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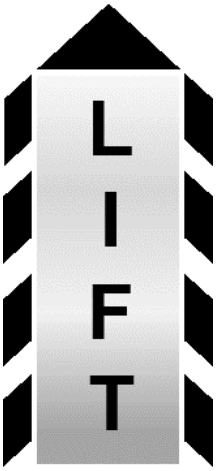

STUDY PROTOCOL

Full Title:	**Lessening the impact of fatigue in inflammatory rheumatic diseases: a randomised clinical trial**
Study Acronym:	**LIFT**
Sponsor:	**University of Aberdeen, King's College, Aberdeen, AB24 3FX**
Sponsor Reference Number:	2.049.16
Funder:	Arthritis Research UK
Grant Number:	21175
Chief Investigator:	Prof Gary Macfarlane
Co-Chief Investigator	Dr Neil Basu
IRAS ID:	216267
REC Reference Number:	17/WA/0065
R&D Reference Number:	216267/1060155/141467
Clinicaltrialsgov Number:	NCT03248518
Version Number and Date:	08.10.2020 version 11

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PROTOCOL APPROVAL

Lessening the impact of fatigue in inflammatory rheumatic diseases: a randomised clinical trial

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

Prof Gary Macfarlane		08 October 2020
Chief Investigator	Signature	Date (dd/mon/yyyy)

LIST OF ABBREVIATIONS

ASDAS	Ankylosing Spondylitis Disease Activity Score
AxSpA	Axial Spondyloarthritis
BILAG	British Isles Lupus Activity Group
BRAF-MDQ	Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire
CBA	Cognitive Behavioural Approach
CF	Chalder Fatigue Scale
CHaRT	Centre of Healthcare Randomised Trials
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risk Scheme
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-reactive protein
CTU	Clinical Trials Unit
DAS28	Disease Activity Score 28
DMC	Data Monitoring Committee
DTI	Diffusion Tensor Imaging
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte Sedimentation Rate
FA	Fractional Anisotropy
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
HADS	Hospital anxiety and depression scale
ICECAP	Investigating Choice Experiments for the preference of older people CAPability measures for adults
IRD	Inflammatory Rheumatic Disease
MAR	Missing at random
MRI	Magnetic Resonance Imaging
NHS	National Health Service
PA	Physical Activity
PASAT	Paced Auditory Serial Addition Test
PEP	Personalised Exercise Programme
PRoNTo	Pattern Recognition for Neuroimaging Toolbox
QALY	Quality Adjusted Life Years
QOL	Quality of Life
RA	Rheumatic Arthritis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPE	Rating of Perceived Exertion
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
S-VLA	Valued Life Activities short form
SWAT	Study Within A Trail
TDF	Theoretical Domains Framework
TSH	Thyroid Stimulating Hormone
VBM	Voxel-based morphometry
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

SUMMARY

Fatigue is pervasive, disabling and challenging to manage across all inflammatory rheumatic diseases (IRDs).

Primarily, we seek to advance the implementation of fatigue alleviating physical activity support programmes and cognitive-behavioural treatments within health services. We will individually test these interventions against usual care across multiple, rather than single, IRDs to enable improved patient access and resource utilisation. The interventions will be delivered centrally, by either telephone or internet-based audio/video calls such as Skype or Jabber, with a view to further enhancing cost-effectiveness.

The conduct of such a pragmatic study also presents a unique opportunity to a) investigate the underlying mechanisms of fatigue in order to optimise future interventions and b) identify the moderators of physical activity and cognitive-behavioural therapy efficacy so as to inform future stratified studies and patient triage pathways.

If successful, this study has the potential to unlock widespread access to much needed therapies and will provide vital insights into this commonly neglected patient priority.

1 INTRODUCTION

1.1 Background

Despite major advances in the management of inflammatory rheumatic diseases (IRDs), patients remain burdened by their disease and cite fatigue as a principal problem. In rheumatoid arthritis (RA), for example, as many as 80% of patients report significant fatigue [1] and over 70% consider fatigue to be equal to pain in terms of burden [2]. Moreover, fatigue is a crucial determinant of impaired quality of life (QOL) [3,4] and a predictor of work disability [5,6]. Indeed, over 75% of patients identify fatigue as the main barrier to remaining in employment [7]. Studies in other IRDs, such as axial spondyloarthritis (AxSpA) and systemic lupus erythematosus (SLE), have reported similar fatigue prevalence of 66-85% [8,9] and have found the impact of fatigue on QOL and employment to be equally pronounced [10-12]. In spite of these profound consequences, patients feel this symptom is clinically ignored [13,14][1,2] and rheumatologists admit ignorance regarding its management [15].

