PROTOCOL

FULL TITLE: Personalised Exercise-Rehabilitation FOR people with Multiple long-term conditions (multi-morbidity) PERFORM: Feasibility study

VERSION NUMBER v2.0

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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 publically 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:_____

Sponsor Representative Name:

Sponsor Representative Signature: _____

Date:_____

Principal Investigator Name:

Principal Investigator Signature:_____

Date:_____

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Funder(s)	NIHR PGfAR NIHR202020
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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 Rehabilitabtion
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 Involvment
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

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, rehabilitaition, randomised controlled trial, feasibility study

TRIAL SUMMARY

Trial Title	Personalised Exercise-Rehabilitation FOR people with Multiple long-term conditions (multi-morbidity) PERFORM: Feasibility Study	
Trial Design	A 2-group parallel randomised feasibility study with embedded process and economic evaluations. Participants will be randomised to intervention (PERFORM rehabilitation programme + usual care) or control (usual care alone)	
Trial Participants	People with two or more long term conditions (LTCs) at least one of which has evidence of benefit from an exercise-based intervention	
Planned Sample Size	60 participants with 2:1 intervention/control randomisation to intervention or control to be recruited across foursites.	
Follow up duration	3-months post randomisation. 4 month post randomisation maintenance session 6 month post randomisation maintenance session	
Planned Trial Period	Start date: June 2023 End Date: June 2024	
Overarching aim	To assess the feasibility and acceptability of the PERFORM intervention and study methods and assess whether progression criteria are achieved and full trial is warranted.	
	Objectives	**Outcome Measures**

Co-primary feasibility objective(s)	To assess whether pre-specified progression criteria are met to progress to the full randomised trial to assess clinical and cost-effectiveness of the PERFORM intervention.	Progression criteria. • Percentage of target patients recruited in 4.5 months recruitment period • Retention at 3-months follow up • Intervention adherence (attendance of ≥60% of sessions)
Secondary feasibility objectives	To further refine the intervention and programme theory. To assess the feasibility and acceptability of data collection tools. To obtain estimates of key cost drivers. To assess risks of bias/contamination.	From process evaluation interviews Proportion of patients with complete outcome data at 3-month follow up and process evaluation patient interviews From economic evaluation Outcome blinding breaks and access to PERFORM intervention by control group

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).

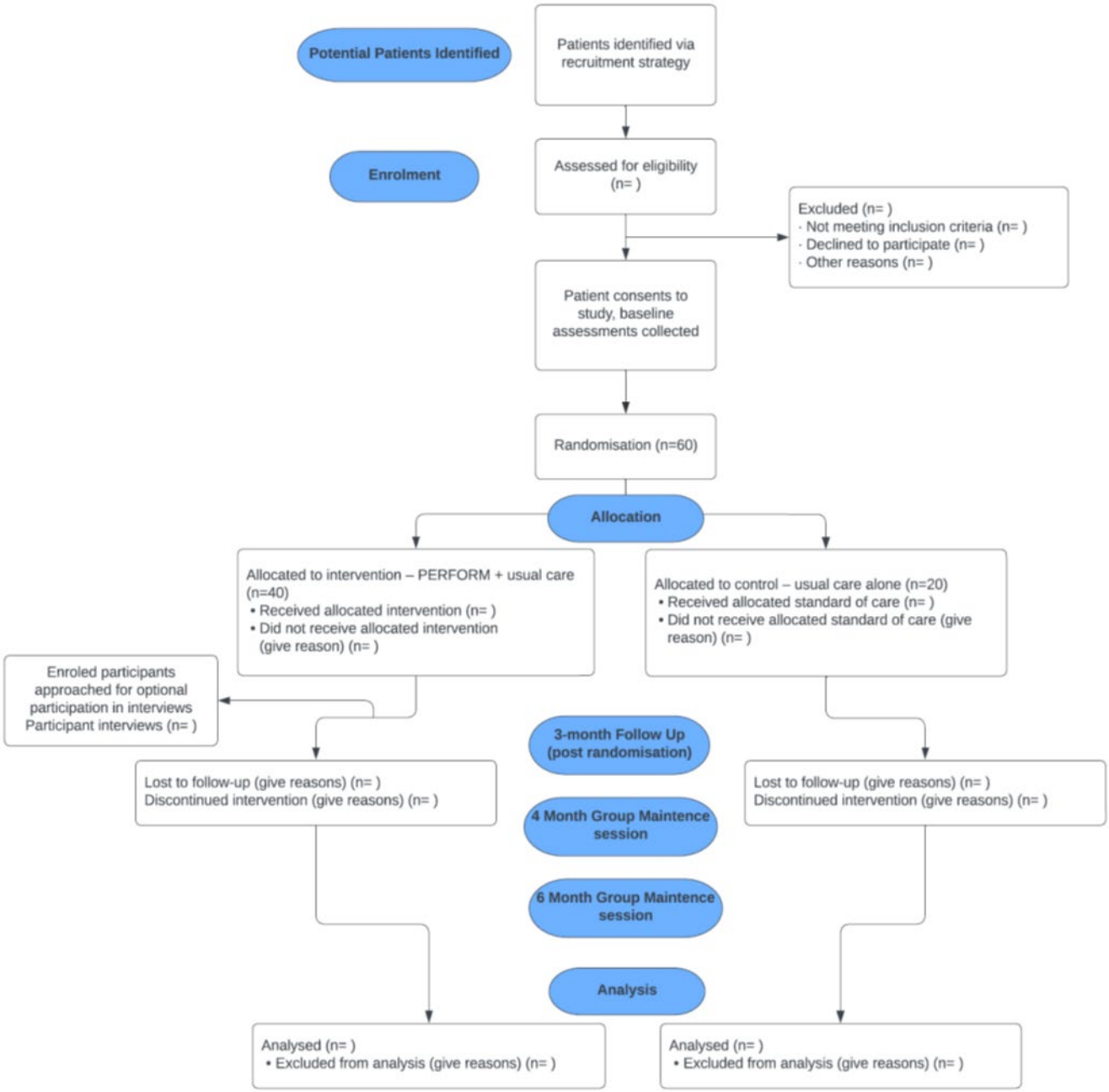
The PAG will evolve through the lifetime of the project and recruit new members (trial participants) to support PAG activities and dissemination events having first-hand experience of the intervention.

