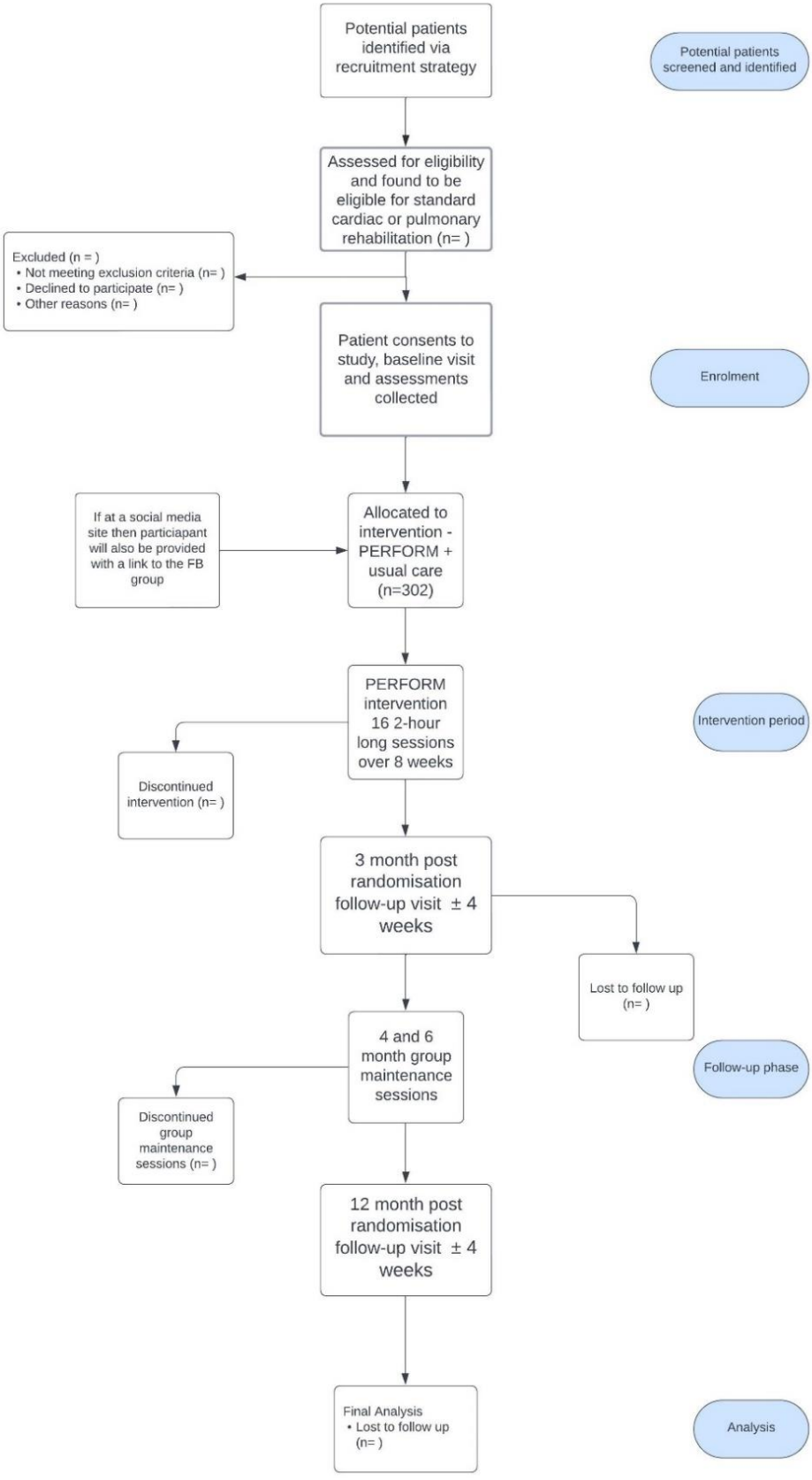
The routine reports reviewed by the PSC will include a summary of all SAEs. SAEs identified as related, life-threatening or resulting in death will be reported annually to the PSC members for review, unless requested more frequently by PSC. The decision regarding frequency of review may be re-evaluated by the PSC members throughout the study delivery, and then reported to the Sponsor for continuity in safety reporting.

Trial Design FLOW CHARTS

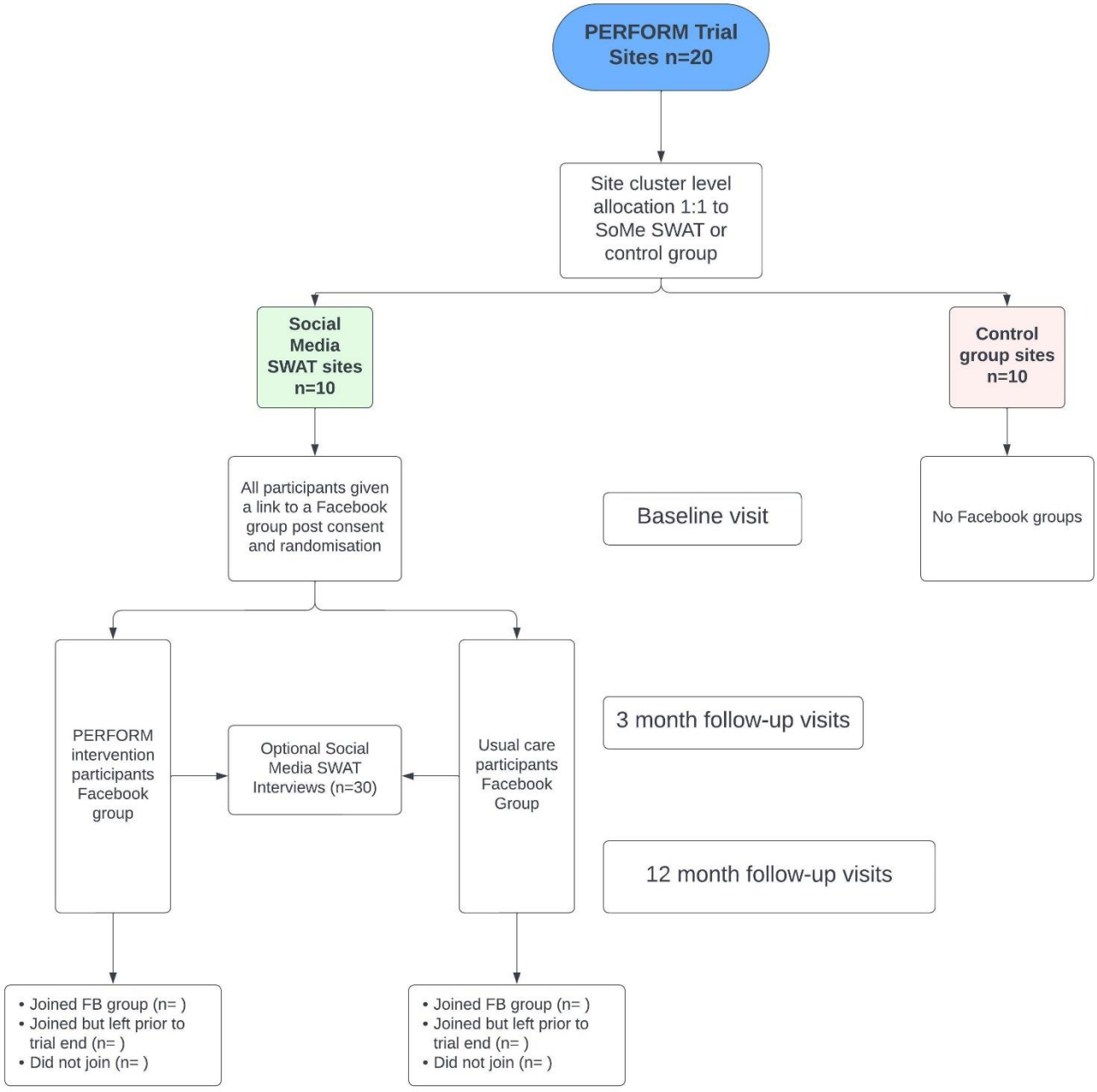
Randomised Controlled Trial Flow Chart



Prospective Cohort Study Flow Chart



Social Media SWAT Flow Chart



1. INTRODUCTION AND BACKGROUND INFORMATION

1.1 Introduction

Multiple long-term conditions (MLTCs) (or 'multimorbidity') are defined as the presence of two or more long-term health conditions with an individual and affects around 19.2 million people in the UK as of 2019 (1). MLTCs are a key challenge facing global health care systems and the numbers of people living with MLTCs in United Kingdom is projected to increase to 35.3 million by 2049 (1). The presence of MLTCs is associated with an increased risk of mortality and hospitalisation, higher healthcare costs and functional decline resulting in reduced health-related quality of life (HRQoL) (2–6).

There is a lack of effective interventions to support the management of people with MLTCs (7-10), particularly those with a focus on minimising functional decline and supporting self-management of complex health problems. Rehabilitation: 'the action of restoring someone to health or normal life illness' remains a core component of health service provision and addressing the unmet rehabilitation need for people with MLTCs has been recognised as a international healthcare priority. (10)

The overarching aim of the Personalised Exercise Rehabilitation FOR people with Multiple LTCs (PERFORM) research programme is to better understand the impact of living with MLTCs and develop and evaluate a novel integrated rehabilitation intervention for this population. Our PERFORM programme consists of five linked work packages (WPs).

WP1: Identifying people with MLTCs likely to benefit from rehabilitation

WP2: MLTC rehabilitation intervention (PERFORM) development/workforce planning

WP3: Feasibility study for full multicentre RCT of the PERFORM intervention with embedded process evaluation and an assessment of the collection of health economic outcomes for people with MLTCs

WP4: Comprehensive cohort study – combining a multicentre RCT and PCS) with health economic and process evaluation assessing the clinical and cost-effectiveness of for people with MLTCs

WP5: SWAT – assessing the role of social (SoMe) on multicentre RCT recruitment and retention

This protocol document incorporates WP4 and WP5.

1.2 Background

Multimorbidity affects approximately 27% of the UK adult population and the proportion of patients living with MLTCs increases with age (11). A meta-analysis of 193 international studies found that the prevalence of multimorbidity was 28% in those under 59 years, 47.6% in those 59 to 73 years and 67.0% in people ≥ 74 years (12). Overall, 33.8% of those patients with MLTCs had both a physical and mental health long term condition. Younger age groups

had a significantly higher proportion of both physical and mental health conditions compared to older age groups who just have physical comorbidities - 56.5% in those aged 18-24 compared to 23.7% in those aged 75-84 (11). A review of data from the Understanding Society UK Longitudinal Study showed that rates of multimorbidity are highest in the white British population, those that are out of the workforce either due to retirement or poor health, and those that live in urban centres (13). Multimorbidity is also more prevalent in females than males (30% vs 24.4%) and among those with lower socioeconomic status (11).

An analysis by Jani in 2019 into findings from the UK Biobank showed that for patients with ≥ 4 cardiometabolic LTCs such as heart attack, stroke and diabetes, all-cause mortality was over 3 times higher than those with no LTCs. For those with ≥ 4 non-cardiometabolic LTCs all-cause mortality was nearly 3 times higher, and patients with only 1 LTC were 1.5 times more likely to die than those with no LTCs. They ranked 24 individual LTCs which had the greatest statistically significant association with higher all-cause mortality, and the 24 conditions identified then informed the PERFORM trial inclusion conditions (3).

A recent systematic review on the impact of multimorbidity on healthcare costs and utilisation in the UK identified 17 relevant studies (14). Multimorbidity was associated with an increase in all types of healthcare costs and primary and secondary care utilisation. For example, those with 4 or more LTCs were some 14 times more likely to have an unplanned potentially preventable hospitalisation compared to a person without LTCs. Those with any number of MLTCs were noted to use primary care health services 2.56 more times than those with 0-1 long-term conditions. There was an increase in total costs with the cost per person increasing for each additional long-term condition. Patients with 1–3 conditions were seen to use between 1.55 and 2.85 times more the mean expected total cost of individuals without any morbidity in this systematic review.

It was observed that different diseases combinations resulted in different total costs. For example, any combination with depression was seen to increase primary costs therefore depression is the main cost-increasing condition across all age ranges (14). In addition, multimorbidity increases hospital costs, care transition costs, dental care use, and emergency department use. However, despite the burden of multimorbidity on mortality, healthcare costs and service utilisation, and on the patient HRQoL, a recent Cochrane review (15) confirmed that there are still no specific treatments to improve clinical outcomes or reduce hospitalisation in multimorbidity. None of the 26 trials reviewed were based on a model of personalised rehabilitation and did not have a prominent component focusing on restoring exercise performance and functional capacity thus reducing the individuals' level of disability associated with LTCs. In summary, there is a lack of data describing clinically effective and cost-effective interventions for those patients with multiple LTCs.

1.3 Rationale for PERFORM intervention programme

The most consistently provided exercise rehabilitation service for people in the UK with LTCs is cardiac and pulmonary rehabilitation. In the UK, cardiac and pulmonary services are well developed and funded through current NHS commissioning arrangements (16) i.e. >200

programmes with workforce training provided by national bodies to support the delivery of high-quality care (British Thoracic Society and British Association for Cardiovascular Prevention and Rehabilitation) Participants in CR and PR experience important benefits, including a reduction in symptom burden, improved physical capacity and enhanced HRQoL for those with these candidate conditions (17,18,19). CR and PR are also cost effective (20,21) and a target growth area in the NHS-England Long Term Plan. (22) However, there currently remains poor provision of exercise based supervised rehabilitation programmes for other LTCs.