This situation reflects the poor availability of suitable interventions within modern health care systems such as the NHS, but this is not to say that effective treatments do not exist. There is now considerable consensus across the health care community that non-pharmacological interventions, specifically cognitive behavioural approaches (CBA) and programmes designed to support increased physical activity, are valuable treatments which help IRD patients manage the functional challenges of their disease such as fatigue [16,17].

Our current team has made key contributions to the evidence base, which supports the use of these treatments for fatigue in IRDs [18-20].

However, current health care systems routinely contribute to substantial barriers to the implementation of these therapeutic options.

Firstly, existing studies – including our own – have only developed bespoke disease-specific models of care, which vary in content, structure and method of delivery. Inevitably, this necessitates the development of multiple particular skill sets for the care providers if they are to equitably serve their diverse patient populations – a time consuming, costly and inefficient undertaking.

Secondly, patients find it challenging to commit to regular face-to-face treatment sessions (a common underpinning of existing CBA and exercise interventions). This is often due to a combination of health complications and the time-constrained nature of modern life, particularly relevant to those patients still in employment.

Thirdly, individual patients report substantial variation in their preference and response to the distinct interventions of CBA and physical activity [21,22].

1.2 Rationale for Study

It has becoming increasingly clear that:

a) similarities exist across chronic IRD disorders regarding the nature and likely mechanisms which maintain fatigue – such as dysfunctional activity behaviours [23-25] and illness beliefs [14,26,27], and so the application of standardised generic, rather than disease-specific, interventions may prove effective

b) alternative, more flexible, methods of remote delivery such as telephone and internet-based audio/video calls can be just as effective as traditional face to face interventions [28,29] and

c) in the future, the identification of baseline patient preferences and characteristics which can predict differential treatment effects (moderators) will be vital to inform a personalised triage approach to care [22,30].

Therefore, we propose a pragmatic trial, which will use pre-developed cognitive behavioural therapy and graded exercise therapy interventions, already considered the standard of care in heterogeneous primary fatigue populations. We have adapted them to a CBA and personalised exercise programme (PEP) so they may also be generically applicable across IRD-fatigue populations. We will now test whether these key non-pharmacological interventions can individually reduce fatigue, when delivered by the rheumatology team, across a mixture of IRDs using telephone or internet-based audio/video calls. In doing so, we will be able to explore potential moderating factors which may allow for the future triage of patients according to the most suitable intervention, but in addition investigate the precise mediators of the effect of treatment on IRD-related fatigue. The overall time scale of the LIFT study is summarised in a GANTT chart (Figure 1).