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 WPs 3-5 (feasibility study and main trial). PSC 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 of WP3 to advise/address any WP3 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 with PERFORM co-chief investigators, study manager, the sponsoring organisation, and representatives from the clinical research networks. The PSC will consider progression to full trial (WP4) following completion of the feasibility study (WP3). 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 FLOW CHART



1. BACKGROUND

There is a growing burden of multimorbidity (presence of >2 long term conditions (LTCs) within an individual) (1) due to increasing life expectancy among those with chronic conditions. Importantly, data indicates that there is a relatively higher mortality risk in younger individuals (2) and increased prevalence in deprived areas. (3)

Multimorbidity is associated with a reduced health-related quality of life (HRQoL), functional decline, increased mortality and increased healthcare utilisation, including emergency admissions. (2–6) There is a paucity of effective interventions for multimorbidity (7-9) 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. Addressing the unmet rehabilitation need is a global priority. (9)

A substantial body of evidence has demonstrated improvements in functional capacity and HRQoL and reduced hospital admissions following structured exercise-based rehabilitation 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. (11-16) The format of these programmes is remarkably similar: commonly extend over 8-12 weeks and comprise of individually prescribed and supervised exercise alongside symptom management and self-management support. However, the 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 multimorbidity. Furthermore, the workforce are specialists in cardiovascular or pulmonary rehabilitation are not necessarily equipped to manage rehabilitation needs for other long-term conditions or indeed to cope with the co-occurrence of multiple conditions. Therefore, patients with multiple LTCs (alongside their cardiac or respiratory disease) do not benefit fully from a single disease focused programme as they have more complex needs spanning multiple conditions.

We propose an innovative integrated approach to rehabilitation that provides equity of access for people with multimorbidity, and includes a structured programme of supervised exercise training, complex health needs assessment (including medication review), and self-management support of common symptoms spanning different LTC: Personalised Exercise Rehabilitation FOR people with Multiple LTCs (PERFORM) intervention.

1.1 Rationale

Access to exercise-based rehabilitation was identified as a priority by our patient and public involvement (PPI) representatives. The term 'multimorbidity' was unpopular and our group requested we change this throughout the application to 'people living with multiple LTCs', which is the term we will use hereafter, wherever possible. People living with multiple LTCs experience an accumulation of symptom and treatment burden (the workload of self-management) (14) and increasing disability. (16)

Single disease-based care which is not person centred or efficient. Participants in cardiac (CR) and pulmonary rehabilitation (PR) experience important benefits; a reduction in symptom burden, improved physical capacity and enhanced HRQoL for those with these candidate conditions (10,11,17) CR and PR are also cost effective (18,19) and a target growth area in the NHS-England Long Term Plan. (20) Our innovative approach extends the scope of rehabilitation, spreading positive health gains more widely to people managing multiple LTCs, extending beyond those with either a cardiac or respiratory LTC. The development and implementation of a PERFORM intervention will: target the long-term burden of chronic illness, provides more equitable access to health care system rehabilitation for a broad range of LTCs, and importantly be person centred with the potential to improve the health and well-being of more people.

1.2 Review of existing evidence

LTCs are the main challenge facing the health care system in the UK and around the world. LTCs are conditions for which there is currently no known cure, and which are managed with drugs and other non-pharmacological treatments, for example: conditions such as diabetes, cardiovascular disease, chronic renal disease, COPD, arthritis, peripheral vascular disease and inflammatory bowel disease and importantly mental health conditions including anxiety and depression. About 15 million people in England have a LTC (21). Those living with multiple LTCs need a broader approach, than the current single disease focused delivery that dominates health service delivery. The use of many services to manage individual diseases can result in duplication of effort as many LTCs require attention to the same lifestyle factors and is therefore inefficient. Unsurprisingly, current approaches are onerous for patients because of poor coordination and integration, and result in fragmented care which increases treatment burden for the individual.

Multimorbidity is regarded a major global health challenges and identifying clusters of common conditions and their determinants is a key research priority based on a key policy report from Academy of Medical Sciences. (22) The prevalence of difference clusters of LTCs has been studied with a recent systematic review describing 51 studies that examine the prevalence of LTC clusters. (23) However, all the included studies involved cross sectional analysis and did not examine the influence of different clusters of LTCs on HRQoL or adverse health outcomes. Secondly, the numbers of LTCs considered in the included studies for defining multimorbidity clusters were quite limited, with a median of 16 LTCs. A recently published large community study in UK defined multimorbidity clusters in different age groups and compared the risk of mortality and health service use. (24) However, this study did not examine the impact of wider demographic, social and lifestyle factors on multimorbidity clusters and differences in quality of life across various clusters. While a study from Denmark investigated differences in HRQoL for various multimorbidity clusters in their population, their study was very limited, considering only 15 LTCs in defining multimorbidity clusters (25). In summary, there is an evidence gap in research of relationship of multimorbidity clusters with adverse healthcare outcomes and HRQoL, particularly studying the impact of wider sociodemographic, lifestyle and function measures on multimorbidity clusters and using a comprehensive list of LTCs in defining multimorbidity clusters.