For several single LTCs including chronic obstructive pulmonary disease (COPD), post-myocardial infarction/revascularisation, heart failure, peripheral vascular disease, chronic renal disease, transient ischaemic attacks, and osteoarthritis (18, 23-27) a substantial body of evidence has demonstrated improvements in functional capacity, HRQoL and reduced hospital admissions following structured exercise-based rehabilitation. The nature of these programmes are similar to those of CR and PR i.e. they commonly extend over 8-12 weeks and include individually prescribed and progressed exercise (to promote fitness and strength), multidisciplinary support to facilitate effective self-management, symptom management, encouraging healthy lifestyle behaviours (e.g. smoking cessation, activity and diet) and managing mood.

In summary current delivery of exercise-based rehabilitation programmes is fundamentally limited in two important ways:

(1) Provision is dominated by services targeted at cardiovascular and pulmonary conditions, with little or no availability for other LTCs.

(2) Existing rehabilitation programmes are single disease in focus and not designed to consider the complex health needs of people living with MLTCs. Furthermore, the CR and PR workforce are not necessarily equipped to manage the needs for other LTCs or the co-occurrence of multiple conditions. Therefore, patients with MLTCs (alongside their cardiac or respiratory disease) may not necessarily benefit fully from a single disease focused programme.

We aim to extend the scope of rehabilitation and its positive health gains more widely to people with MLTCs. During WP1, we identified people with LTCs most likely to benefit from exercise rehabilitation (3). There were 23 conditions in the core list of which participants must have 2 or more, and a further 21 additional conditions which we have specified in our eligibility criteria. This total of 44 long-term conditions which will extend the exercise-based rehabilitation access beyond those with solely a cardiac or respiratory LTC.

In WP2 the PERFORM intervention was developed with key stakeholders and consumers with the intention of targeting the long-term burden of chronic illness, providing more equitable access to health care system rehabilitation for people with MLTCs, and importantly being person-centred with the potential to improve the health and well-being of more people. The exercise-based group intervention was designed to run for 8 weeks, 2-hour long sessions twice a week for 6 weeks and then 2 hours once a week for the final 2 weeks. The first hour was the exercise component and the second hour a series of 14 health and wellbeing

presentations and discussions. The PERFORM intervention was then tested in clinical practice in the WP3 feasibility study.

1.4 Review of WP3 Feasibility Study

WP3 is the Feasibility study with embedded process evaluation; a multi-centre, parallel two group RCT with individual 2:1 allocation to the PERFORM exercise-based intervention plus usual care (intervention) or usual care alone (control). The trial was conducted across 3 UK sites – 2 in secondary care settings and 1 in a physical therapy clinic in the community. The sample size was 60 people with MLTCs, defined as two or more long-term conditions with at least one having evidence of the beneficial effect of exercise. The feasibility study will inform the WP4 RCT and PCS outcomes, intervention design, site and participant recruitment.

1.4.1 Results of protocol milestones and stop/go criteria

The objective of the feasibility trial was to assess whether pre-specified progression criteria were met to progress to the full RCT to assess the clinical and cost-effectiveness of the PERFORM intervention. Progression criteria were agreed with the project funder and the Programme Steering Committee (PSC).
The following progression criteria were assessed:

- Recruitment: calculated as percentage recruitment target (60 MLTC participants) met at end of 4.5 months recruitment period.
- Retention: calculated as the percentage of MLTC patients randomised with complete EuroQoL (EQ-5D) data (our current proposed primary outcome for the full RCT) at 3 months follow up.
- Intervention adherence: proportion of MLTC participants allocated to PERFORM intervention achieving ≥60% of sessions attended at end of supervised intervention (i.e., ≥10 out of the 16 sessions). Adherence will be measured for each individual participant, which will be collected using attendance registers.

Table 1. Progression Criteria Ranges

		Red	Amber	Green
Recruitment % of N=60 patient target in 4.5 months		<75%	75-99%	100%
Retention at 3 months (% of patients with complete EQ-5D data at 3 month follow up)		<65%	65-79%	80-100%
Intervention adherence	Attendance	<40% of patients attend ≥ 60% of sessions	<50% of patients attend ≥ 60% of sessions	60%-100% of patients attend ≥ 60% of sessions

Table 2. Results of feasibility progression criteria

		Final %
Recruitment % of N=60 patient target in 4.5 months		100%
Retention at 3 months (%of patients with complete EQ-5D data at 3 month follow up)		To be updated with results when available
Intervention Adherence	Attendance	To be updated with results when available

The ongoing WP3 randomised feasibility study may impact the final study design described in this WP4 protocol including the:

(1) final choice of outcome measures

(2) detailed procedures of recruitment of sites and RCT and PCS participants

(3) PERFORM intervention design including content and delivery.

This section will be updated once the results of the feasibility study have been analysed.

1.5 Collaboration with Australia.

A research team led by Professor Anne Holland at the Monash University in Australia were awarded funding in 2023 by the Medical Research Future Fund to evaluate the PERFORM intervention across nine Australian sites – PERFORM-AUS.

Although both PERFORM and PERFORM -AUS will address the clinical and cost effectiveness of the PERFORM intervention in people with LTCs there some important differences and synergies in study designs between the two countries studies. These are summarised below.

PERFORM versus comparator of (no rehabilitation) usual care:

- PERFORM: UK RCT of PERFORM plus standard care (no rehabilitation) vs standard of care (no rehabilitation) in 604 people with MLTCs not eligible for CR or PR across 20 sites. Primary outcome of EQ-5D-5L and a number of secondary outcomes including hospital admission.
- PEFORM-AUS: RCT of PERFORM plus standard care (no rehabilitation) vs standard of care (no rehabilitation) in 440 people with MLTCs not eligible for CR or PR across 9 sites. Primary outcome of hospital admission at 12 months. For its primary outcome, PERFORM-AUS has a required sample size of 1044. Hospital admission data from PERFORM and PERFORM-AUS RCTs will therefore be pooled to achieve this sample size target.

PERFORM versus comparator of CR or PR

- PERFORM: PCS comparison of PERFORM to CR or PR in 302 people with MLTCs eligible for CR and PR (i.e. have cardiac or pulmonary disease) across 20 sites. Comparator patient data will be obtained from NHS Digital national CR and PR audit data. Primary outcome of EQ-5D-5L.
- PERFORM-AUS: RCT comparison of PERFORM to CR or PR in 302 people with MLTCs eligible for CR and PR (i.e. have cardiac or pulmonary disease) across 9 sites. Primary outcome of EQ-5D-5L at 3 months.

2. RESEARCH QUESTION /OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Randomised Controlled Trial (RCT):

2.1.1 Aim

To assess the clinical and cost-effectiveness of the addition of the PERFORM intervention to standard care compared standard of care alone in people with MLTCs not suitable for referral to standard CR or PR.

2.1.2 Objectives

To assess the clinical effectiveness and cost-effectiveness of the addition of the PERFORM intervention to usual care (intervention group) compared to usual care (control group) in people with multiple LTCs not eligible for referral to a standard CR or PR.

To identify barriers and facilitators to future wide scale implementation and develop an implementation toolkit.

2.1.3 Primary Outcome

Generic HRQoL assessed by the EQ-5D-5L index score (28) at 3-months follow up.

2.1.4 Secondary Outcomes

The following proposed patient outcomes will be collected at baseline (pre-randomisation), 3-month follow up (post randomisation) and 12-month follow-up (post randomisation):

- HRQoL: EuroQoL (EQ-5D-5L) VAS(28)
- Exercise/functional capacity: incremental shuttle walk test (ISWT)(29)
- Endurance Shuttle Walk Test (30,31)
- 4 Metre Gait Speed (MGS) (32)
- Strength: Hand Grip Strength (33)

- Mood: Patient Health Questionnaire-9 (PHQ-9) (34)
- Generalised Anxiety Disorder Assessment-7 (GAD-7) (35)
- Physical activity: International Physical Activity Questionnaire (IPAQ) (36)
- Frailty: Functional Assessment of Chronic Illness Therapy; Fried Exhaustion and Weight Loss (37,38)
- Fatigue (FACIT-F) (39)
- Pain: Brief Pain Inventory (BPI) (40)
- Health and disability: WHODAS (41)
- Breathlessness: Dyspnoea-12 (42)
- Sleep: Medical Outcome Study Sleep Scale (MOS Sleep Scale) (43)
- Cognition: MoCA (44)
- Multimorbidity Treatment Burden Questionnaire (MTBQ) (45)
- ICEpop CAPability Measures for Adults (ICECAP-A) (46)
- Exercise adherence: Exercise Adherence Rating Scale (EARS) (47)
- Hospitalisations and overnight hospital admissions at 12 months
- Clinical events – mortality, primary care contacts, and social and healthcare utilisation including medication

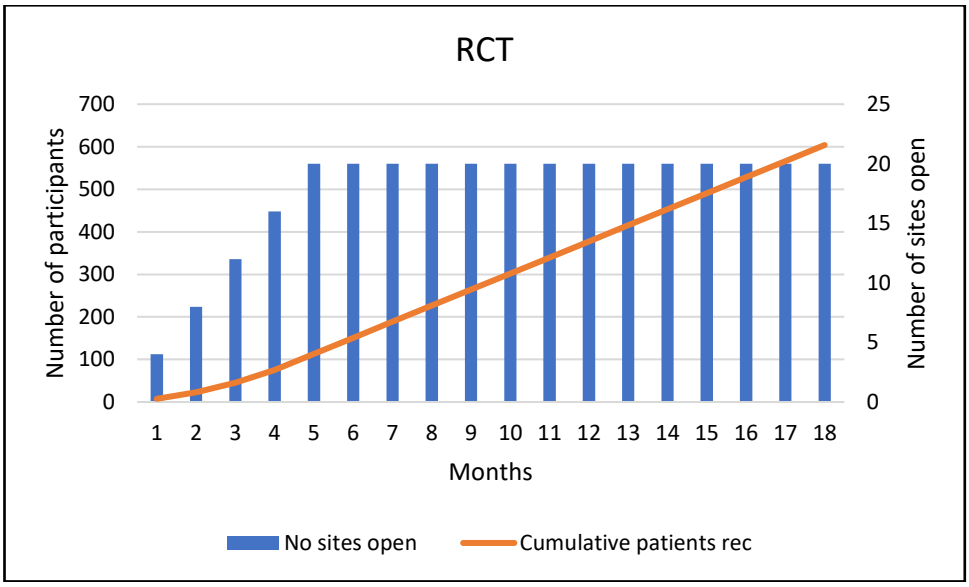
All primary and secondary outcomes will be collected at the baseline assessment visit and at the 3- and 12-month follow up, except EARS which is collected only after completion of PERFORM intervention programme at 3 and 12-months follow up.

2.1.5 Risks of bias/contamination

Given the nature of interventions, participants and clinicians will not be blinded to group allocation. However, we will seek to keep outcome assessors at the 3 and 12 month follow up blinded. Any outcome assessor blind breaks will be recorded. Contamination will be assessed by asking control participants to report whether they knew anyone in the intervention group of the trial and whether they had access to any PERFORM intervention resources.

2.2 6-month internal pilot

A 6-month internal pilot phase will be used to demonstrate acceptability and feasibility of randomisation and recruitment commensurate with timely completion. Based on steady state target recruitment rate of 1.8875 patients/month/site (see recruitment graph below) and all 20 sites open, by the end of pilot internal phase we aim to recruit 135 participants.



Graph 1. Steady state recruitment graph

Table 3. Internal pilot phase progression criteria

	Red	Amber	Green
Recruitment % of patient target in 6-months	<60%	60-89%	≥90%
Total number of patients recruited by month 6	<90	90-135	≥135

Red: Halt recruitment.
Amber: Progress if action plan to mitigate problems can be determined and agreed with Programme Steering Committee.
Green: Continue recruitment.

2.3 Prospective Cohort Study (PCS):

2.3.1 Aim

To assess the clinical and cost-effectiveness of PERFORM in people with multiple LTCs suitable for referral to standard CR and PR.

2.3.2 Objectives

To assess the clinical effectiveness and cost-effectiveness of the addition of the PERFORM intervention to usual care compared to standard CR and PR plus usual care (control group) in people with multiple LTCs.
To identify barriers and facilitators to future wide scale implementation and develop an implementation toolkit.

2.3.3 Primary & Secondary Outcomes

Primary and secondary outcomes for consented cohort study patients as listed in RCT above.

The consented study patients will have their outcomes compared observationally to a control group of patients receiving standard CR or PR using routinely collected data from the National Audit of Cardiac Rehabilitation (NACR) database or National Respiratory Audit Programme (NRAP). We will ensure that key outcomes such as EQ-5D-5L are added to this routine data for the period of study data collection.

2.4 SWAT: Aim, Objectives and Outcomes

2.4.1 Aim.

To assess the use of Social Media (SoMe) to reduce trial attrition.

2.4.2 Objectives.

To test the hypothesis that SoMe creates a community of support for RCT participants and thereby reduces trial attrition, generating new evidence of SoMe theory within clinical trials. To examine whether and how SoMe may meaningfully improve rehabilitation outcomes, such as HRQoL, reduced programme attrition, increased attendance, and expose barriers and faciltators for clinical trial engagement.

2.4.3 Primary Outcome

The primary quantitative outcome of the SWAT will be trial 'retention' defined as the proportion of RCT participants who provide a primary outcome (EQ-5D-5L) assessment at 12-months follow up.

2.4.4 Secondary Outcomes

Proportion of RCT patients with completed primary outcome at 3-months follow up

Proportion of RCT patients with completed ISWT at 3-months follow up
Proportion of RCT patients with completed ISWT at 12-months follow up

For those on PERFORM intervention - Proportion of PERFORM intervention patients completing ≥60% of intervention sessions

2.4.5 Exploratory endpoints/outcomes

The impact of social media on quality of life and mental health,

- HRQoL: EuroQoL (EQ-5D-5L)(50)
- Mood: Patient Health Questionnaire-9 (PHQ-9) (56)
- Generalised Anxiety Disorder Assessment-7 (GAD-7) (57)

Additionally, social media use will be explored for the following baseline patient characteristics - age, IMD rank, ethnicity and education level.