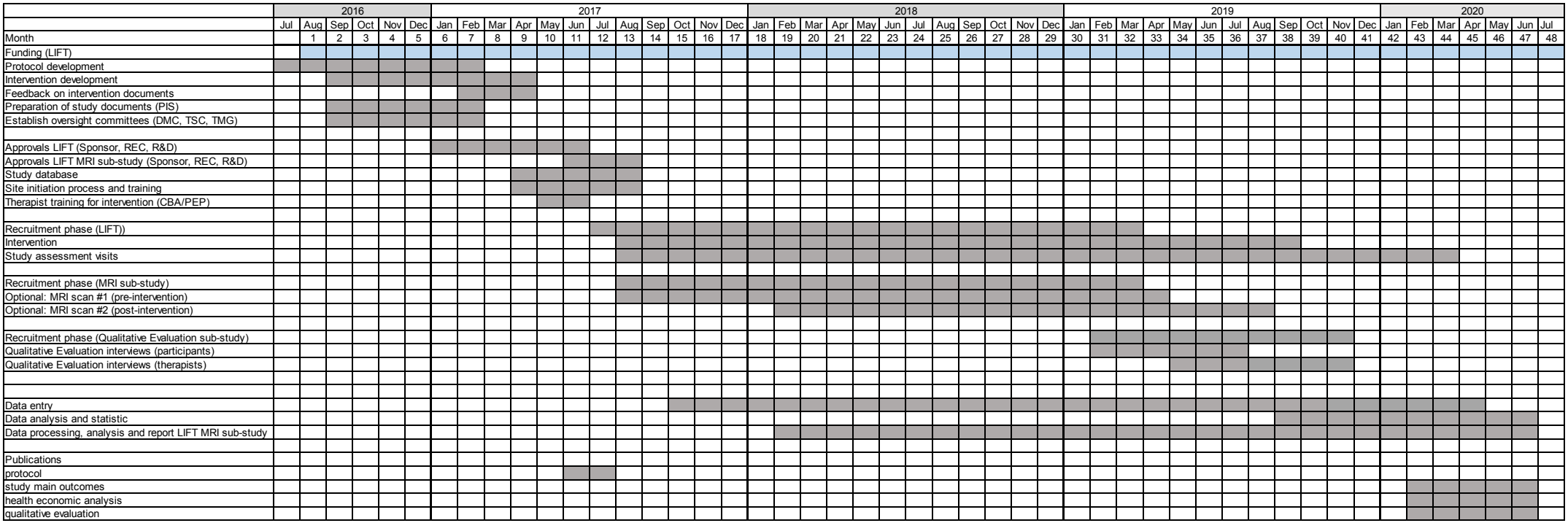


Figure 1. GANTT chart of LIFT study, LIFT MRI sub-study and qualitative evaluation sub-study

2 STUDY OBJECTIVES

2.1 Primary Objective

Primarily, we seek to test our hypothesis that usual care in addition to either standardised CBA or PEP interventions is more effective than usual care alone to lessen the impact and severity of fatigue after 56 weeks.

2.2 Secondary Objectives

We will also explore the underlying moderators (in order to inform future patient triage) and mediators (in order to optimise future interventions) of IRD related fatigue.

3 OUTCOMES

All outcome and mediator data will be assessed at randomisation (baseline) and then, on average, 10 weeks, 28 weeks and 56 weeks thereafter (by questionnaire unless stated) in all participants. The outcome measures at each time point and their source (i.e. questionnaire, medical record, blood sample, diary) are summarised in the study matrix (see 3.8).

3.1 Primary Outcome

The primary outcome fatigue is determined with the Chalder Fatigue Scale (CF) [31] using the Likert scoring, assessing the physical and mental symptoms of fatigue, and the Fatigue Severity Scale (FSS) [32] assessing the impact of fatigue after 56 weeks. If the effect of intervention is positive on the CF, then the FSS outcome will be formally analysed. Should the intervention have no effect on the CF, then an explorative analysis of the FSS outcome will be performed (details see 10.2).

3.2 Secondary Outcomes

The secondary outcomes are:

- *Fatigue:* Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire [33] (BRAF-MDQ) assessing physical, living, cognition and emotional aspects of fatigue
- *Quality of life & health utility index:* Short Form-12 [34] assessing functional health and wellbeing from the patient's perspective
- *Pain:* Pain numerical rating scale [35] assessing pain intensity
- *Anxiety and depression*: Hospital anxiety and depression scale (HADS) [36]
- *Sleep:* Sleep problem scale [37]
- *Impact on work:* Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) [38]
- *Impact on activities:* Valued Life Activities Scale (short form S-VLA) [39]
- *Global outcome*: change of global health

3.3 Mediator/moderator data

While many outcome measures may also function as mediators, or their baseline values as moderators, more detailed cognitive, behavioural, clinical and physical data will be important in order to fully characterise these factors.

Cognitions and behaviours: Brief Illness Perception Questionnaire [40], Behavioural Response to Illness Questionnaire [41]

Clinical: Presence of fibromyalgia [42], serological status, erosive status, disease duration, previous and current pharmacological therapies, disease activity: self-reported, DAS28 for RA (mandatory), , other disease specific activity measures (non-mandatory), inflammation (CRP/ESR), presence of other co-morbidities (Charlson Comorbidity Index).

Physical: Physical activity profiles measured by an activity monitor (*activ*PAL, Paltechnologies Ltd, Glasgow). The *activ*PAL will be fitted to the participant at each assessment session and participants instructed to remove the device and post it back to the research team after seven days in the stamped addressed envelope provided to them.