The recent update of the Cochrane Review of interventions for multimorbidity (personal communication SuS, submission date planned 2020), includes a total of 29 randomised controlled trials (RCTs) focusing on either specific combination of two health conditions (e.g., cardiac disease and diabetes) or a broader range of conditions and tended to focus on elderly

people. Whilst all interventions involved multiple components, they could be divided broadly into either organisational interventions (e.g. case management or addition of a pharmacist to the clinical care team) or patient-oriented interventions (e.g., self-management support groups or community-based diet and physical activity programmes). Meta-analysis of the RCTs results, showed little or no differences compared to best usual care in outcomes, including clinical measures (e.g., blood pressure, glycaemic control), HRQoL, level health service use and medication use. However, none of these trials appeared to be based on a model of personalised rehabilitation for people with multiple LTCs 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. The authors of this Cochrane Review proposed that interventions that focused upon physiotherapy treatments that aimed to improve functional capacity to support physical activity and achievement of activities of daily living may be more effective, but there was a need for further studies with this type of intervention particularly for people living with multiple LTC's across a range of ages (7). Despite this Cochrane Review recommendation, there is very limited RCT evidence to date reporting this type of exercise intervention in the literature, which should be personalised, prescribed and progress on an individual basis for people with LTCs (see below). In summary, there is a lack of data describing effective and cost-effective interventions for those with multiple LTCs, (7,8) making this global health challenge a key research priority.(9)

1.2.1 Clinical effectiveness and cost-effectiveness of exercise-based rehabilitation for LTCs

Exercise is a core component in the prevention of numerous chronic diseases and has been shown to be effective in the treatment of at least 26 LTCs. (26) Furthermore, there are convincing data describing the clinical effectiveness of structured exercise-based rehabilitation interventions in numerous LTCs, (10-15, 27) the structure and content of which are extremely consistent across high income countries, i.e., an 8-12 weeks course comprising a package of individually prescribed and progressed exercise to build fitness and strength, alongside a programme of multidisciplinary support to facilitate effective self-management, including but not limited to, symptom management, encouraging healthy lifestyle behaviours (e.g. smoking cessation, activity and diet) and managing mood disturbances. The rehabilitation intervention is preceded by a comprehensive assessment (this would cover as a minimum objective measure of functional capacity, HRQoL, symptom burden and mood disturbances). The duration of the intervention is principally based on the anticipated duration of exercise training to observe a physiological gain. (28) The data describes consistent improvements in HRQoL, symptoms, functional exercise capacity, anxiety and depression, activities of daily living, self-efficacy, and a reduction of symptoms. (17, 29). The primary outcome for these trials has typically been disease specific HRQoL (i.e. developed specifically for use in single disease groups) (30-32) or exercise capacity (commonly field walking tests, such as the minute walking test or incremental shuttle test). (33, 34)

A systematic review has confirmed there is evidence supporting the cost-effectiveness of CR for individuals but that the generalisability of study findings was limited due to the exclusion of patients with comorbidities as would typically be found in a real- world setting. (35) Comparable data exists for PR describing reductions in hospital admissions. (16) Exercise interventions for COPD have an estimated cost per quality-adjusted life year (QALY) of around £2-8k compared to inhaled drugs of between £7-187k per QALY. (18) The World Health Organisation have called for a global effort informed by their 'Rehabilitation 2030' policy (36) to

make rehabilitation accessible and affordable globally, recognising that it is necessary to keep people as independent as possible, and be economically productive. There is a misconception that rehabilitation is a luxury ("non-essential") service and is generally undervalued by health care systems.

1.3 Development of rehabilitation services for LTCs.

The most consistently provided services for people with LTCs is CR and PR, there remains poor provision of exercise based supervised rehabilitation programmes for other LTCs. In UK, PR and CR services are well developed and funded through current NHS commissioning arrangements (37). i.e. >200 PR and CR programmes (contributing to national audit programmes) with workforce training provided by national bodies to support the delivery of high-quality care (British Thoracic Society (BTS) and British Association for Cardiovascular Prevention and Rehabilitation (BACPR). However, there is currently no consistent provision of, or training for exercise-based rehabilitation programmes for other single LTCs. Some exceptions include isolated services developed for people with peripheral vascular disease, (38), arthritis (ESCAPE pain programme: Enabling Self-management and Coping with Arthritic Pain through Exercise a face-to-face group programme delivered in approximately 80 sites across the UK). (15) The structure and content of the programme delivered for arthritis is remarkably like CR and PR with a focus on supervised exercise and self-management, not surprisingly symptom management focusing on pain (as, for example compared to breathlessness) but will also include components addressing stress management, medication management and behaviours commensurate with a healthy lifestyle.

In recognition of this poor access to rehabilitation for people with multiple LTCs, the UK Chartered Society of Physiotherapy recently published the "RightoRehab" report/campaign. (39) This report identified that: "A radical modernisation is needed to ensure the quality and consistency of community rehabilitation services, offering an approach that is tailored to meet people's needs and priorities". In response to this report, in early 2020, the Chartered Society of Physiotherapy co-ordinated The Rehabilitation Alliance: a collaboration of 24 charities, trade unions, and professional bodies that have coalesced to lobby for equal access to high quality community rehabilitation services for all. The overarching aims of the Alliance are to:(1) develop a national strategy for quality rehabilitation, making it an essential component of healthcare, expand and modernise rehabilitation services to meet the scale of the need; (2) grow the multi-disciplinary workforce: (3) learn from the response to the COVID-19 pandemic on how to shape future rehabilitation needs; and (4) measure the need and impacts of rehabilitation. The Rehabilitation Alliance proposes that to meet these aims 'service disruption' is necessary to change the architecture of the current rehabilitation services.

1.4 Impact of rehabilitation programmes for LTCs

Accumulating co-morbidities compromises rehabilitation outcomes. (40) Although the precise reasons for this remain unclear, it may be reasonable to speculate that these programmes are designed specifically for a single disease and staff have expert knowledge and skill in that area but are less well equipped to managed other LTC's that may compromise the benefit of the programme to the individual. There has been some modest 'adaptations' (and little disruption) of services described in the literature. Research by the co-applicants describes accommodating patients with chronic heart failure into a conventional PR programme, acknowledging the lack of access for those with heart failure to a standard CR programme (41). A pilot RCT showed clinical outcomes to be consistent with CR programmes, (41). Arguably this project did not extend the scope but rather streamlined the service delivery and

thereby reduced the treatment burden for the individual. The scope of this programme has now extended to become a 'Breathlessness Rehabilitation Programme', which was acknowledged as an important innovation in the NHSE Long Term Plan (20). A feasibility trial has looked at extending the scope of CR services to participants post transient ischaemic attack and mild stroke. There were subtle changes in the structure of the programme reported but a much greater emphasis on workforce training and support. However, with appropriate training and support, this study showed that the integration of the new population into an existing service was both feasible and acceptable to all patient groups and staff. (42) These reports were not specifically focusing on those with multiple LTCs rather combining single disease cohorts.