3 TRIAL DESIGN

A comprehensive study with concurrent multicentre superiority RCT and PCS with embedded process and economic evaluations and a 6-month internal pilot phase. There is a SWAT to test whether providing study patients access to social media will improve their retention in the study.

3.1 RCT Design

RCT patients are those with ≥2 LTCs at least one of which has evidence of benefit from an exercise-based intervention but are **not** eligible for referral to a standard CR or PR programme. RCT patients will be randomly allocated 1:1 to either intervention (PERFORM rehabilitation programme + usual care) or control (usual care alone). This will be conducted across twenty sites with a total of 604 participants recruited over an 18-month period, with 302 participants in each arm. There is a 3-month and 12-month follow up after randomisation.

3.2 PCS Design

PCS patients are those with ≥2 LTCs who **are** eligible for referral to a standard CR or PR programme (i.e. have an index diagnosis of post-MI, post-revascularisation, stable angina, heart failure and chronic obstructive lung disease). These patients will all be assigned to the PERFORM intervention and their outcomes compared (observationally) to a contemporaneous cohort of patients receiving standard CR or PR using routinely collected data from the National Audit of Cardiac Rehabilitation (NACR) database or National Asthma and COPD Audit Programme (NACAP). This will be conducted across the same twenty sites as the RCT, with N=302 PERFORM intervention participants. There is a 3-month and 12-month follow up. The PCS participants will not be randomised.

3.3 Study within a Trial – WP5 The role of social media

We examine the value of using social media within the RCT described above in WP4, using a study within a trial (SWAT) approach and an embedded qualitative enquiry of patient engagement in research.

Sites will be allocated 1:1 at a cluster level to the SoMe intervention group (N=10 sites) or SoMe control group (N=10 sites). The sites allocated to the SoMe intervention will provide a direct link to a social media group to all of their recruited participants after randomisation at the baseline visit.

To mitigate the risk of contamination with the WP4 question of the impact of multimorbid intervention, we will ensure that participants allocated to the SoMe intervention are members of a SoMe group that comprises either all PERFORM intervention participants or all PERFORM control participants (and not a mix of the two). We therefore believe that this SWAT has a low threat to the validity of our PERFORM effectiveness question addressed by WP4.

4 TRIAL SETTING

The RCT, PCS and the SWAT will be conducted across the same 20 study sites.

The study sites will be centres that have an established cardiac/pulmonary or existing exercise rehabilitation programme that can be adapted to deliver the PERFORM intervention. The sites will offer supervised rehabilitation within either an acute hospital or a community service.

Patients will be recruited from both primary and secondary care pathways including cardiac and pulmonary registers and clinic lists, outpatient clinics, primary care referrals and other relevant pathways as outlined in section 6.2.

Follow-up procedures will be conducted on NHS premises or the non-NHS study sites. Conduct of the study will be led by a local principal investigator, supported by a research nurse/fellow and/or relevantly trained rehabilitation staff at each site, all of whom are trained in Good Clinical Practice and in the requirements of the study protocol.

5. PARTICIPANT ELIGIBILITY CRITERIA

5.1 RCT Inclusion Criteria

- Adults ≥18 years old
- Able and willing to provide informed consent
- To be mobile (including the use of walking aids)
- Breathlessness symptoms when hurrying on level ground or walking up a slight hill (adapted from MRC 2 or above)
- 2 or more long terms conditions from the lists below– with at least one LTC identified from work package 1 as having evidence of the beneficial benefits of exercise. The data identified that individuals must have a diagnosis of **at least one** of the following:
    - Arthritis
    - Asthma
    - Atrial fibrillation
    - Bronchiectasis
    - Cancer
    - Chronic kidney disease
    - Chronic obstructive pulmonary disease (COPD)
    - Connective tissue disease (pain)
    - Coronary heart disease
    - Dementia
    - Depression
    - Diabetes mellitus
    - Heart failure

- Hypertension
- Long-COVID
- Multiple sclerosis
- Osteoporosis
- Painful condition
- Parkinson’s disease
- Peripheral vascular disease
- Polycystic ovarian syndrome
- Psychoactive substance misuse
- Stroke or transient ischaemic attack

Patients could also have one of the following conditions from the list below:

- Anorexia nervosa or bulimia
- Anxiety
- Chronic fatigue syndrome
- Chronic liver disease
- Chronic sinusitis
- Diverticular disease
- Endometriosis
- Epilepsy
- Glaucoma
- Inflammatory bowel disease
- Irritable bowel syndrome
- Meniere’s disease
- Migraines
- Pernicious anaemia
- Prostate disorders
- Psoriasis or eczema
- Schizophrenia or bipolar affective disorder
- Thyroid disease
- Treated constipation
- Treated dyspepsia
- Viral hepatitis

5.2 RCT Exclusion Criteria

Individuals will be excluded for the following:

- Unable to give consent for the study
- Unable to communicate in English (carer or support worker may be available)
- Known contraindications to exercise (as defined by the American College of Sports Medicine) ("ACSM's guidelines for exercise testing and prescription 11th Ed. 2021.") to include
    - Unstable cardiac disease
    - Current fever
    - Significant aortic aneurysm (more than 5.5 cm)
- Unable to attend in-person training sessions
- Participation in an exercise rehabilitation programme in the last 6 months
- Unstable psychiatric disorder that limits or disrupts group-based interventions
- On an End of Life pathway with a prognosis of less than 12 months survival
- Active malignancy (on chemotherapy/radiotherapy/planned urgent surgery)
- For people on a surgical waiting list a pragmatic decision will be made on a case-by-case basis of the type of surgery, urgency and likely wait times
- Pregnancy
- Under 18's
- Living in a Nursing Home.
- Unsafe to exercise in a group without 1:1 supervision (e.g. significant risk of falls, significant psychiatric issues)
- Greater than 80% predicted on the ISWT at initial assessment

5.3 PCS Eligibility Criteria

Participants in the PCS will have the same eligibility criteria as listed for the RCT above. They must also be eligible for standard CR or PR, e.g., have a diagnosis of one of the following conditions:

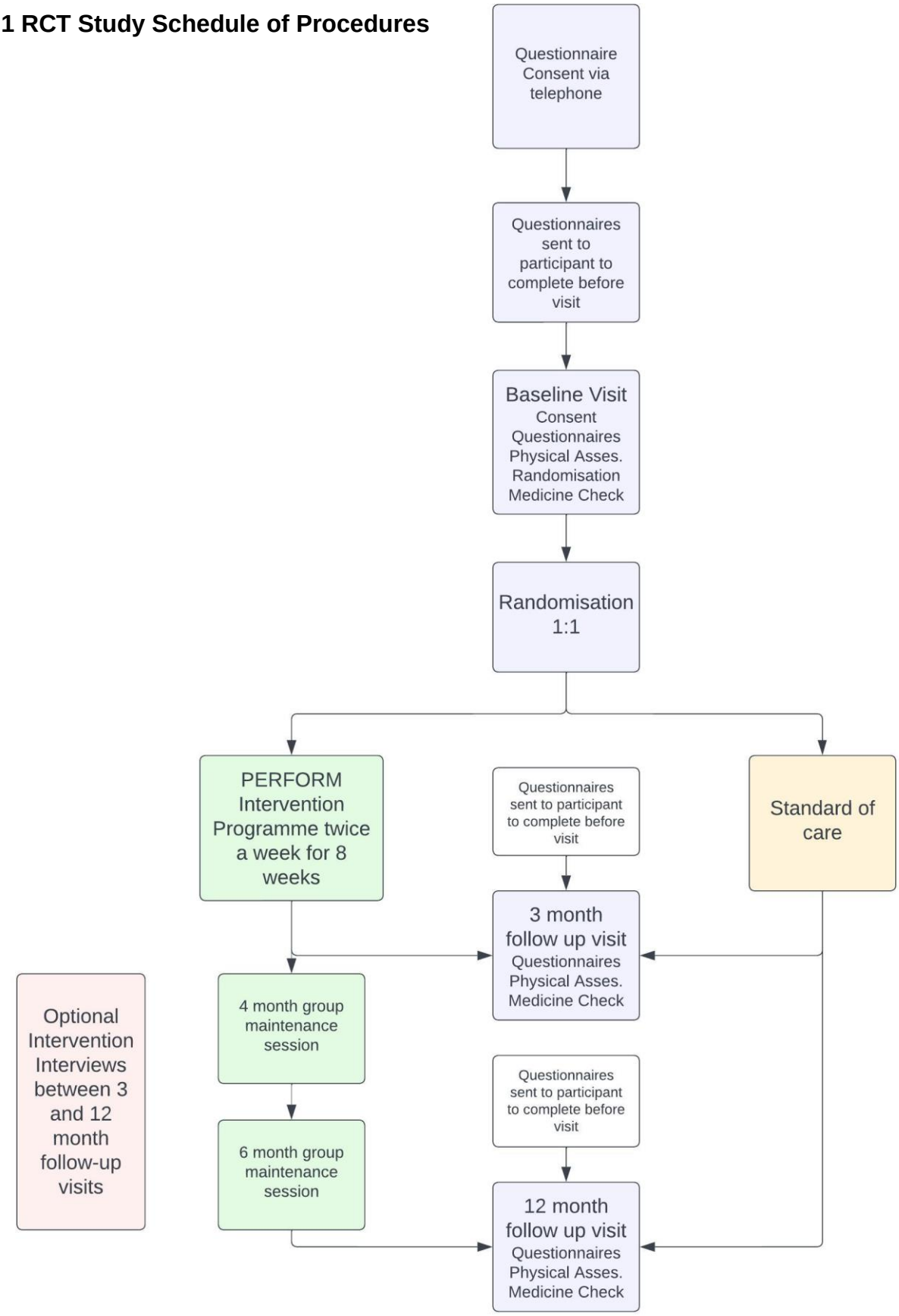
- Post-MI, Post-revascularisation, Stable angina, Heart failure, Chronic Obstructive Pulmonary Disease, Bronchiestasis

5.4 SWAT Eligibility Criteria

There are no specific eligibility criteria for the Social Media study within a trial – all participants will be included.

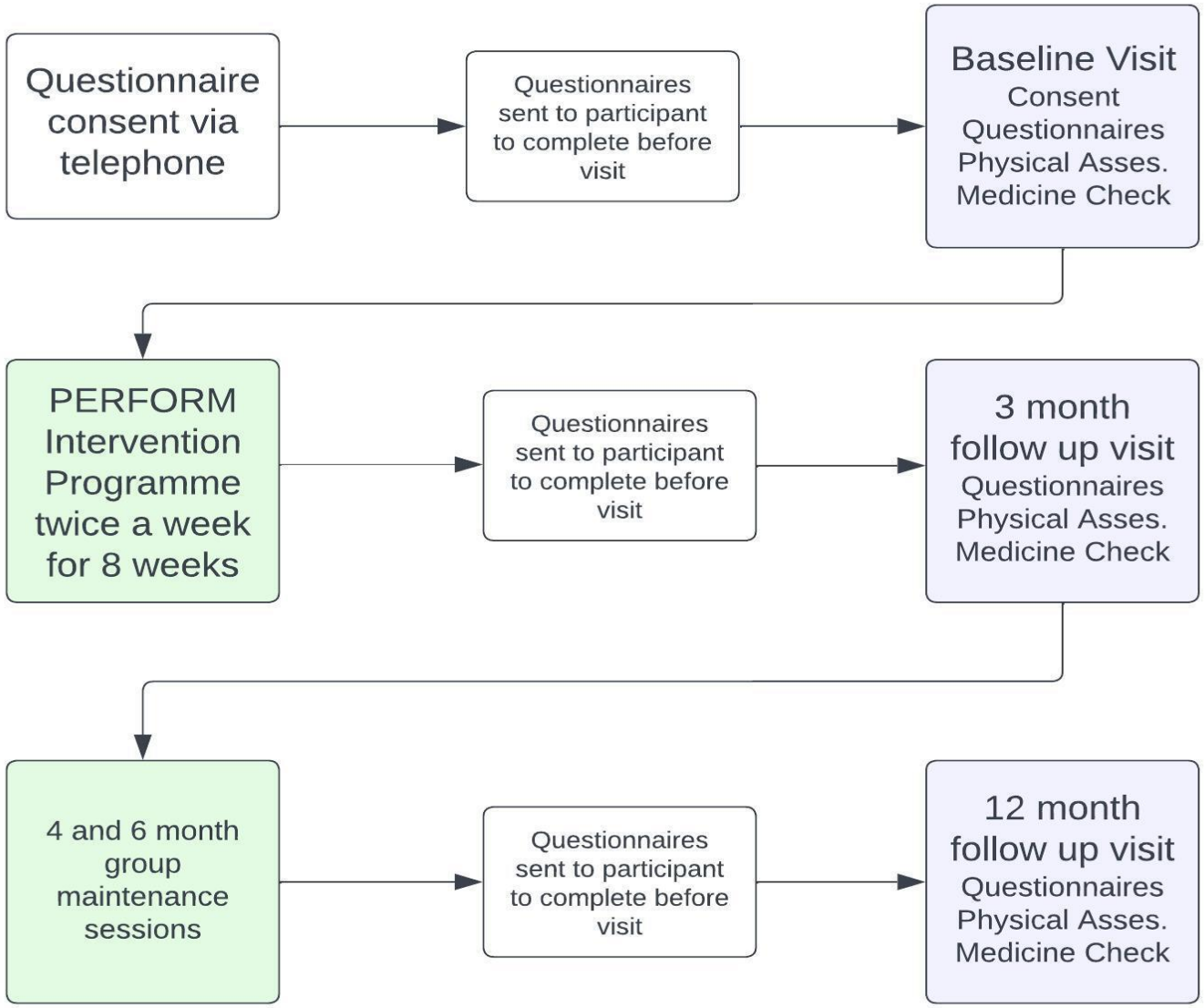
6. STUDY PROCEDURES

6.1 RCT Study Schedule of Procedures



Procedures	Randomised Controlled Trial Study Visits									
	Pre Screening	**Screening and Baseline**	**Initial Physical Assessment Form** (After randomisation at baseline visit)	**Intervention Phase** (Within 4 weeks of randomisation/ baseline visit)	**Programme Discharge Form** (Immediately after last intervention session)	**3-Month Follow-Up** (3 months post-randomisation ± 4 weeks)	**4-month group maintenance Session** (Intervention patients only 4-month post randomisation)	**6- month group maintenance Session** (Intervention patients only, 6-month post randomisation)	**Optional Intervention and SWAT interviews between 3 and 12 months**	**12-Month Follow-Up** (12 months post randomisation ± 4 weeks)
Invitation	X									
Eligibility assessment		X								
Informed consent		X								
Socioeconomic questions		X								
Medical History		X								
Physical assessments, ISWT, ESWT, 4MGS, HG		X				X				X
Outcome Questionnaires		X				X				X
Resource use questions		X				X				X
SAE check		X				X				X
Conmedications check		X				X				X
Randomisation 1:1 to PERFORM intervention or usual care		X								
Sites in Social Media Arm offer Facebook group link to participants		X								
PERFORM intervention group		X	X	X	X	X	X	X	X	X
Usual care/control group		X				X				X
Optional Interviews									X	