Quantifying aerobic fitness: we will employ a step test, which involves participants wearing a heart rate monitor and stepping onto a 10 inch high box for three minutes at different stepping rates (stage 1:17, stage 2:26 and stage 3: 34 steps per minute – guided by a metronome). Participants stop the test if the heart reaches 65% of predicted maximal heart rate (220-age or 190-age if participant is prescribed beta-blocker) at the end of any stage. In addition, values of Borg Rating of Perceived Exertion (RPE) are collected. One minute of rest is given between stages and maximal oxygen uptake is estimated from heart rate recordings according to established equations [43].

Neuroimaging data: Participants will have an option to undertake a multi-modal magnetic resonance imaging (MRI) brain scan (see Appendix 2)

3.4 Quantitative process evaluation

3.4.1 Patient preference

Participants will be given short synopsis of all three treatments, usual care, CBA and PEP interventions as treatment for IRD-related fatigue. They will then be asked about which treatment they would choose if they had a choice, as well as about their strength of preference.

3.4.2 Patient adherence and acceptability

Patient adherence to the interventions will be monitored via attendance records kept by the therapists. In addition, participants receiving the CBA or PEP interventions will be contacted by telephone interview by member of trial office Aberdeen at time of session 4 (approximately week 8) and session 8 (approximately week 26). They will be asked to indicate on a scale from 0 (not at all) to 10 (completely), if they think that this treatment is the right approach and their willingness to engage and adhere to the intervention. At the same time, the therapists will be asked during supervision to what extent they think that the participant has engaged with treatment and adhered to the agreed actions and

plans. Intervention acceptance by participants will be evaluated in all three treatment arms using the Client Satisfaction Questionnaire [44] at 28 weeks.

3.5 Qualitative process evaluation

We will conduct qualitative evaluations of both participants who received CBA or PEP and rheumatology health care professionals who will deliver the interventions (see Appendix 3).

3.6 Economic evaluation

An economic evaluation will be conducted from both a health care system and societal perspective. Participants will be asked to record in a diary all types and duration of hospital admissions, frequency of visits to hospital for outpatient attendances, and other visits to or from relevant health professionals (e.g. general practitioners, nurse practitioners, physiotherapists) and specify whether the main reason for the visit was fatigue. The participant will be asked to keep the diaries between the baseline and third assessment visit (approximately 28 weeks). Furthermore they will be asked to keep diaries for two weeks after the third assessment visit and two weeks before they return for the last assessment visit. National sources of unit cost data will be applied to value resource use (HRG Reference Costs, Unit Costs of Health and Social Care). The costs associated with delivery of the interventions will be estimated using records kept by therapists of the number and duration of calls per patient.

Patients will be asked to report any contacts with private practitioners, and the costs of over the counter medication/complementary therapies purchased. This also includes additional expenses related to their condition or fatigue as well as if there was an impact on paid and unpaid work.

Health-related quality of life data will be collected using the SF-12 and these data will be converted to quality of life weights using published tariffs. These data will then be used to calculate Quality Adjusted Life Years (QALYs). As the intervention may affect general well-being as well as reduce fatigue, we will also collect values for changes in well-being data using the ICECAP instrument [45] and changes in life satisfaction [46].

3.7 Collection of blood sample for future ethically approved research

Patients will be given the option to provide additional blood samples which will be stored in a designated freezer at the University of Aberdeen. These are a maximum of 3 tubes per visit of 1x PAXgene RNA (visit 1, 2, 3), 1x PAXgene DNA (visit 1 only), 1x serum (visit 1, 2, 3). All samples will be transferred to a designated freezer at the Imaging Centre of Excellence, Queen Elizabeth University Hospital in Glasgow and stored until analysis. Additional consent for their use in future unspecified studies will be obtained.