We are aware of only two published reports to date that have assessed the impact of a structured rehabilitation programme for people with multiple LTCs: one small pilot trial (n=16) (43) and a single centre service evaluation (44). Whilst both studies support the feasibility of such rehabilitation provision and also indicate potential improvements in functional capacity, they are limited by their small sample size and single centre status. Furthermore, given their feasibility/pilot design, neither of these two studies informs what should be the appropriate primary outcome for a trial of rehabilitation for people with multiple LTCs. A consensus event was undertaken by co-applicants (RE/SS) to explore suitable outcomes for a combined rehabilitation programme for COPD and chronic heart failure. (45) Both clinicians and patients proposed that the most appropriate measure for either research or a clinical service was HRQoL but stopped short of identifying a preferred measure. A Delphi panel co-ordinated by one of the co-applicants (SuS) including 26 experts from 13 countries aimed to develop a consensus-based list of core outcome measures within multimorbidity research. This Delphi exercise also found HRQoL to be the highest scored outcome alongside mental health outcomes, and mortality. (46) A recent systematic review explored treatment priorities of those living with LTC's and compared to the priorities considered important by clinicians that would inform their treatment decisions. (47) Although the included studies and trial data were highly heterogenous, this review showed that for patients their consistent preference towards 'maintaining independence', 'staying alive', 'pain relief' and 'symptom relief'. The authors concluded that preserving functional ability as a key priority for patients living with LTCs. Besides this limited investigator driven research for people with multiple LTCs we could find no reports of rehabilitation specifically for people with multiple LTCs but did find reports of PR services beginning to accept those with heart failure on social media.

Overall, the single-disease framework by which most health care and workforce training is provided is arguably not fit for the challenge of individuals with multiple LTCs. Indeed, a landmark paper in the Lancet on multimorbidity concluded that a 'complementary strategy is needed, supporting generalist clinicians to provide personalised, comprehensive continuity of care' (3). This can feasibly be extrapolated to call for a comprehensive rehabilitation strategy for people with multiple LTCs

2. RESEARCH QUESTION /OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

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 multiple LTCs and develop and evaluate a rehabilitation intervention for this population. Our PERFORM programme consists of five linked work packages (WPs)

WP1: Identifying people with multiple LTCs likely to benefit from rehabilitation

WP2: Intervention development/workforce planning

WP3: Feasibility study for full RCT with embedded process evaluation and health economic evaluation

WP4: Multicentre RCT and prospective cohort study

WP5: Role of Social Media within mutlicentre RCT

This protocol document refers to WP3 – PERFORM Feasibility Study

2.1 Primary Objective

2.1.1 Aim

To implement the PERFORM intervention across three sites and assess the feasibility and acceptability of the PERFORM intervention and study methods and assess whether progression criteria are achieved and a full trial (WP4) is warranted.

2.1.2 Objectives

- To assess study recruitment and retention.
- To assess the feasibility, acceptability of the intervention exploring barriers and facilitators. to uptake and engagement from both participant and healthcare provider perspectives.
- To assess fidelity and reach of the intervention.
- To further refine the intervention and programme theory.
- To assess the feasibility and acceptability of data collection tools.
- To obtain estimates of key cost drivers.
- To assess risks of bias/contamination.

D: Design – randomised controlled trial

P: Population – People with mutiple long-term conditions (mutlimorbidity)

I: Intervention – PERFORM intervention + usual care

C: Control - usual care alone

O: Outcome(s) – feasibility and acceptability of the PERFORM intervention and study methods

T: Time - baseline (pre-randomisation) and 3-months post-randomisation

2.2 Outcome Measures

The primary outcome of this feasibility study will be to assess whether pre-specified progression criteria are met to progress to the full randomised trial to assess clinical and cost-effectiveness of the PERFORM intervention (WP4). Progression criteria will be agreed with the Programme Steering Committee at the start of study. Our funded application proposed criteria based on recruitment, retention, and intervention adherence (session attendance) and engagement from clinician reports and patient self-reports (see Table below).

		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

Red: Do not progress to the main trial
Amber: Progress if action plan to mitigate problems can be determined and agreed with the Programme Steering Committee.
Green: Progress directly to the main trial.

2.3 Definition of co-primary feasibility outcome(s)

The following outcomes will be co-primary outcomes as they all form part of the progression criteria:

- Proportion of recruitment target recruited, calculated as percentage recruitment target (60 participants) at end of 4.5 months recruitment period
- Retention at 3 months, calculated as the percentage of patients randomised with complete EQ-5D data at 3 months follow up.
- For patients randomised to the PERFORM intervention: proportion of patients achieving ≥60% of sessions attended at end of intervention[a]

[a] Proportion of sessions attended will be calculated from the number of sessions attended out of the scheduled 12 sessions.

2.4 Defintion of other feasibility outcomes

2.4.1 Feasibility and acceptability of data collection tools: will be measured by proportion of patients randomised with complete patient-related outcome data at 3 months follow up.

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

- HRQoL: EuroQoL (EQ-5D-5L)
- Exercise/functional capacity: incremental shuttle walk test (ISWT);
- 4 Metre Gait Speed (MGS)
- Strength: Hand Grip Strength
- Mood: Patient Health Questionnaire-9 (PHQ-9);

- Generalised Anxiety Disorder Assessment-7 (GAD-7)
- Physical activity: International Physical Activity Questionnaire (IPAQ)
- Frailty: Functional Assessment of Chronic Illness Therapy; Fried Exhaustion and Weight Loss
- Fatigue (FACIT-F)
- Pain: Brief Pain Inventory (BPI)
- Health and disability: WHODAS
- Breathlessness: Dyspnoea-12
- Sleep: Medical Outcome Study Sleep Scale (MOS Sleep Scale)
- Cognition: MoCA
- Multimorbidity Treatment Burden Questionnaire (MTBQ)
- ICEpop CAPability Measures for Adults (ICECAP-A)
- Clinical events – mortality & hospital admissions (& primary care contacts); and social and healthcare utilisation (including medication (assess at follow up only))

The following proposed patient outcome will only be collected at 3 months follow up (post randomisation)*:

- Exercise adherence: Exercise Adherence Rating Scale (EARS)

*This list of patient outcomes will be finalised following stakeholder consultation that forms part of WP2 and any changes will be submitted as an ethics amendment.