6.2 PCS Study Schedule of Procedures



Schedule of Procedures	PCS Visits								
	Pre Screening	**Screening and Baseline**	**Initial Physical Assessment Form** (After randomisation at baseline visit)	**Intervention Phase** (Within 4 weeks of randomisation /baseline visit)	**Programme Discharge Form** (Immediately after last intervention session)	**3-Month Follow-Up** (3 months post-randomisation ± 4 weeks)	**4-month group maintenance Session** (Intervention patients only 4-month post randomisation)	**6-month group maintenance Session** (Intervention patients only, 6-month post randomisation)	**12-Month Follow-Up** (12 months post randomisation ± 4 weeks)
Invitation	X								
Eligibility assessment		X							
Informed consent		X							
Cohort study: No randomisation		X							
Socioeconomic Questions		X							
Medical History		X							
Physical assessments, ISWT, ESWT, 4MGS, Handgrip strength		X				X			X
Outcome questionnaires		X				X			X
Resource use data collection questionnaire		X				X			X
SAE check		X				X			X
Conmedications check		X				X			X
PERFORM intervention			X	X	X	X	X	X	X

6.3 SWAT Schedule of Procedures

The N=10 social media sites will be given the details of 2 Facebook groups – one for participants taking part in the PERFORM intervention programme and one for control (usual care) group participants. Once a participant has been consented, and randomised in the RCT, they will be provided the link for the relevant Facebook group by a member of the site team. This will be done by leaflet, by a QR code, or by WhatsApp or email. The site staff will have no further involvement with the social media groups.

The N=10 SWAT control group sites will not provide Facebook group details to their consented participants.

6.4 Recruitment

6.4.1 Participant Identification

Individuals will be recruited from a number of sources, including from relevant specialists, and both primary and secondary care.

- Primary care services
    - Will refer participants to community-based exercise centres via their standard referral pathways.
    - If needed to mitigate against low recruitment and with support of the CRN, GP practices will return expressions of interest (EOIs) and will be approached to act as PIC sites. The GP practice PIC sites and their mNCAs will be submitted as an amendment at a later date if they are needed due to low recruitment.GP practice internal staff will then identify eligible patients and invite them to take part in the study by posting an invitation letter, study PIS, and reply slip with return envelope. Interested patients will then return the reply slip to their relevant research site in the provided return envelope for the study team to contact them to join the study.
- Opportunistic recruitment via specialist clinics:
- Secondary care clinics (single disease focused clinics where the data collected in WP1 identified the ‘clinical disease’ as an important disease in our review of exercise-based rehabilitation in long term conditions and the multi-morbid clusters) - clinical staff will identify potential participants and share the PIS with the patient, this will include contact details/reply slip and pre-paid envelope to contact the study team if they are interested in taking part. Research staff may also attend clinics to directly share the PIS and discuss the study with patients identified as having 2 or more LTCs, but contact will be initiated by a member of the clinical care team.
- Long Covid pathways (in primary and secondary care) - clinical staff will identify potential participants and share the Patient Information Sheet with the patient with contact details/reply slip and pre-paid envelope to contact the study team if they are interested in taking part.
- Physiotherapy outpatient clinic referral list (primary and secondary care) - clinical staff will identify potential participants and share the Patient Information Sheet with the patient with contact details/reply slip and paid envelope to contact the study team if they are interested in taking part.

- Pain Clinics commonly delivered in primary and secondary care - clinical staff will identify potential participants and share the Patient Information Sheet with the patient with contact details/reply slip and paid envelope to contact the study team if they are interested in taking part.
- Clinicians and other healthcare staff familiar with the study protocol and inclusion and exclusion criteria will also use any opportunity when in contact with potential participants and will share the Patient Information Sheet with the patient with contact details/reply slip and paid envelope to contact the study team if they are interested in taking part.

Recruitment strategy from specialist clinic lists / databases:

- To mitigate against low recruitment from opportunistic recruitment from specialist clinics, searches for eligible patients from hospital systems/databases will be conducted by a healthcare professional / relevant clinical administrator that has a 'legitimate relationship' with the patient such as a clinician. Some NHS sites also consider research staff to be embedded within clinical teams and are therefore regarded as 'part of the clinical team'. The search would include people who have been under the specialist clinic within the last year, but do not have to be under active follow-up. The lists of potentially eligible participants and their contact details will be sent via secure means (Trust to Trust email or nhs.net to nhs.net email) to an administrator (clinical or research administrator). A letter of invitation will be sent on behalf of the clinician (or health or social care professional) and the research team. The invitation letter will provide an overview of the study and invite potential participants to call the research team should they be interested in taking part. The invitation letter will also clearly state that if there is no contact from the patient within 2 to 3 weeks, they may be followed up with a telephone call.

  The lawful basis for accessing patient details in this way is covered by Legitimate Interests (as identification of the patient is conducted by someone with legitimate access).

  Any patient lists and identifiable data derived from these searches will be deleted at the end of the study.

6.4.2 Screening and Eligibility Assessment

A pre-screening eligibility check will be conducted from a participant's medical notes, GP referral or via telephone to check the eligibility criteria:

Screening will be based upon the following criteria

- Disease profile that matches the data from WP1 of PERFORM that identified Individuals with long term conditions that is amenable to exercise. These include cardiac disease, respiratory disease, cardio-metabolic disease (including diabetes), Long COVID, painful conditions, depression and neurological conditions.
- Disease severity (with the exception of exclusion criteria) will not influence screening.
- No laboratory-based tests will inform screening.
- Exclusion criteria (see above 5.2)

Where pre-screening eligibility is confirmed, a screening call will be arranged to provide further information about the study and to check their suitability to take part in the study. Participant

Information Sheets and a Questionnaire Completion Information Sheet will be sent to the participant following the screening call if the participant indicates they would like to take part.

A screening log will be completed for all patients who meet the eligibility criteria and who have been approached for the PERFORM study, whether by verbal invitation or an invitation letter. The following information will be collected on the screening log; Site ID, Screening Date, Patient Initials, Year of Birth, Age, Male/Female, No of LTCs, Eligible as per protocol Yes/No, Eligible for RCT/PCS, Screened in person Yes/No, Enrolled Yes/No and Reason for Exclusion if not enrolled.

Further screening to check the eligibility criteria will take place before informed consent at the baseline assessment visit.

6.4.2.1 Co-enrolment

Co-enrolment is to be discussed with the potential participant during eligibility checks and screening to determine if the participant is currently taking part in any other research studies. If the participant is already in an observational or questionnaire only study then co-enrolment would be permitted. If the participant is already in a CTIMP or interventional study then they would not be able to take part in PERFORM until their participation in the other trial had ended. If the potential participant has been in any type of research study recently but they are out of the trial follow-up period then they are able to take part in PERFORM.

6.4.3 Informed Consent

The Site Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study, including the collection of identifiable participant data.

The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

The participant will be given as long as they would like to consider the information in the PIS and ask any questions and/or do any research regarding information provided in the PIS.

Participants will be provided with a 'Questionnaire Completion Information Sheet' at the same time as the main Participant Information Sheet. This is to give participants the option of completing the questionnaires prior to the baseline visit instead of at the visit. Each questionnaire takes a few minutes to complete and the combined time is approximately 30-60 minutes. By completing them at home, it will mean that the baseline visit will take less time and will place less burden on participants at the time of the visit. After having time to consider, a member of the site study team will contact them to ask if they would like to participate in the PERFORM trial. If the participant indicates yes, then they will be given the option to consent to early questionnaire completion. As this is via telephone consent, the staff member will read out each consent statement and ask the patient if they agree to each one. The staff member will initial and date all the statements. This consent form will be counter signed by the PI or another member of the research team. The original copy will be filed in the ISF, one copy will be provided to the participant and one copy will be stored in the participant's medical record.

If the participant wants to take part in the PERFORM trial but does not want to telephone consent to early questionnaire completion, they will be able to do them at the time of the visit with the assistance of the researcher.

When the participant attends the baseline visit the researcher will go through each of the consent statements with them on the main consent form and ask the patient to initial if they agree to each one. Both the participant and the site researcher will print, sign and date the consent form.

For the post-intervention interviews, participants will be given the option to consent to the Glasgow study team contacting them about participating in the interviews at their baseline visit (when informed consent is taken for the main study). There will be a separate consent form and PIS for the interviews, which will be given to participants to read and consider. Where consent is provided, participants contact details will be securely shared with the Glasgow study team by the site. The participants will then be contacted by the interviewers to set up their virtual interview, where the interviewer will go through the consent form statements one-by-one with the participant at the beginning of the interview session. The interviewer will initial next to each box that the participant agrees to, and the interviewer will sign and date the bottom of the consent form. A print-out of the electronically signed consent form or the original wet-signature consent form will be filed in an ISF at the Glasgow site (see Section 11.2). A copy (physical or electronic) of the interviewer-signed consent form will be sent to the participant.

For the SWAT interviews, participants will be given the option to consent to the University of Salford study team contacting them about participating in the interviews at their baseline visit (when informed consent is taken for the main study). There will be a separate consent form and PIS for the interviews, which will be given to participants to read and consider. Where consent is provided, participants contact details will be securely shared with the Salford study team by the site. The participants will then be contacted by the interviewers to set up their virtual interview, where the interviewer will go through the consent form statements one-by-one with the participant at the beginning of the interview session. The interviewer will initial next to each box that the participant agrees to, and the interviewer will sign and date the bottom of the consent form. A print-out of the electronically signed consent form or the original wet-signature consent form will be filed in an ISF at the Salford site (see Section 11.2). A copy (physical or electronic) of the interviewer-signed consent form will be sent to the participant.

6.5 Randomisation

6.5.1 RCT Randomisation

The LCTU will supply a web-based randomisation system from a third party (Sealed Envelope Ltd.). Participants in the RCT will be individually randomised in a 1:1 ratio to intervention or control. Once the participant has provided written consent to the study and a healthcare professional has confirmed eligibility, randomisation will be performed randomly allocated in a 1:1 ratio to either PERFORM rehabilitation programme or standard of care. Randomisation will be minimised on age (<75 years vs ≥75 years), sex, and number of LTCs (≤3 LTC vs >3 LTC) within site strata. To maintain concealment and minimise selection bias, randomisation will be performed after the baseline visit using the valuated password-protected web-based randomisation system Sealed Envelope supported by Leicester CTU to ensure concealment. They will be allocated a Randomised Controlled Trial Participant ID in the format RXX(Site no.)-XXX(Participant no.)

6.5.2 PCS Randomisation

Participants in the PCS will not be randomised. They will be allocated a Prospective Cohort Study Participant ID in the format PXX(Site no.)-XXX(Participant no.) via Sealed Envelope.

6.5.3 SWAT Randomisation

Sites will be allocated 1:1 at a cluster level to the SoMe intervention group (N=10 sites) or SoMe control group (N=10 sites) at the point of sponsor green light. All participants in the Social Media sites will be offered a direct link to a Facebook group once they have been randomised in the RCT or allocated a PSC place. No further randomisation will occur.

6.6 Study Assessments

6.6.1 Baseline Assessments

The baseline assessment visit will be completed by a trained healthcare professional following informed consent. It is anticipated that the duration of the visit will be approximately 2 hours.