3.8 Study Matrix

	Source	Items		Proposed assessment [weeks]			
			S	0	10	28	56
Demographic data							
Date of birth, gender, marital status, employment status, level of education	Q	5		✓			
Characteristics of study population							
Overall health	Q	1		✓			
Physical activity (typical self-reported)	Q	1		✓			
Experience of fatigue for more than 3 month	Q / CRF	1	✓	✓			
Average level of fatigue	Q / CRF	1	✓	✓			
Thyroid function test	B or MR			✓			
Urea and electrolytes	B or MR			✓			
Full blood count	B or MR			✓			
Serological status	MR			✓			
Erosive status	MR			✓			
Disease duration	MR			✓			
Presence of other co-morbidities (Charlson Index)	MR/CRF			✓	✓	✓	✓
History of suicide attempts	MR/CRF			✓			
Inflammation (CRP/ESR)	B			✓	✓	✓	✓
Current pharmacological therapies	MR			✓	✓	✓	✓
Blood pressure	T			✓			
Primary Outcome							
Chalder Fatigue Scale (Likert scoring)	Q	11		✓	✓	✓	✓
Fatigue Severity Scale (FSS)	Q	9		✓	✓	✓	✓
Secondary Outcomes							
BRAF-MDQ (fatigue)	Q	20		✓	✓	✓	✓
HADS (anxiety and depression)	Q	14		✓	✓	✓	✓
Short Form-12	Q	12		✓	✓	✓	✓
Pain numerical rating scale	Q	1		✓	✓	✓	✓
Sleep problem scale	Q	4		✓	✓	✓	✓
Work Productivity and Activity Impairment Questionnaire	Q	6		✓	✓	✓	✓
Valued Life Activities Scale (short 14 items)	Q	14		✓	✓	✓	✓
Global outcome	Q	1			✓	✓	✓
Additional mediator/moderator data							
Cognitions and behaviours							
Brief Illness Perception Questionnaire	Q	9		✓	✓	✓	✓
Behavioural Response to Illness Questionnaire	Q	21		✓	✓	✓	✓
Clinical							
Presence of fibromyalgia	CRF	8		✓			✓
Disease activity (self-reported)	CRF	2		✓	✓	✓	✓
Disease activity DAS28 for RA (mandatory), ASDAS, BILAG, replaced with disease specific activity measures (non-mandatory)	CRF/MR			✓	✓	✓	✓
Physical							
Physical activity profiles, over a 7 day period	T			✓	✓	✓	✓
Quantifying aerobic fitness (step) test (weight, VO_2 max and Borg Rating of Perceived Exertion)	T			✓	✓	✓	✓

	Source	Items		Proposed assessment [weeks]			
			S	0	10	28	56
Neuroimaging (optional)							
Multi-modal MRI scan	SC			x		x	
Quantitative evaluation							
Patient preference	Q	2		✓			
Patient adherence (attendance records)	SR			x	x	x	
Patient engagement and adherence (telephone call)	Q	3			x	x	
Patent engagement and adherence (therapist view)	Q	2			x	x	
Patient acceptability (Client Satisfaction Questionnaire)	Q	8				✓	
Qualitative process evaluation							
Qualitative evaluation in participants (5% sample)	I						
Qualitative evaluation in therapists (all)	I						
Economic evaluation							
Health care costs from participants per diaries	D			✓	✓	✓	✓
Additional (personal) costs for participant per diaries	D			✓	✓	✓	✓
Cost associated with delivery of therapy	SR			✓	✓	✓	✓
Health related quality of life using SF-12 for calculation of QALY				✓	✓	✓	✓
Changes in well-being data using ICECAP	Q	5		✓	✓	✓	✓
Changes in life satisfaction	Q	1		✓	✓	✓	✓
Optional blood sample for future ethically approved research							
1 x PAXgene RNA				✓	✓	✓	
1 x PAXgene DNA				✓			
1 x serum				✓	✓	✓	

Key: B, blood sample taken specifically for LIFT; **CRF**, part of case report form completed by research nurse during visit; **D**, separate diary for participant to keep; **I**, interviews performed after the last follow-up visit; **MR**, information extracted from medical record; **Q**, data derived from questionnaire; **S**, information obtained during pre-study invite; **SC**, Scanner; **SR**, information extracted from LIFT study records and logs; **T**, test done specifically for LIFT; **x**, outcome collection at same time frame but separate from assessment visit

4 STUDY DESIGN

The LIFT study is a multi-centre, three-arm randomised controlled trial testing usual care alone versus usual care with additional adapted CBA or PEP therapies (see 4.3).