*2.4.*2 Estimates of key cost drivers.

Details are provided in the economic evaluation section (section 9).

2.4.3 Risks of bias/contamination.

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 arm of the trial and whether they had access to any intervention resources.

2.4.4 Further refine the intervention and programme theory

This will be completed at end of WP3 using data primarily from the process evaluation.

2.4.5 Feasibility and acceptability of data collection tools:

The proportion of 60 feasibility study patients with complete outcome data at 3-month follow up. Information on perceived outcome completion burden will be collected in patients interviews (see process evaluation, section 9).

2.4.6 Feasibility, acceptability of the intervention exploring barriers and facilitators to uptake and engagement from both participant and healthcare provider perspectives.

This will be assessed through qualitative interviews with patients and PERFORM intervention providers – see process evaluation section. This will also be assessed based on the adherence to the intervention (i.e. number of sessions attended out of the intervention program); adherence will be measured for each individual participant, which will be collected using attendance registers taken at each exercise session.

2.5 Exploratory endpoints/outcomes

Not applicable

3. TRIAL DESIGN

A parallel two group randomised feasibility study with nested process and economic evaluation. Patients will be randomly allocated to either intervention (PERFORM rehabilitation programme + usual care) or control (usual care alone). The feasibility study will be conducted across four sites with a total of 60 participants recruited over a 4.5 month period, with 40 participants randomised to the intervention group and 20 participants to the control group with a 3 month follow up after randomisation and a further 2 group maintenance sessions at 4 and 6 month post randomisation.

4. TRIAL SETTING

The feasibility study will be conducted across four study sites.

The study sites will be centres that have an established cardiac or pulmonary 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. 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 Inclusion Criteria

- Adults ≥18 years old
- Able and willing to provide informed consent
- To be mobile (including the use of walking aids)
- 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
- Atrial fibrillation
- 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 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 a exercised 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.
- Pregnant women
- Under 18's
- Living in a Nursing Home.
- Unsafe to exercise in a group without 1:1 supervision (e.g. significant risk of falls)

6. STUDY PROCEDURES 6.1 Schedule of Procedures

Procedures	Feasibility Study Visits							
	Pre Screening	**Screening and Baseline**	**Intervention Phase** (within 4 weeks of randomisation)	**Discharge appointment** (1 -2 weeks after completion of Intervention)	**3-Month Follow-Up** (3 months post-randomisation ± 4 weeks)	**Optional Interviews** (after completion of Intervention Phase for participants)	**4 month group maintenance Session** (Intervention patients only 4 month post randomisation)	**6 month group maintenance Session** (Intervention patients only 6 month post randomisation)
Invitation	X							
Eligibility assessment		X						
Informed consent		X						
Randomisation		X						
Baseline assessments		X						
Intervention or control			X					
Intervention discharge assessment				X				
Outcome questionnaires		X			X			
Follow-up assessments					X			
Resource use data collection questionnaire					X			
Patient & provider interviews						X		
Maintenance session							X	X

6.2 Recruitment

Individuals will be recruited from a number of sources, including from relevant specialists, primary and secondary care, with the support of the CRN in primary and secondary care.

- Primary care services - with support of the CRN, GP practices will return expressions of interest (EOIs) and will be approached to act as PIC sites. 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.

6.3 Screening

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 6.2)
- Over the age of 18.

6.4 Payment

For the main study visits (baseline and 3-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 intervention participant who completes the interview activities will be offered a £20 voucher for taking part. HCP will not receive payment for participation in interviews.

http://www.hra.nhs.uk/documents/2014/05/hra-guidance-payments-incentives-research-v1-0final-2014-05-21.pdf

6.5 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.

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 feasibility 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. The original, wet-signature consent form will be filed in an ISF at the Glasgow site, along with a copy of the consent transcription (see Section 11.2). A copy of the interviewer-signed consent form will be sent to the participant.

6.6 Randomisation

The LCTU will supply a web based randomisation system from a third party (Sealed Envelope Ltd.). Participants will be individually randomised in a 2:1 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 2:1 ratio to either PERFORM rehabilitation programme or standard of care. Randomisation will be minimised on site. To maintain concealment and minimise selection bias, randomisation will be performed after the baseline visit using a valuated password-protected web-based randomisation system supported by Leicester CTU to ensure concealment.

6.7 Baseline data

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

6.8 Study Assessments

6.8.1 Baseline Assessments

- Inclusion/exclusion and study entry verification
- Demographics including:
  Date of birth
  Gender
  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 respiratory frequency)
- Concomitant medicine check

Measures of physical capacity:

- **Exercise capacity**
  – Incremental shuttle walking test
  The incremental shuttle walk test (ISWT; Singh et al., 1992 [50]) 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

- **Physical frailty (as part of Fried; Fried et al., 2001 [51])**
  - 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)
  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 (51).

Symptom burden:

- **Overall health**
  – EQ-5D-5L
  The EQ-5D-5L (EuroQol Group, 1990 [52]) 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) 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 [53]) 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 [54]) 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 [55]) 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 [56]) 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 [57]) 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 [58]) 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 [59]) 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 [60]) 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 [61]) 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 (51).
  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 [62]) measures 5 capabilities (stability, attachment, autonomy, achievement, and enjoyment) that are important to quality of life.
  Time to complete: 5 minutes

- **Exercise adherence**
  – Exercise Adherence Rating Scale (EARS)
  The Exercise Adherence Rating Scale (EARS; Newman-Beinart et al., 2017 [63]) 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

The questionnaires will be presented in a consistent order and completed under supervision or with a healthcare professional as necessary. There is an opportunity to complete a number of assessments in between the practice and repeat ISWT. It is planned to complete the baseline assessments in one visit.