- Inclusion/exclusion and study entry verification
- Informed consent
- Demographics including:

  Date of birth

  Gender and assigned sex at birth

  Ethnicity

  Marital/civil partnership status

  Living situation

  Smoking status

  Employment status

  Education status

Address (postcode)

Socio Economic Status

Caring responsibility

- Medical History (including long term conditions,)
- Vital signs (height, weight, resting blood pressure, resting heart rate and resting respiratory saturation)
- Concomitant medicine check
- Healthcare Resource Use Data Collection Questionnaire

Measures of physical capacity:

- **Exercise capacity**
  – Incremental shuttle walking test
  The incremental shuttle walk test (ISWT; 29) is an externally paced, incremental test that requires patients to walk around a 10m course at a speed dictated by an audio tape. The walking speed progressively increases each minute, for a maximum of 12 minutes, with the test terminated when the patient is no longer able to keep up with the target walking speed. Individuals will perform the ISWT twice pre-intervention for familiarisation purposes with the highest distance achieved used for exercise prescription, and once post-intervention.
  Time to complete: 20 minutes

  – Endurance shuttle walking test
  The endurance shuttle walk test (30,31) is a constant-load exercise test which measures the ability of the participant to sustain a given sub-maximal exercise capacity. It requires patients to walk around a 10m course at a speed dictated by an audio tape. The appropriate walking speed is chosen according to the total distance performed in the baseline ISWT. Standard instruction is given to each participant before the test. The participant is asked to walk as long as possible until they are unable to continue. Individuals will perform the ESWT twice pre-intervention for familiarisation purposes and the endpoint of the test is how long the participant walks at the constant endurance speed.
  Time to complete: 20 minutes

- **Physical frailty (as part of Fried; Fried et al., 2001 [32])**
  - 4 Metre Gait Speed (MGS)
  The time (in seconds) taken to walk 4m at a usual pace will be recorded.
  Time to complete: 2 minutes

- **Strength**
  – Hand Grip Strength (HGS) (33)
  Maximum handgrip strength will be measured using a dynamometer, performed three times on both the dominant and non-dominant hand. The highest score is taken per hand. This measure also part of the Fried frailty assessment (37).

Symptom burden:

- **Overall health**

  – EQ-5D-5L

  The EQ-5D-5L (EuroQol Group, 1990 [28]) consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The former has 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels (no problems, slight problems, severe problems, extreme problems). The patient is asked to select an appropriate level for each dimension. The EQ VAS records the patient's self-rated health on a visual scale that ranges from 'the best health you can imagine' to 'the worst health you can imagine'.

  Time to complete: 5 minutes

- **Fatigue**

  – FACIT

  The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F; https://www.facit.org [39]) is a 13-item questionnaire that assesses self-reported fatigue. Patients are asked to respond to each item using a 4-point Likert scale ranging from 0 (not at all) to 4 (very much). After the negatively stated items are reversed, a total score is calculated with higher scores indicating greater fatigue.

  Time to complete: 5 minutes

- **Pain**

  – Brief Pain Inventory

  The Brief Pain Inventory (BPI; Cleeland and Ryan,1991 [40]) measures the intensity of pain and degree of pain relief provided by medications. The BPI also measures interference of pain in the individual's life, including the degree that pain interferes with general activity, walking, work, mood, relations with others and sleep.

  Time to complete: 5 minutes

- **Mood (anxiety)**

  – Generalised Anxiety Disorder Assessment (GAD-7)

  The Generalised Anxiety Disorder Assessment (GAD-7; Spitzer et al., 2006 [35]) is used to assess the presence and/or severity of anxiety. The measure comprises of 7 items that the patients scores between 0 (not at all) and 3 (nearly every day), with higher scores representing a greater level of anxiety.

  Time to complete: 5 minutes

- **Mood (depression)**

– The patient health questionnaire (PHQ-9)

The patient health questionnaire (PHQ-9; Kroenke et al., 2001 [34]) is used to screen, diagnose, monitor and assess the severity of depression. The measure includes 9 items that patients score between 0 (not at all) to 3 (nearly every day), with higher scores indicating increased depression severity.

Time to complete: 5 minutes

- **Health and Disability**
  – World Health Organisation Disability Assessment

  The World Health Organisation Disability Assessment (WHODAS; World Health organisation, 2012 [41]) is a 36-item measure that assesses disability in adults age 18 years and older.

  Time to complete: 10 minutes

- **Breathlessness– Dyspnoea -12**

  The dyspnoea 12 questionnaire (Yorke et al., 2010 [42]) includes 12 items that are scored between 0-3; a total score is then calculated that provides a global score of breathlessness severity that includes both physical and affective elements. Higher scores represent greater sensations of breathlessness.

  Time to complete: 5 minutes

- **Sleep**
  – Medical Outcome Study Sleep Scale (MOS Sleep)

  The Medical Outcome Study Sleep Scale (MOS Sleep; Hays et al., 1992 [43]) is a 12-item questionnaire that assesses sleep disturbance, sleep adequacy, somnolence, quantity of sleep, snoring, and awakening short of breath or with a headache.

- **Cognition**
  – The Montreal Cognitive Assessment

  The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005 [44]) is a 30-point cognitive screening test designed to help detect mild cognitive impairment and Alzheimer's disease. It includes items that assess short-term memory, visuospatial abilities, orientation, executive function, concentration, attention, and working memory.

  Time to complete: 10 minutes

- **Physical activity**
  – International Physical Activity Questionnaire (IPAQ)
  The international physical activity questionnaire (Craig et al., 2003 [36]) is a self-reported measure for physical activity. To complete the measure individuals must recall their physical activity from the past 7 days.
  Time to complete: 5 minutes

- **Treatment burden**
  – Multi-morbid treatment burden questionnaire (MTBQ)
  The Multi-morbidity Treatment Burden Questionnaire (MTBQ; Duncan et al., 2020 [45]) is a 10-item questionnaire that aims to measure treatment burden in patients with multi-morbidity.
  Time to complete: 5 minutes

- **Frailty**
  – Fried exhaustion & weight loss
  Self-reported exhaustion will be assessed using 2 questions from the Center for Epidemiologic Studies Depression (CERS-D) scale. Weight loss will be assessed as self-reported unintentional weight loss in the last year. For this, patients will be asked if they have unintentionally lost more than 4.5kg in the last 12 months. These measures are part of the Fried frailty assessment (37,38).
  Time to complete: 5 minutes

- **Capability and wellbeing**
  ICEpop CAPability measure for Adults (ICECAP-A)
  The ICEpop Capability Measure for Adults (ICECAP-A; Al-Janabi et al., 2012 [46]) measures 5 capabilities (stability, attachment, autonomy, achievement, and enjoyment) that are important to quality of life.
  Time to complete: 5 minutes

The questionnaires are contained within a Participant Questionnaire Booklet, separate to the Participant CRF. Participants are given the option to consent to completing the questionnaires in advance of the visit or completing them at the in-person research visits. The questionnaire booklet may be sent out in advance of the baseline, 3-month or 12-month research visit for the participant to complete within their own time and to return to the researcher at the visit. This is to reduce participant and researcher burden at the time of the visit as the combined time to complete all questionnaires is approximately 60 minutes. The researcher will be able to quality check the responses and complete any unfinished questionnaires on their return. As the primary outcome the EQ-5D-5L will be completed under supervision at the visits. The MOCA and Fried frailty will be completed in person too.

If a participant states that they would rather do the questionnaires at the time of the baseline, 3 or 12 month follow up visit they will be presented in a consistent order and completed under supervision or with a healthcare professional as necessary.

It is best practice to leave 30minutes in between each of the shuttle measurements. There is an opportunity to review assessments and complete a number of assessments in between the practice and repeat ISWT and ESWT. It is planned to complete each of the baseline, 3-month and 12-month follow-up assessments in one visit.

6.6.2 Rehabilitation phase

For those participants randomised to the rehabilitation programme in the RCT or participating in the cohort study, the rehabilitation phase will commence within 4 weeks of the baseline assessment visit. Individuals will be invited to participate in the PERFORM intervention (see 7.1).

6.6.3 3-month Follow-up assessments

The 3-month follow up visit will take place at 3 months post randomisation (± 4weeks).

- All measures identified above will be repeated, excluding consent, demographic information and medical history. All outcome measures will be conducted by a blinded assessor who will have no knowledge of previous test results or treatment allocation. The following outcome measure of exercise adherence will also be included in the 3-month follow-up.
- **Exercise Adherence Rating Scale (EARS)**
  The Exercise Adherence Rating Scale (EARS; Newman-Beinart et al., 2017 [47]) includes 6 items that directly assesses adherence behaviour. The EARS is scored on a 5-point Likert scale from 0 (completely agree) to 4 (completely disagree). Items 1, 4 and 6 are reverse scored, resulting in a score between 0 and 24. A higher score indicates better exercise adherence.
  Time to complete: 5 minutes
- **Facebook Use Questionnaire**
  For those participants in the Social Media SWAT there will be an additional set of questions looking at their participation and engagement in the Facebook group.
- Participants will be given the option of being sent the participants questionnaires in advance of the 3-month follow-up visit to complete at home. They will bring the completed questionnaires in with them for the visit.
- If the participant indicates that they are unable to attend for the 3-month visit they can complete the EQ-5D-5L, Healthcare resource use questionnaire and SAE check over the telephone. This has to be done within the visit window.
- If the site staff are unable to get in contact with the participant for the 3-month follow-up visit then they may collect the participants status from secondary care hospital records or from the participants GP. This is to complete the end of trial, protocol deviation and death forms.

6.6.4 12-month follow-up assessment

The 12-month follow up visit will take place at 12 months post randomisation (± 4weeks).

- All measures identified above will be repeated, excluding consent, demographic information and medical history. All outcome measures will be conducted by a blinded assessor who will have no knowledge of previous test results or treatment allocation. The following outcome measure of exercise adherence will also be included in the 3-month follow-up.
- **Exercise Adherence Rating Scale (EARS)**
  The Exercise Adherence Rating Scale (EARS; Newman-Beinart et al., 2017 [47]) includes 6 items that directly assesses adherence behaviour. The EARS is scored on a 5-point Likert scale from 0 (completely agree) to 4 (completely disagree). Items 1, 4 and 6 are reverse scored, resulting in a score between 0 and 24. A higher score indicates better exercise adherence.
  Time to complete: 5 minutes
- **Facebook Use Questionnaire**
  For those participants in the Social Media SWAT there will be an additional set of questions looking at their participation and engagement in the Facebook group.
- Participants will be given the option of being sent the participants questionnaires in advance of the 3-month follow-up visit to complete at home. They will bring the completed questionnaires in with them for the visit.
- If the site staff are unable to get in contact with the participant for the 12-month follow-up visit then they may collect the participants status from secondary care hospital records or from the participants GP. This is to complete the end of trial, protocol deviation and death forms.
- If the participant indicates that they are unable to attend for the 3-month visit they can complete the EQ-5D-5L, Healthcare resource use questionnaire and SAE check over the telephone. This has to be done within the visit window.

6.6.5 Intervention Optional interviews

Participants randomised to the PERFORM exercise intervention will be given the opportunity to participate in optional interviews to aid qualitative process data on the PERFORM intervention. After the main intervention period and 3-month trial data collection is complete, participants that consented at baseline to being contacted for the interviews will be contacted to take part in patient interviews by researchers from the University of Glasgow. They will also re-interview some intervention participants after the 4- and 6-month maintenance sessions. Participants will be sampled to ensure a mix of gender, engagement with the intervention and multi-morbidities. A separate PIS and consent form will be used, and the interviews will be conducted virtually (either via telephone or online web system, i.e. zoom or Teams) by the research team at the University of Glasgow. These interviews will be audio recorded and transcribed for later analysis (see section 11.2). There will be a £20 voucher provided to participants after they have finished the optional interview.

6.6.6 Social Media SWAT Optional Interviews

Participants within the n=10 allocated Social Media SWAT sites will be given the opportunity to participate in optional interviews to aid qualitative process data on the social media intervention. After the main PERFORM rehabilitation intervention period and 3-month trial data collection is complete, participants that consented at baseline to being contacted for the interviews will be contacted to take part in these optional interviews by researchers from the University of Salford. Participants will be sampled to ensure a mix of gender, engagement with the Facebook group and multi-morbidities, n=30. A separate PIS and consent form will be used, and the interviews will be conducted virtually (either via telephone or online web system, i.e. zoom or Teams) by the research team at the University of Salford. These interviews will be audio recorded and transcribed for later analysis (see section 11.2). There will be a £20 voucher provided to participants after they have finished the optional interview.

6.7 Expenses and payments

For the main study visits (baseline, 3 and 12-month follow up), travel expenses up to £10 per visit will be offered to participants. The payments will be managed at each participating centre, and proof of purchase provided (receipts, bus tickets, etc.).

For the interviews, each participant who completes the intervention or social media interview activities will be offered a £20 voucher for taking part. HCPs will not receive payment for participation in interviews.

6.8 Assessment and management of risk

Benefits – the anticipated benefits of the intervention are an improvement in health-related quality of life, and a reduction in symptom burden. The risk of harm with exercise-based interventions is very low. The risk of an adverse event with an exercise intervention is highest in those with pre-existing cardio-vascular disease.

These complication rates are low, it should be noted that patients were screened and exercised in medically supervised settings equipped to handle cardiac emergencies.

Staff will be trained to deliver exercise interventions to individuals with multiple long-term conditions and adapt the training programme as necessary, taking into account individuals baseline exercise capacity, symptoms and response to the exercise programme. The progression of exercise will be reviewed weekly and progressed as appropriate.

There is no anticipated risk to the research team.

If the participants have any concerns about the delivery of care, they will be directed towards the Patient Advice and Liaison Service within the respective trusts where the intervention is to be delivered.

The investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including if the participant loses mental capacity.

6.9 Pandemic Adaptations

In the event of a pandemic, we will operate the following regimes with full advice and approvals from infection control leads at the participating sites. All infection control measures will be instigated. All programmes will run with 'social distancing' of participants. All cleaning procedures will be followed. There is national guidance for PR developed by the British Thoracic Society and this will be used as a reference document for our programme. In the event of a lockdown, we have contingency funding to develop a digital programme.

6.10 Early discontinuation/withdrawal of participants

Participants can withdraw from the study at any point, without giving a reason and without any prejudice. If a participant withdraws from the study, or loses the capacity to consent for themselves, data collected up until the point of withdrawal/loss of capacity will be retained and used in the study.