4.1 Study Description

Eligible participants will be identified from about 3600 patients with IRD attending major secondary care rheumatology services in the UK (see also study flow chart under 4.2). Potential participants will be identified using local databases/clinic lists and will then be mailed or given a pre-study invite, which will include questions about fatigue (see 5.2). Potentially eligible participants will be invited to attend a baseline assessment where, if appropriate, they will be consented, the eligibility confirmed and randomised. Recruits will be randomly assigned to either a course of usual care and CBA or PEP, or usual care alone (see 6). Those in the CBA and PEP groups will receive a course of treatment involving 7 sessions delivered by telephone/ internet-based audio/video call. A booster session will be conducted 22 weeks after the start date of treatment (see 4.3). We expect that active CBA and PEP therapy will start at between 2 and 8 weeks post-randomisation,

with an average of 4 weeks after baseline. Follow-up data will be collected from all participants at 10 weeks, 28 weeks and 56 weeks after randomisation adjusted for the average delay of 4 weeks. The timeline for assessment and delivering of interventions is summarised in Figure 2 below.

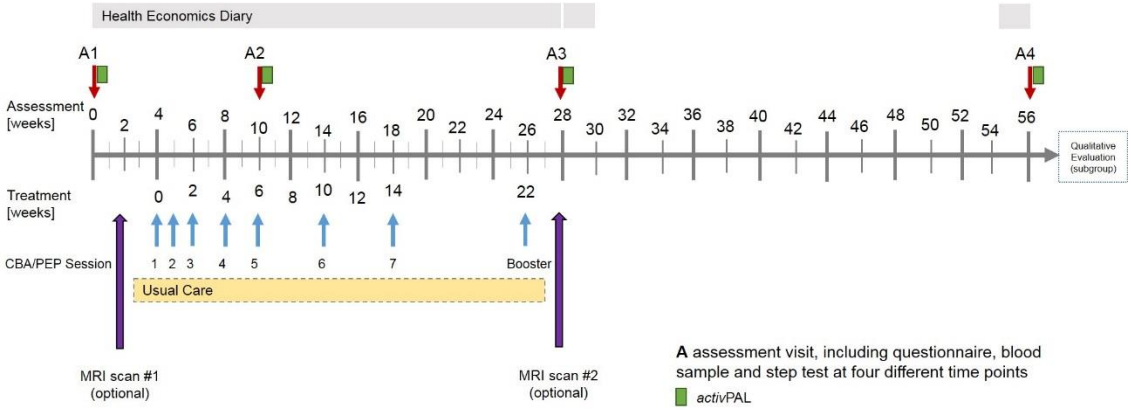
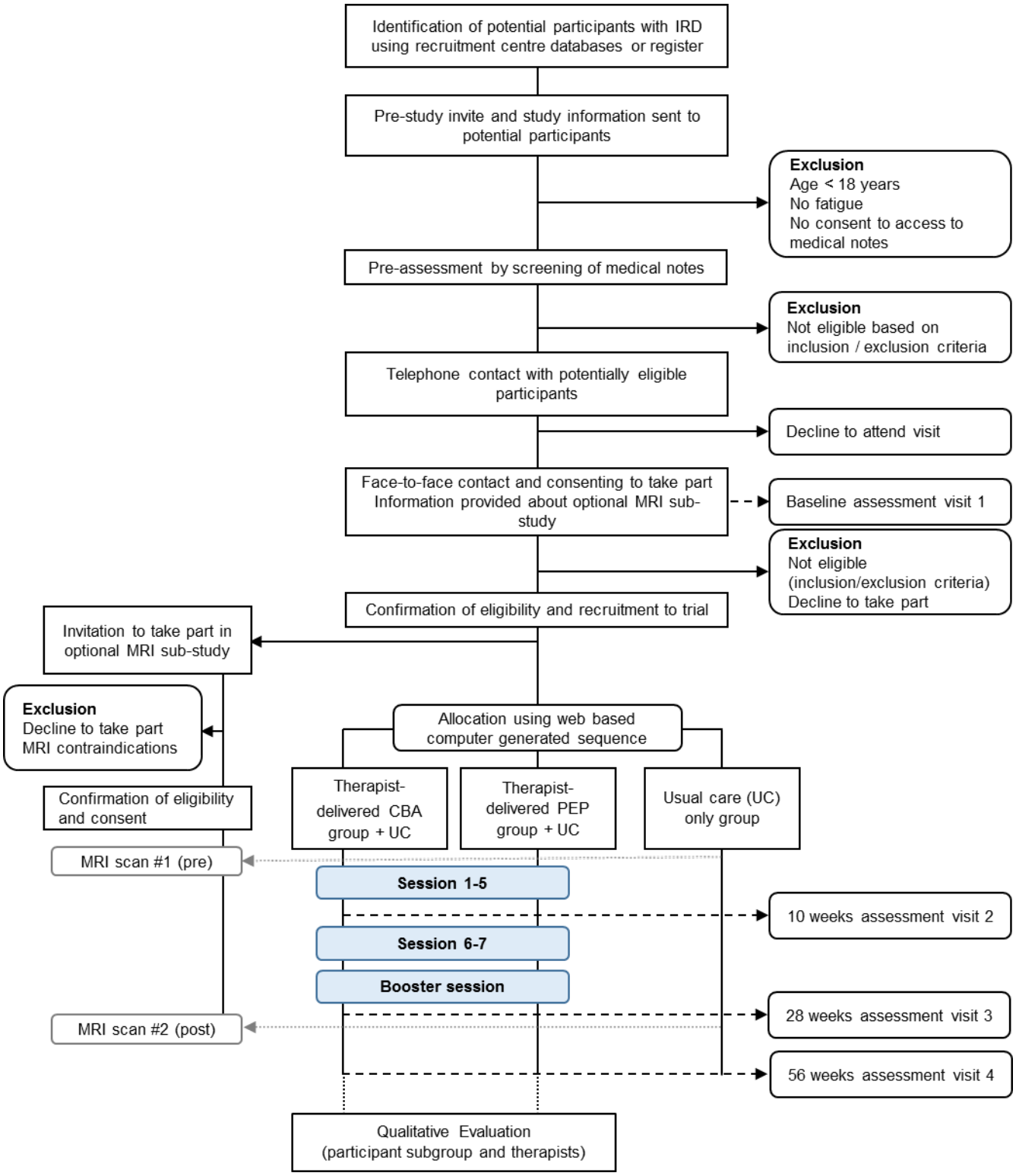