6.8.2 Rehabilitation phase

For those participants randomised to the rehabilitation programme, it will commence within 4 weeks of the baseline assessments. Individuals will be invited to participate in the PERFORM intervention (see 7.1).

6.8.3 Follow-up assessments

Follow up will be undertaken at 3-month follow up (3 months post randomisation).

- All measures identified above will be repeated. All outcome measures will be conducted by a blinded assessor who will have no knowledge of previous test results or treatment allocation.

6.8.4 4 and 6 month group maintenance sessions

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

6.8.5 Optional interviews

After the main intervention period and trial data collection is complete (3 months), participants that consented at baseline to being contacted for the interviews, and were randomised to the PERFORM exercise intervention, will be considered for taking part in patient interviews. We will also interview some intervention participants after the 4 and 6 month maintenance sessions. They will be sampled to ensure a mix of gender, engagement with the intervention and multimorbidities. 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).

Healthcare professionals who undergo the training for delivering the PERFORM rehabilitation programme and deliver the intervention in WP3 will also be invited to take

part in HCP interviews.We will aim to interview at least two per site. 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).

6.9 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.

6.10 COVID 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 pulmonary rehabilitation 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 of a digital programme. This will be developed by a Leicester software company (HARK2) who have worked with the team previously to develop a bespoke respiratory and cardiac website to support a remotely delivered rehabilitation programme.

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

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 the study, whether or not considered related to the study. For this study, only those deemed related to the PERFORM rehabilitation programme (intervention) or study assessments will be documented on an AE log and in the patient's medical notes.
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, only those deemed related to the PERFORM rehabilitation programme (intervention) or study assessments will be documented on an AE log and in the patient's medical notes.
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.
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 feasibility study due to the nature of the patient population and feasibility aspect 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 it's 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.

Detailed guidance can be found here:
http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

6.13.1 Reporting Procedures for Serious Adverse Events

All SAEs related to the PERFORM study or rehabilitation programme (intervention) occurring from the time of written informed consent until the 3 month follow up visit must be reported to the Sponsor immediately and within 24 hours of becoming aware of the event. These related SAEs will be reported using appropriate forms 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 physician (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 clinican from the reporting site is unavailable at the time of identification of a SAE the 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. INTERVENTION & CONTROL

7.1 Intervention group

The PERFORM rehabilitation programme will comprise an 8 week supervised rehabilitation programme, 6 weeks, twice weekly then 2 weeks, once a week that will be offered in either a primary or secondary care setting. Each session will last for 2 hours (1hr of 'move and improve

exercise sessions, and 1hr 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.

The rehabilitation programme will comprise an exercise component with an accompanying education 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 health 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 a discharge appointment in most cases this will take place 1-2 weeks following the last rehabilitation session.

Each 'move and improve' exercise session will offer an individually prescribed and progressed aerobic walking programme (a combination of walking (treadmill where available). In addition resistance training will be delivered that will be individually prescribed and progressed.

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 bout of exercise. This will be recorded for the aerobic and resistance programme.

Participants are then invited to take part in 2 further group maintenance sessions, one 4 months after randomisation and one 6 months after randomisation, this will give participants the opportunity to review their long-term progress and address any further questions. After these visits the participant will return to their usual care.

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

7.2 Control group

Both intervention and control groups will receive usual care, i.e. continue to manage their disease as advised by their primary/secondary care team. This will be continuation with usual medication and follow up visits at either primary or secondary care as scheduled. After the initial assessment, patients allocated to control will continue with their usual care alone.

8. PROCESS EVALUATION

The process evaluation will explore in detail, the feasibility and acceptability of both the intervention, and the study design and it will be conducted following the Medical Research Council guidelines for process evaluation of complex interventions. (64) We will develop a Process Evaluation Framework and Qualitative Analysis Plan to guide data collection and

analyses. A key aim of the process evaluation will be to assess and refine the programme theory in preparation for a full trial. In addition, it will assess: (i) intervention elements, i.e. acceptability, context, fidelity, exposure, reach and (ii) study related elements i.e. acceptability of study methods including recruitment, outcome measures and contamination.

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 study team, building on methods used in our prior intervention studies.(65) We will assess 24 individual initial assessments and 24 follow-up/discharge visits (n=8 per site). We will assess (by direct observation/researcher site visit) 6-9 of the group exercise sessions (2-3 visits per site), these will include a mixture of early, mid and late sessions per group. Finally, we will audio record all (where possible and where all participants of the group have consented) of the 'Health and Wellbeing' self care support sessions and assess a sample of 24-30 of these (8-10 per site), reflecting the full range of session-topics. Two team members will rate these sessions and inter-rater reliability will be assessed using Gwet's AC1. (66) We will also: (i) ask therapists to report confirmation that intended content (exercises, self-care topics, facilitation techniques) were taught, (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 completion of a weekly Progress Tracker diary during the first 12 weeks of the intervention). (67) Quantitative process evaluation data will be presented descriptively using mean (standard deviation) and median (interquartile range) for continuous variables and count (percentage) for categorical variables.

Qualitative process data will include semi-structured telephone interviews with patients (n~30) and staff (n~12). Patients will be purposively sampled to include a range of conditions, gender, age, socioeconomic status and engagement with the intervention. We will also aim to interview those who did not attend the intervention or those who were low attenders to inform improvements to the intervention. We will recruit from study participants who will be asked to consent to being contacted about the interviews as part of the baseline assessment. They will then be contacted to see if they are willing to take part in the interviews. Two intervention staff and two referrers per site (n=6) will be interviewed to inform recruitment for the main study and identify any implementation issues.