In some instances, a participant may wish to discontinue the PERFORM rehabilitation programme but is happy to return for the 3-month or 12-month follow-up visits. Please ensure that the follow-up assessor remains blinded for the visits but that someone from within the team documents the discontinuation of the rehabilitation programme in the participants medical notes and fills in the end of trial completion form.

If a patient states they do not wish or are unable to return in person for a follow-up visit then a researcher may offer them the option to complete the EQ-5D-5L, Healthcare Resource Use Questionnaire and SAE check over the telephone. This is to be done within the stated visit window and not at any other time-point.

6.11 End of trial

This study will end when the specified number of participants have been recruited, all participants have completed their last follow up visit, data validation has taken place and the database is locked and statistical analysis complete.

6.12 Storage and analysis of clinical samples

There will be no blood or tissue samples collected.

6.13 Recording and reporting of SAEs

6.13.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study. For this study, any AEs will be documented in the patient's medical notes as per local trust procedure.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event. For this study, any AEs will be documented in the patient's medical notes as per local trust procedure.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. For this study, only SAEs deemed related to the PERFORM rehabilitation programme (intervention) or study assessments will be reported and reviewed by the PSC and Sponsor. SAEs will be reviewed by the site PI to determine relatedness. SAEs will be recorded in the participant CRF.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. For this study, only SAEs deemed related to the PERFORM rehabilitation programme (intervention) or study assessments will be reported and reviewed by the PSC and Sponsor. SAEs will be reviewed by the site PI to determine relatedness.
Expected Serious Adverse Events/Reactions	Only related SAE/SARs will be reported for the PERFORM study due to the nature of the patient population and design of this study. There are no expected serious adverse events/reactions, however due to the exercise nature of the PERFORM rehabilitation programme and assessments, injuries such as musculoskeletal injuries, etc. may be deemed related and 'expected' as such. These will be evaluated on a case-by-case scenario and will be decided by PI and/or CI.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label, an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

6.13.2 Reporting Procedures for Serious Adverse Events

All SAEs will be collected for all participants in the RCT and in the PCS from the time of written informed consent until the 12 month follow up visit and recorded on the SAE log in the participant CRF and entered into the SAE log on the online trial database.
Once sites are made aware of an event, the PI or delegated clinician at each site must assess whether the SAE is related to the PERFORM study or rehabilitation programme (intervention). If an SAE is related it will be reported to the sponsor immediately and within 24 hours of becoming aware of the event using SAE Report Form B -Non-CTIMP and according to the Sponsor SOP for reporting serious adverse events. Additional information will be provided if requested to the Sponsor and main Research Ethics Committee (REC). The Principal Investigator or another delegated healthcare professional (as agreed by the Sponsor) is responsible for the review and sign off of the SAE and the assessment of causality (i.e. whether an event is related to a study procedure or intervention).

If a delegated clinician from the reporting site is unavailable at the time of identification of a SAE an initial report without assessment of whether the event was related to the study or intervention should be submitted to the Sponsor. This must be completed immediately and within 24 hours of the study team becoming aware of the SAE, and must be followed-up by medical assessment as soon as possible thereafter.

The Sponsor will perform an initial check of the information and ensure that the SAE line listing is reviewed by the Director of Research & Innovation. All SAE information must be recorded on an SAE form and sent to the Sponsor. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to the Sponsor.

Copies of all documentation and correspondence relating to SAEs will be stored in the TMF and / or ISF

For each SAE the following information will be collected:

a) full details in medical terms and case description
b) event duration (start and end dates, if applicable)
c) action taken
d) outcome
e) seriousness criteria
f) relationship to the study procedure or intervention

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

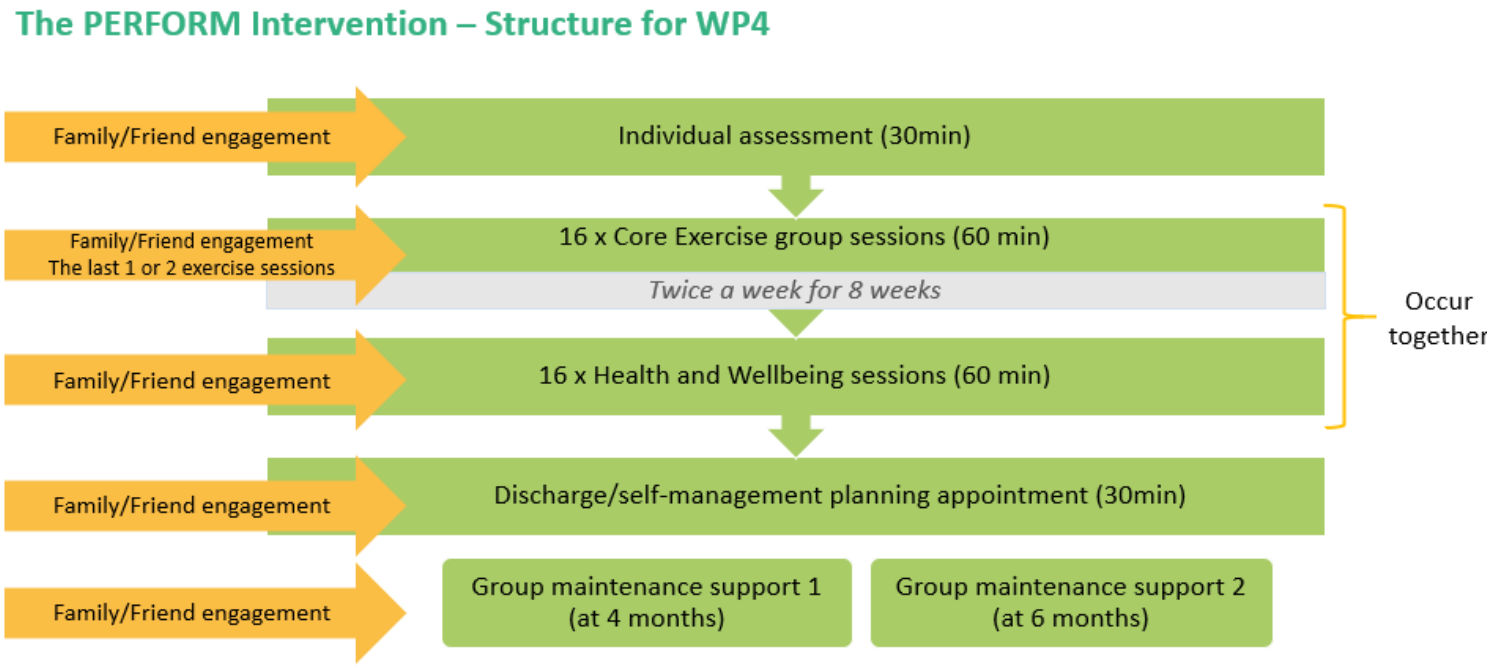
6.14 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the Sponsor and the relevant REC of the measures taken and the circumstances giving rise to those measures

7. PERFORM REHABILITATION INTERVENTION AND COMPARATOR

7.1 PERFORM Intervention

The PERFORM rehabilitation programme will comprise of an 8-week supervised rehabilitation programme, that will be offered in either a primary, secondary care or community setting. There will be 2 sessions a week and each session will last for 2 hours. The first hour comprises of the 'Move and Improve' exercise sessions, and the second hour is the patient 'Health and Wellbeing' self-care support session and Q&A/opportunity to interact with the group. The intervention will be offered within 4 weeks of randomisation. There will be an initial individual assessment prior to the 8-week programme with an appropriately trained healthcare professional to gauge a participant's physical baseline. This will take place at the baseline visit after the participant has been randomised.



The rehabilitation programme will comprise a personalised exercise component with an accompanying education programme. The 'Move and Improve' exercise sessions will offer an individually prescribed and progressed programme including a warm-up, an aerobic and strength component, and a cool-down each week. Participants will also be encouraged to complete a home exercise programme that will be closely monitored. A home exercise booklet will be provided as

well as a progress tracker standardised exercise diary that will ask participants to record exercise frequency, duration and symptom scores post exercise. This will be recorded for the aerobic and resistance programme.

The 'Health and Wellbeing' self-care support sessions / educational package will offer advice and support for behaviour change to support positive lifestyle changes and symptom management. Much of the advice will be appropriate to all participants for example healthy eating, the benefits of exercise, stress management and relaxation techniques, medicines adherence, and exacerbation of symptoms. The aim of the education 'health and wellbeing' package is to support symptom management, risk factor management and enhance self-management skills. The education programme will be delivered by healthcare professionals delivered as informal and interactive sessions. The information will be supplemented by written leaflets and material to support the individual to share with their family and carers. After the 8-week programme the participant will have an end of programme discharge conversation. This will take place at the time of their last session.

There is no national benchmarking for staff to participant ratio, but we will take guidance from PR and CR standards recommending a maximum of 1:8 ratio, with a minimum of two healthcare professionals in any session.

Both intervention and control groups will receive usual care, i.e., continue to manage their disease as advised by their primary/secondary care team

7.1.1 4- and 6-month group maintenance sessions

Patients randomised to the PERFORM intervention exercise programme will be invited to attend 2 group maintenance sessions, one at 4-months post randomisation and another at 6-month post randomisation. These sessions will be an opportunity to provide additional support to participants, review long-term progress and address any further questions they may have. After these visits, the participant will return to their usual care.

7.2 RCT Control group

The RCT control group will receive usual care alone. After the baseline visit and randomisation, patients allocated to control will continue with their usual care which is a continuation of usual medication and routine appointments. They will then return for only the 3 month and 12-month follow-up visits.

7.3 SWAT Intervention

We will co-create, manage, and moderate secret (non-searchable, closed where only invited members can see the name of the group, participants and posts) online community groups to provide peer support and reduce trial attrition. Facebook is one of the most suitable platforms used by patients, does not require specialist training or development resources, costs nothing, easy to use and accessible from mobile phones. The purpose of the groups is to foster peer-to-peer engagement, on-going discussions, access to trial information, sharing of knowledge and personal experiences (not necessarily related to study outcomes) but 'real time' feedback on trial

implementation. SoMe will complement the structure of multiple formats of rehabilitation programmes, including home based and digital delivery with the potential to reduce rehabilitation isolation. Moderators of groups and participants will be trained and supported by social media experts and dedicated social media managers. Patient moderators, PERFORM participants and rehabilitation staff will be trained to safely use SoMe through expert support, increasing digital literacy. This is not an embedded study on participant recruitment but an in-depth study of engagement strategies to sustain involvement, increase outcome retention rates and inform rehabilitation programmes of how patients want to be involved.

Participants in the N=10 sites allocated to the social media intervention will receive an invitation following randomisation with instructions to join the corresponding online group to which they are randomised (PERFORM intervention or PERFORM control group). Trial participants can join the online group via the direct link provided or they can choose not to, without their rights or participation in the main trial affected.

Online networks provide an opportunity to keep research participants engaged throughout the study and to be presented with dissemination materials.
The group description will explain and remind users of the group purpose and they will receive guidance on the operating rules of the group, the netiquette. Notifications of activity can be set by individuals to signal group activity, information provision and discussions. Trial participants can leave or disengage from a SoMe group when they wish without it affecting their participation in the trial or the need to inform the moderators; people who leave the group will be invited to provide feedback as to why they left (exit poll). Participants of the two groups will remain separate throughout the study to prevent influencing the patient experience of the trial intervention.

The online groups will be moderated to ensure the online space remains a positive fostering environment. Moderators have a crucial role in sustaining group interest in discussions, developing trust, relationships amongst individuals, providing content and influencing techniques all contribute to engagement. Patients (n=4) will act as group moderators (with support from experts) as patients relate to one another through shared lived experiences; moderation time will be fully reimbursed. Moderators will be recruited from the PAG, stakeholder events, WP3 pilot and/or different trial sites. An experienced social media manager will train and support moderators, on the use of Facebook groups and notifications, how to manage their own Facebook profile (privacy settings), content curation (news stories, trial news), support and tailored advice. Training strategies and support will be provided face to face, Facebook private message, WhatsApp group and by phone.

Within the two Facebook groups online questions (called polls) will be used to explore topics throughout the study to gather the experiences of the RCT participants. Discussion topics may include for example the need for rehabilitation, engagement in the trial, aspects of the trial such as the frequency of different tests, why are they performed, depending on the interventions they may discuss maintenance sessions, barriers and facilitators to rehabilitation and motivations for participant engagement in the study. Discussion threads will be analysed using different netnography methods, such as journaling and recording (48). Anonymous conversation text will be extracted to highlight and generate a deeper understanding of how and whether the social media groups influence trial retention.

7.4 SoMe Control Group

If a site is allocated to the SoME control group, they will not invite their randomised participants to join a SoMe community. Their interactions with the trial intervention and rehabilitation staff will be limited to the scheduled intervention sessions and the research follow-up visits with no additional SoMe questions.

8. PROCESS EVALUATION

8.1 RCT

The parallel mixed methods process evaluation will explore the mechanisms of action of the intervention and factors influencing its effective delivery. It will be conducted following the Medical Research Council guidelines for process evaluation of complex interventions (49). A key aim of the process evaluation will be to assess and refine the programme theory in preparation for future large-scale roll-out of the intervention. Key domains of the process evaluation will focus on: i) intervention elements, including acceptability, context, fidelity, exposure, reach, factors influencing effectiveness and (ii) study related elements i.e. contamination. It will also explore barriers and facilitators of future large-scale deployment of the PERFORM intervention from the perspectives of patients, health professionals, health service managers, commissioners, and policymakers. We will develop a Process Evaluation Framework and Qualitative Analysis Plan to guide data collection and analyses.

Quantitative process data will include attendance at sessions and fidelity assessments. The fidelity assessment will be completed using randomly selected audio and video recorded sessions and a fidelity checklist developed by the trial team, building on methods used in our prior intervention studies (50) and the PERFORM feasibility study. We will audio record a sample of post-exercise 'Health and Wellbeing' sessions (4 sessions per site for 8 sites, 32 sessions in total), reflecting the full range of session-topics (two examples for each of the 16 topics) and apply a fidelity checklist to the audio-recordings. We will select sites purposively to ideally include a range of settings (community, hospital), levels of deprivation, ethnic diversity and where possible urban and rural sites. Two team members will rate an initial sample of the recorded sessions (4-8 of each type) and inter-rater reliability will be assessed using a simple percentage agreement score for each checklist item (applying an 'acceptable error' of +/-1 point) (51). We will also: (i) ask staff delivering the PERFORM intervention to report (via a therapist CRF) whether intended content (i.e., exercises, self-care topics, facilitation techniques) was delivered, (ii) ask therapists to report both clinic observations of adherence to exercise and their assessment of home exercises performed by patients unsupervised, and (iii) patient reports of exercise adherence (based on intervention participants completing a weekly Progress Tracker diary during the supervised first 8 weeks)(47).

Qualitative process data will include semi-structured telephone interviews with intervention participants (up to 30) and delivery staff (up to 20) and policymakers and managers (up to 15). Patients will be purposively sampled to ensure diversity in multimorbidity profile, age, gender, socio-economic status and engagement with the intervention. Patient participants will be asked to consent to being contacted about the interviews as part of the main trial baseline assessment. They will then be contacted by researchers at the University of Glasgow to see if they are willing to take part in the interviews, and if so, further informed consent will be obtained. We will interview

staff (n= up to 20) involved in delivering the intervention as well as staff involved in referral and other aspects of the study to inform potential roll out of the intervention. For the healthcare staff we will aim to have diversity in gender, role and study site.

Interviews will take place after the three month follow up point and will explore patient experiences of the intervention; impact (and mechanisms of impact) of the intervention; barriers and facilitators to engagement (and ongoing maintenance of self-care behaviours), staff training, suggestions for improvements as well as contextual and system-level factors influencing intervention impact and future intervention delivery. Interview schedules will be guided by the PERFORM programme theory and Normalisation Process Theory (NPT) (52), an implementation theory that has been used extensively to explore the processes underpinning implementation, embedding and integration of service innovations. We will explore potential mechanisms of intervention effectiveness and of engagement with the intervention. Interviews will be audio recorded and transcribed verbatim.

Qualitative data will be analysed using thematic analysis with 20% double coded to enhance reliability (53). Themes identified from intervention staff and patient data regarding intervention delivery will be conceptualised through an NPT lens (52) and a theoretical lens based on the programme theory/logic model (54). Recommendations for refining/improving the intervention will be summarised and used to refine the intervention materials and the facilitator-training course. We will further refine the programme theory to explore the impact of system and individual factors on intervention engagement and effectiveness, building on the findings from WP3 and adding depth and insights into any areas that would benefit from further investigation (identified in WP3). If the intervention is found to be effective, we will use the data on barriers and facilitators to develop an implementation toolkit to support future wide scale implementation

Intervention fidelity data will be summarised descriptively (e.g. means & standard deviations) by session, by facilitator (where possible) and by site.

8.2 SWAT

Individual participant interviews will be undertaken in a purposive sample of SoMe users (n=20) and non-users (n=10) to explore individual contextual experiences, and to understand the nuanced ways in which SoMe may impact the outcomes. Interviews will predominantly be undertaken by telephone or virtual environment, face to face available to a small number who show a preference. Factors such as experience with SoMe, personal contact, ease of drop out, peer to peer support and reminders, positive feedback, barriers and facilitating factors, and buy in will be interrogated. Patient participants will be asked to consent to being contacted about the interviews as part of the main trial baseline assessment. They will then be contacted by researchers at the University of Salford to see if they are willing to take part in the interviews, and if so, further informed consent will be obtained.

9. ECONOMIC EVALUATION

Given the study design, the economic evaluation will comprise the following components:
1) Economic evaluation alongside RCT
2) Economic evaluation alongside a PCS
3) Exploration of PERFORM workforce impacts and
4) Long-term economic modelling beyond RCT/PCS

9.1 RCT

All health care, personal social service (PSS) resource, employment data, and personal costs will be prospectively measured using an economic evaluation questionnaire that will be tested in the WP3 feasibility study and tailored to the resource use requirements of this population with multiple LTCs (informed by WP1 resource use analysis). A 'within-trial' cost-utility analysis will be conducted from the perspective of the UK National Health Service (NHS) and Personal Social Service (PSS) using the principle of intention-to-treat, following recommendations for good practice (55,56).
Resource use will be valued using readily available sources including the national schedule of NHS reference costs (2019) (57) and health and social care unit costs (58). Costs, combined with quality adjusted life years (QALYs, derived using the EQ-5D instrument) will be presented on the incremental cost effectiveness plane (59, 60). Joint uncertainty in costs and outcomes will be represented on a cost effectiveness acceptability curve (CEAC) and prevailing UK willingness to pay thresholds for cost-effectiveness employed (55). Missing data will be imputed using multiple imputation methods (61). Both economic evaluations will adopt an NHS and PSS perspective, employ a discount rate of 3.5% and will further explore a societal perspective within broader sensitivity analysis to be reported and presented in line with current methods guidance (62).
Both the trial and cohort study economic evaluations will adopt a cost-utility analysis framework. In addition, incorporation of the full spectrum of outcomes beyond the QALY (EQ-5D) within a cost-consequences analysis framework will generate evidence for pragmatic decision making alongside a conceptual analysis of economies of scope arising in this population with multiple LTCs. A Health Economics Analysis Plan (HEAP) detailing the
economic analysis of the within-trial and cohort study will be developed and agreed with Programme Management Group and PSC/DMEC.

9.2 PCS

The economic analysis will follow the same statistical approach outlined for the main trial data analysis (general linear model; between group comparison of intervention and control participants; minimising potential confounding by adjusting for likely prognostic factors). Unlike the economic evaluation alongside the RCT however, the cost data will comprise only routinely available resource use from the NACR/NACAP databases focussing on key cost drivers (hospitalisation) combined with EQ-5D data (to be added).

9.3 Economic analysis of workforce impacts

This RCT and cohort study economic evaluation component will also provide an opportunity to inform broader workforce impacts and other service configuration resources required to deliver the PERFORM intervention (facilities, equipment) identified during the intervention development stage. Discussions with the PERFORM clinical and intervention development team will assist with the process of identifying, measuring and valuing any workforce impacts. Further, we will consider conducting a budget impact analysis, estimating the annual cost of implementing the intervention (incorporating workforce impacts) for those eligible in the UK. This may inform feasibility of implementation at scale, which is particularly relevant for an intervention with a large eligible population, such as PERFORM.

9.4 Long-term economic modelling beyond RCT/PCS

Depending upon the within trial and PCS economic evaluation findings, a longer-term economic evaluation model may be developed.

9.5 Health Economics Analysis Plan (HEAP)

Based on the feasibility study findings, a Health Economics Analysis Plan (HEAP) covering the economic analysis of the definitive within-study and cohort study will be developed and agreed with Programme Management Group and PSC/DMEC. The HEAP will describe in detail the economic evaluation comprising the previously described components:

1) Economic evaluation alongside RCT

2) Economic evaluation alongside a PCS

3) Exploration of PERFORM workforce impacts

4) Long-term economic modelling beyond RCT/PCS

10. DATA ANALYSIS

10.1 Sample size calculation

10.1.1 RCT

In order to achieve the objectives (see above) of this study, a total of 604 patients will be recruited over 18 months. A sample size of 604 (302 per arm) participants yields 90% power to detect a minimum clinical important difference (MCID) in the primary outcome (EQ-5D-5L index score) of 0.05 at the 5% significance level (63-68). This assumes a standard deviation (SD) of 0.24 (based on unpublished data from the HARP rehabilitation programme for individuals with multi long-term conditions) (63) & published data from 3D trial, (64) a within patient correlation coefficient of 0.71 for the follow-up and baseline measurements (conservatively based on the lower 95% CI from HARP, unpublished), and reassuringly is slightly lower than the REACH-HF trial observed for correlation of similar time points, point estimate=0.73 (65) and an assumed loss to follow-up of up to 20%. (63-68) A mean improvement in of EQ-5D of 0.06 (95% CI: 0.04 to 0.07, unpublished data) in paired pre-post data in 435 patients with multiple LTCs following the HARP rehabilitation intervention (63) demonstrates this MCID is achievable irrespective of the number of LTCs (2 to ≥5).

10.1.2. PCS

PCS: A further 302 patients will be recruited into the PERFORM intervention for PCS. An available data approach will be taken for the controls. The 2019 National Audit of Rehabilitation report indicates that some 50% of all 68,074 receiving CR in England, Wales and Northern Ireland had two or more LTCs.

10.1.3 SWAT

SWAT: At site level, 604 RCT participants will be allocated to either the SoMe intervention group (~N=302, 10 sites) or control group (~N=302, 10 sites). All PCS participants will also be allocated to the SoMe intervention group (~N=101) or control group (~N=101). Based on assumed trial retention of 80% at 12-months follow-up in the control, this sample size will allow to detect a between group difference in attrition of ≥9% at ≥80% power and 5% alpha

10.2 Statistical analysis plan

The statistical analysis plan will be fully described in the detailed statistical analysis plan (SAP). A statistical analysis plan will be finalised prior to final data lock and any deviations from the statistical plan will be reported in the statistical report.

10.2.1 RCT

Analyses will be carried out in accord with CONSORT reporting guidelines. Participant participation from screening to completion of the final follow-up assessment will be reported.

From screening log data, we will report recruitment both as a percentage of those invited and as a percentage of those screened in person.

Baseline patient characteristics and outcome scores will be descriptively summarised by PERFORM intervention and PERFORM control groups. Our primary analysis will apply a general linear model for both primary and secondary outcomes take an intention-to treat approach based on a between group comparison of intervention and control participants with available data at follow-up, adjusting for baseline outcomes (where appropriate), centre, and minimisation variables (age, sex, number of LTCs). To account for any potential clustering in the PERFORM intervention group, our analysis will fit centres as a random effect. Secondary analysis will extend the primary analysis hierarchical model with a repeated measures comparison at both 6 and 12-month follow-up points. A sensitivity analyses for the primary outcomes will be carried out using the primary analysis population imputing using multiple imputation as well as scenario analyses. Adverse events and serious adverse events will be reported descriptively by group

The estimated between-group effects will be presented using both absolute and relative measures, with associated 95% confidence intervals, where appropriate. No correction of P-values for multiplicity of testing will be undertaken. However, the analysis for the primary outcome will be performed before all other analyses and the P-values of all subsequent analyses interpreted in the context of multiple testing.

10.2.2 PCS

Analysis will be conducted and reported in accord with STROBE guidelines. Given the observational nature of this comparison, baseline patient characteristics and outcome scores will be summarised descriptively by group and compared statistically. Participant participation from screening to completion of the final follow-up assessment will be reported. Our primary analysis will apply a general linear model for both primary and secondary outcomes between group comparison of intervention and control participants with available data at follow-up adjusting baseline value. We will seek to minimise potential confounding by adjusting for likely prognostic factors, including age, sex, ethnicity, socioeconomic status, number of LTCs, as well as any variables with a statistically significant imbalance between the two groups at baseline. Secondary analysis will extend the primary analysis hierarchical model with a repeated measures comparison at both 3 and 12-month follow-up points plus an imputation analysis (as detailed above for the RCT). Adverse events and serious adverse events will be reported descriptively by group.

As for the RCT, no correction of P-values for multiplicity of testing will be undertaken. However, the analysis for the primary outcome will be performed before all other analyses and the P-values of all subsequent analyses interpreted in the context of multiple testing.

10.2.3 SWAT

SWAT: Analyses will be carried out in accord with CONSORT reporting guidelines for cluster RCTs. Participant participation from screening to completion of the final follow-up assessment will be reported. Baseline patient characteristics will be descriptively summarised by SOME intervention and SOME control groups. The primary and secondary outcomes of the SWAT will be analysed using general logistic models.

As for the RCT, no correction of P-values for multiplicity of testing will be undertaken. However, the analysis for the primary outcome will be performed before all other analyses and the P-values of all subsequent analyses interpreted in the context of multiple testing.

10.3 Subgroup analyses

RCT: Exploratory analyses of the primary outcome will be carried out in the following sub-groups: site, minimisation variables, clusters identified in WP1 and important markers of inequity including ethnicity, socio-economic, and deprivation status.

PCS: Exploratory analyses of the primary outcome will be carried out in the following subgroups: individuals eligible for CR and individuals eligible for PR.

SWAT: Not applicable.

10.4 Adjusted analysis

RCT: Analysis will adjust for baseline outcomes (where appropriate), centre, and minimisation variables (age, sex, number of LTCs). To account for any potential clustering in the PERFORM intervention group, our analysis we will fit centres as a random effect.

PCS: Analysis will adjust for baseline value. Analysis will seek to minimise potential confounding by adjusting for likely prognostic factors, including age, sex, ethnicity, socioeconomic status, number of LTCs, as well as any variables with a statistically significant imbalance between the two groups at baseline.

SWAT: Not applicable.

10.5 Interim analysis and criteria for the premature termination of the study

No interim analyses of outcomes are planned, however the RCT has an internal pilot which will report recruitment to the PSC.