Interviews will take place after the intervention is completed and will explore the acceptability of the recruitment process and outcome measures; acceptability of the intervention; impact of the intervention on behaviour; barriers and facilitators to engagement, staff training, suggestions for improvements as well as contextual factors influencing intervention impact. Interview schedules will be guided by the programme theory and Normalization Process Theory (NPT), 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 (68). Themes identified from intervention staff data regarding intervention delivery will be conceptualised through a NPT lens (69) and the patient data through a theoretical lens based on NPT and the programme theory/logic model. Recommendations for refining/improving the intervention will be summarised and used to refine the intervention materials and the facilitator-training course as well as updating the programme theory. Participant quantitative outcomes will be summarised descriptively (e.g. means & standard deviations) by intervention and control group at baseline and follow up.

9. ECONOMIC EVALUATION

9.1 Economic evaluation feasibility study

The feasibility economic evaluation will determine the feasibility of identifying, measuring and valuing the relevant resource use and quality of life data required to conduct the full cost-effectiveness/cost-consequences analysis in the definitive study. Key cost drivers will be identified within this feasibility study using data gathered from a specially designed resource use questionnaire as well as from an intervention costing exercise (identifying and measuring all aspects of resources used to deliver the intervention). All health care, personal social service (PSS) resource, employment data, and personal costs will be measured within this feasibility study. The questionnaire will be tailored to the resource use requirements of this population with multiple LTCs (informed by WP1 resource use analysis). Incorporation of the full spectrum of outcomes beyond the QALY (EQ-5D) within a feasibility cost-consequences analysis framework will further provide initial insights to such a pragmatic economic evaluation for this population with multiple LTCs.

9.2 Economic analysis of workforce impacts

This feasibility 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.

9.3 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 following components:1) Economic evaluation alongside RCT; 2) Economic evaluation alongside a prospective cohort study (PCS); 3) Exploration of PERFORM workforce impacts and 4) Long-term economic modelling beyond RCT/PCS.

10. DATA ANALYSIS

10.1 Sample size calculation

In order to achieve the feasibility objectives (see above) of this feasibility study, a total of 60 patients will be recruited over 4.5 months. Given we are interested in the acceptability of the intervention, for efficiency, we will randomise 40 participants to the intervention group and 20 to the control group. We anticipate a loss to follow up of 20% at 3-months.

10.2 Statistical analysis plan

Aim: to be fully describe in the detailed statistical analysis plan (SAP).

10.2.1 Summary of baseline data and flow of patients

- A CONSORT diagram showing the flow of participants through the study will be produced, including the number of patients screened, randomised and (in the intervention arm) receiving treatment. This diagram will also show the number of randomised patients providing complete EQ-5D data at 3 months (our proposed RCT primary patient outcome).

- Baseline characteristics and measures of the participants will be summarised by randomisation group and overall using mean (standard deviation) and median (interquartile range) for continuous variables and count (percentage) for categorical variables. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.
- The number (percentage) of participants in each analysis population will be tabulated 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.

10.2.2 Co-Primary outcomes analysis

The number recruited and the percentage of the 60 patient recruitment target will be reported and recruitment rate per site reported.

The number and percentage (along with a 95% confidence interval) retained at 3 months, defined as having complete EQ-5D data at 3 months follow up, will be calculated for all patients randomised (ITT population).

The number and percentage (along with a 95% confidence interval) of patients randomised to the PERFORM intervention that attended ≥60% of sessions will be reported. In addition, the percentage of sessions attended by individuals in the PERFORM intervention arm will be summarised using median and inter-quartile range.

10.2.3 Secondary outcome analysis

The number and proportion of patients randomised with complete data for each of the follow-up outcomes (possible outcomes for the subsequent definitive trial) measured at 3 months follow up will be calculated in all randomised patients and by randomised group.

Patient reported outcomes at 3 months follow up and the number of each of the clinical events within 3 months follow up will be summarised by randomised group and overall using mean (standard deviation) and median (interquartile range) for continuous variables and count (percentage) for categorical variables. Intervention-control between group mean differences and 95% CIs will be reported. Given the feasibility objectives of the study, no P-values will be reported.

10.3 Subgroup analyses

Not applicable.

10.4 Adjusted analysis

Not applicable.

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

There are no formal criteria for stopping the study prematurely.

No interim analysis assessing the feasibility stop-go criteria with the possibility of early termination of the study is planned. However, due to the nature of the outcomes of recruitment and retention, these outcomes will be monitored along with serious adverse events throughout the study.

10.6 Participant population

The analysis of the feasibility outcomes will be carried out in the ITT population.

Patient reported outcomes and clinical events will be analysed using the complete case population for the variable being summarised.

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.

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

Feasibility outcomes: For the feasibility outcomes relating to completeness of data there will be no need to account for missing data as this is exactly what the data is measuring fully completed or not (missing). Likewise, the number randomised will not need to account for missing data. For the proportion of sessions by patients in the PERFORM intervention arm, if the data for attendance at any session is truly missing and can be dissolved through data queries, individuals will be assumed to have not attend that session.

Patient outcomes/clinical events: sites will be asked to check completion of patient outcomes in order to mimimise any missing data. If items are missing from within an outcome questionnaire, the appropriate imputation method will be applied to allow outcome scoring. Data presentation for this feasibility study will consider completed outcomes and not impute any complete missing outcomes.

10.8 Other statistical considerations.

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.