10.6 Participant population

10.6.1 RCT

RCT: The primary analysis will be carried out in the ITT population with available data at follow-up for the model being fitted (complete case population). For the primary outcome, further analyses will be carried out in the ITT population with data imputed.

Adverse events will be analysed in the safety population, that all individual randomised with individuals receiving one or more session of the PERFORM intervention being analysed in the PERFORM intervention arm.

A complier average causal effects analyses (CACE) will be carried out for the primary outcome: to estimate the intervention effect in those that complied to the PERFORM intervention. It is proposed that adequate intervention adherence will be defined as attendance at ≥60% of sessions.

10.6.2 PCS

PCS: The primary analysis will be carried out in the ITT population with available data at follow-up for the model being fitted (complete case population). For the primary outcome, further analyses will be carried out in the ITT population with data imputed.

Adverse events will be summarised for all individuals receiving one or more sessions of the PERFORM intervention.

10.6.3 SWAT

SWAT: As the outcomes mainly related to data completion the ITT population will be used without the need for imputation.

10.7 Procedure(s) to account for missing or spurious data

RCT & PCS: Both multiple imputation and scenario analyses will be used to account for missing data in secondary analyses.

SWAT: Not applicable.

10.8 Other statistical considerations.

10.8.1 RCT

Separate listings of SAEs will be presented as line listings; in addition to the description listing will include relatedness to intervention.

The number of serious adverse events will be presented overall and by randomised group. The number of patients with 0, 1, 2 etc events will be summarised overall and by randomised group.

The type and number (percentage) of protocol deviations will also be tabulated overall and by randomised group in the ITT population.

10.8.2 PCS

Separate listings of SAEs will be presented as line listings; in addition to the description listing will include relatedness to intervention.

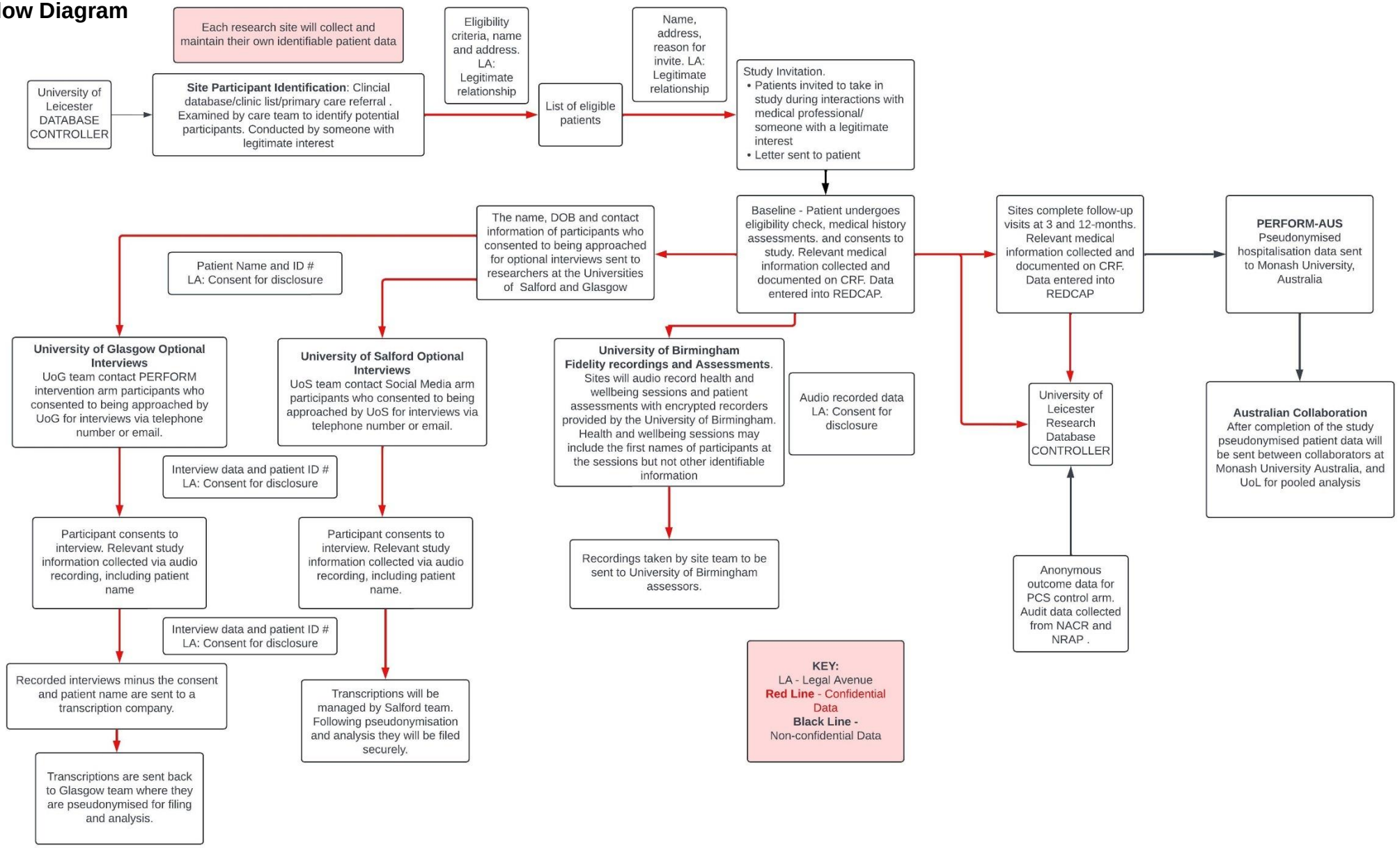
The type and number (percentage) of protocol deviations will be tabulated for individuals enrolled into the PERFORM intervention.

10.8.3 SWAT

The type and number (percentage) of protocol deviations will also be tabulated overall and by randomised group in the ITT population.

11. DATA MANAGEMENT

Data Flow Diagram



11.1 Data collection tools and source document identification

LCTU will be responsible for Data Management for the study and will undertake data validation, database queries/reviews in line with their SOPs.

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when needed

Data collection tools and source document identification

Source Data is defined as the first-place data is recorded; this will include:

- Medical Records
- Paper CRFs
- Participant reported outcome questionnaires

Data collection tools will comprise of:

- Electronic Data Capture Database (transcribed from CRFs) and direct source data entry
- Participant reported outcome questionnaires

The study researchers will seek consent from participants to re-contact them about taking part in future ethically approved research.

11.2 Data handling and record keeping

Records of study participant data will be made on study specific electronic CRFs. Trained member(s) of the site research team will enter data directly into a commercially available web

based Clinical Data Management System (CDMS) provided by the LCTU. On-entry validation checks will be applied where required and data entered will be checked for completeness, accuracy and timeliness by the site research team/trial manager/trial coordinator/data manager, with queries managed using the data clarification functionality within the CDMS system.

A copy of the patient information sheet and study consent form will be given to the participant, a copy will be placed in the hospital notes of all participants and original copies in the Investigator Site File. A sticker or electronic alert will be placed on the cover of the notes (or inside cover) detailing the study title, contact details of the PI and the fact that the notes should not be destroyed for 6 years from the end of the study. All study visits and related SAEs will be recorded in the hospital notes. Where electronic or hybrid medical notes are used it is expected that electronic flags, scanned documents and annotation are included in the medical notes.

For the optional Intervention process evaluation interviews a print out of the electronically signed consent form or an original wet-signature consent form will be stored securely in an ISF at the University of Glasgow.

For the optional SoMe SWAT Interviews a print-out of the electronically signed consent or an original wet-signature consent form will be stored securely in an ISF at the University of Salford.

During the study any paper CRFs and source data documentation will be stored in a secure area accessible to study site staff. Each enrolled participant will be allocated a unique study ID so that the CRFs and electronic database remains pseudonymised.

According to the ICH guidelines for Good Clinical Practice, the trial management team may check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. LCTU will develop a monitoring plan for source data verification (SDV) checks. The informed consent form will include a statement by which the patient allows the Sponsor and LCTU's duly authorised personnel, the Ethics Committee, and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., participant's medical file, appointment books, original laboratory records, etc.) in the event that this study is monitored by the study Sponsor. These personnel must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

A Data Management Plan will be created with specific details on data handling and record keeping.

11.2.1 Social Media SWAT Data Handling

To safeguard the anonymity of Facebook group members, pseudonyms will be assigned, and images will be cloaked (48). No information from the private groups will be disclosed except for the necessary anonymised and cloaked data collected for the for the purpose of the research.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, LCTU, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections- in line with participant consent.

Participants will also be given the opportunity to consent to the research team storing and sharing their anonymised data through secure specialist data centres/repositories relevant to the subject area for use in future research; this will optional and included on individual consent forms.

11.4 Archiving

Personal identifiable data generated by the study will be retained for six years following the notification of the end of the study before being destroyed in a confidential manner.

Following completion of the study data analysis, data and essential study records, including the final study report, will be archived in a secure location, for 6 years after the completion of the study. No study-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

11.5 Data sharing with Australia

At the end of the data collection period, pseudononymised data from the RCT will be sent to external collaborators at PERFORM-Australia. For its primary outcome, PERFORM-AUS has a required sample size of 1044. Hospital admission data from PERFORM-UK and PERFORM-AUS RCTs will therefore be pooled to achieve this sample size target.

12. MONITORING, AUDIT & INSPECTION

The University of Leicester, as Sponsor, operates a risk-based monitoring and audit programme, to which this study will be subject. The LCTU operates a risk-based Quality Management System which will apply to this study with Quality Checks and Quality Assurance Audits performed as required.

The trial manager will undertake quality checks and assurance audits to ensure compliance with protocol, ICH GCP, and regulatory requirements.

All source data, study documents, and participant notes will be made available for monitoring, audits and inspections by the Sponsor (or their delegate), NHS Host Organisation, and the regulatory authorities, should a monitoring visit be undertaken.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Once the initial sponsor review process is complete and a sponsor reference number has been allocated, and all requested documentation has been received and checked, authorisation from the University of Leicester's Research Governance Office will be issued to book further review of the proposed research. The NHS Research Ethics Committee and the Health Research Authority will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will be submitted via Integrated Research Application System (IRAS). The Chief Investigator will ensure that all

regulatory approvals, confirmation of capacity and capability from NHS sites and sponsor greenlight are in place before participants are approached.

For any required amendment to the study, the Chief Investigator, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. Amendments will be implemented upon receiving Sponsor Green Light.

The Research Governance Office's Standard operational procedures will be followed for the duration of the study.

Amendments will be submitted to the sponsor in the first instance for review and approval.

A trial master file will be maintained by the LCTU for the duration of the study and will be stored for six years after the study has ended. Each participating site will also maintain an investigator site file.

13.2 Peer review

This study has been peer reviewed by 2 independent experts working in or around the specialities of this study.

Peer review was also undertaken as part of the NIHR programme grant application process.

13.3 Public and Patient Involvement

Within the programme grant, PPI is constructed as a methodological activity and a Patient Advisory Group has been set up at Glasgow University, this group of patient and public representatives have contributed to the design of the research (including patient facing documentation) and will be involved in the management of the research and dissemination of findings.

13.4 Regulatory Compliance

Before the start of the study, approval will be sought from a REC for the study protocol, informed consent forms and other relevant documents. Any substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study.

All correspondence with the REC will be retained in the Trial Master File and an annual progress report (APR) will be submitted to the REC by or on behalf of the CI within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

The Chief Investigator will notify the REC when the study has ended by completing the end of study notification form and will submit a final report of the results within one year after notifying REC.

13.5 Protocol compliance

If a protocol breach occurs, then the CI will document this in adherence to the University's Standard Operational Procedure SOP Identifying and Reporting Deviations and Serious Breaches of GCP and/or the Protocol for Trials. The CI will seek advice from the research supervisors and the sponsor.

13.6 Data protection and patient confidentiality

All information collected in the study will be kept strictly confidential.

The Chief Investigator will have access to the study documentation and will be the data custodian.

All investigators and research staff who have access to data will comply with the requirements of the General Data Protection Regulation (and other applicable regulations) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Analysis of the trial data will be delegated by the Chief Investigator to the Trial Statistician from the Leicester Clinical Trials Unit and will take place on University of Leicester premises. All collected data and electronic confidential information will be saved on a secure drive at the University of Leicester.

Personal data of consenting participants (contact details) will be shared securely (using the University of Leicester secure file transfer service) with the University of Glasgow and the University of Salford for the purposes of contacting participants regarding the qualitative interviews. It will be destroyed once the interviews have been completed. Other process evaluation data will be shared with the Universities of Glasgow, Salford and Birmingham for analyses (fidelity data).

Pseudononymised patient data will be also shared with our PERFORM-Australia collaborators at the Monash University, Australia and University of Melbourne, Australia.

Data transfer will be completed using the University of Leicester secure file transfer service. Any printed confidential material will be kept in a folder in a locked drawer in a secured room in a secure office environment office at the Universities of Glasgow, Salford and Birmingham.

A risk assessment through the University of Leicester will be completed for the sharing and transfer of pseudonymised data collected as part of this study with the listed collaborators for further analysis as part of the feasibility assessment of this study. This risk assessment will also include the transfer of patient information for the interviews being undertaken virtually through the University of Glasgow and University of Salford.

13.7 Financial

This study has been awarded a grant from the NIHR and financial support will be available for participating sites for study related research costs.

13.8 Indemnity

Sponsorship and insurance for study design and management will be provided by the University of Leicester.

If a participant is harmed due to negligence, this will be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them. Details of this are made available to participants the PIS.

13.9 Post trial care

Not applicable.

13.10 Access to the final trial dataset

The Chief Investigator will have access to the full dataset.

Direct access will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the study to ensure compliance with regulations.

14. DISSEMINATION POLICY

The PERFORM publication and dissemination policy is documented elsewhere.

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