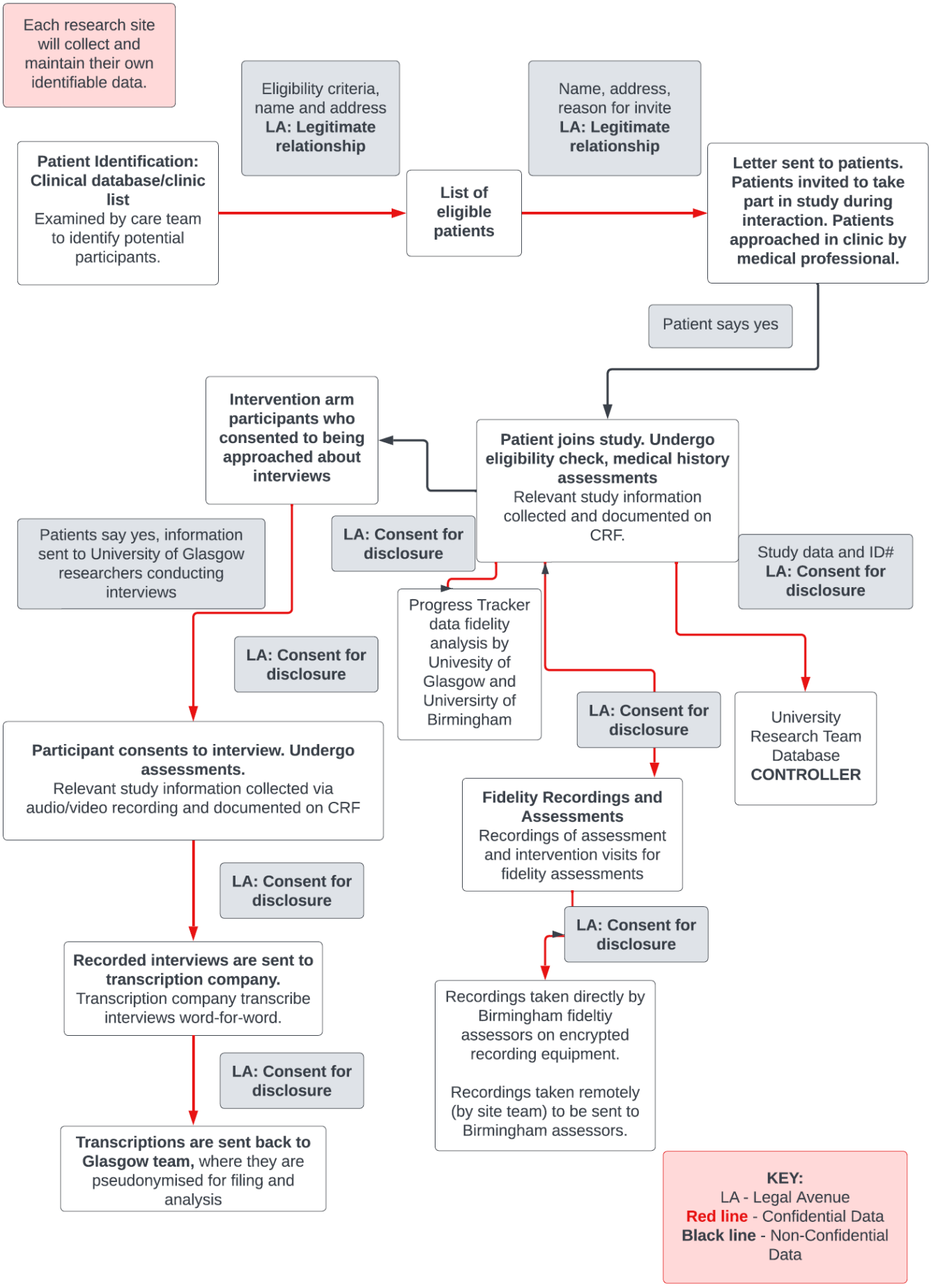
Separate listings of SAEs will be presented as line listings; in addition to the description listing will include relatedness to intervention.

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.

11. DATA MANAGEMENT

Data Flow Diagram


Each research site will collect and maintain their own identifiable data.
Eligibility criteria, name and address LA: Legitimate relationship
Name, address, reason for invite LA: Legitimate relationship
Patient Identification: Clinical database/clinic list
Examined by care team to identify potential participants.
List of eligible patients
Letter sent to patients. Patients invited to take part in study during interaction. Patients approached in clinic by medical professional.
Patient says yes
Intervention arm participants who consented to being approached about interviews
Patient joins study. Undergo eligibility check, medical history assessments
Relevant study information collected and documented on CRF.
Patients say yes, information sent to University of Glasgow researchers conducting interviews
LA: Consent for disclosure
Study data and ID# LA: Consent for disclosure
Progress Tracker data fidelity analysis by Univesity of Glasgow and Universirty of Birmingham
LA: Consent for disclosure
University Research Team Database CONTROLLER
Participant consents to interview. Undergo assessments.
Relevant study information collected via audio/video recording and documented on CRF
LA: Consent for disclosure
Fidelity Recordings and Assessments
Recordings of assessment and intervention visits for fidelity assessments
LA: Consent for disclosure
Recorded interviews are sent to transcription company.
Transcription company transcribe interviews word-for-word.
LA: Consent for disclosure
Recordings taken directly by Birmingham fideltiy assessors on encrypted recording equipment.
Recordings taken remotely (by site team) to be sent to Birmingham assessors.
Transcriptions are sent back to Glasgow team, where they are pseudonymised for filing and analysis
KEY:
LA - Legal Avenue
Red line - Confidential Data
Black line - Non-Confidential Data

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:

- Macro 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 (MACRO). 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 feasibility study consent form and information sheet 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 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 AEs/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 post-intervention interviews consent forms completed virtually by the interviewer with the participant, the original, wet-signature consent form will be filed in an ISF at the Glasgow site, along with a copy of the consent transcription. A copy of the interviewer-signed consent form will be sent to the participant.

Participant and HCP interviews (as part of the interview schedule of this study) will be audio recorded. These recordings will be transcribed for analysis, and all identifying details removed. The audio and video recordings of the intervention sessions will be analysed by the research team and then destroyed once intervention fidelity is checked. All data collected will be stored in securely locked filing cabinets and in password-protected databases. After the project is complete, all data will be securely archived and will be destroyed after six years. Anonymised data will be stored in secure specialist data centre/repository relevant to this subject area and available for future research, should the participant consent to data storage.

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.

11.3 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.

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 feasibility trial data will be undertaken by the Chief Investigator 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 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 University of Glasgow and the University of Birmingham for analyses (fidelity data). 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 University of Glasgow or 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.

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.
Local CRN support should be available to support the entry of participants into this study including PI consent.

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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16. Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	16/05/2023	Amy Branson	Amendment to rehabilitation schedule including the addition of 2 group maintenance visits 4 & 6 months after randomisation