Figure 2. Study time line

The primary outcome measures will be fatigue severity and impact (see 3.1). Secondary outcome measures will include those on quality of life, pain, psychological distress and work ability (see 3.2). Additional clinical, physical activity and psycho-social data will be collated to enable the identification of moderators and mediators (see 3.3 and 3.4). A subgroup of participants will be invited to take part in a nested qualitative evaluation study after they completed the follow-up (see Appendix 3). A subgroup will be invited to take part in an optional nested mechanistic observational MRI sub-study (Appendix 2). The main effectiveness analysis will be via intention-to treat including all participants (see 10).

4.2 Study Flowchart



4.3 Interventions

All participants will receive the usual care intervention and will be posted an Arthritis Research UK education booklet. Participants randomised to the active treatments will also receive either CBA or PEP. The CBA and PEP treatments are adapted from previous fatigue specific cognitive behavioural [47,48] and physical activity interventions [47] to ensure that they are suitable for a remote delivery via telephone or internet-based audio/video call and applicable the broad spectrum of IRD.

4.3.1 Description of interventions

Usual care: Due to issues of treatment access, patient education using Arthritis Research UK's information booklet for self-management of fatigue [49] represents usual care in almost all UK rheumatology centres and is freely available. The leaflet covers the major relevant topics (including fatigue validation, energy management, priorities, sleep, stress, and assertiveness) underpinned by goal-setting and self-monitoring of activity. It encourages, at several key points that the patient asks their rheumatology team for support to work through the booklet. We will not restrict what usual care may involve, but will monitor the care received for all participants as part of our health economics analysis (see 3.6).

The *Cognitive behavioural approach (CBA)* is a structured psychological intervention, which explicitly aims to replace unhelpful beliefs and behaviours with more adaptive ones. In this study, the CBA will target a number of unhelpful behavioural patterns such as 'activity avoidance' and 'all or nothing'. These can lead to negative mood states, which enhance the perception of fatigue even further. Following a brief assessment of individual patients beliefs and behaviours surrounding fatigue, the aim of the treatment is to change unhelpful beliefs and behavioural factors through the application of patient-centred strategies and behavioural activities, which are supported by written materials and regular consultations with rheumatology health care professionals. The participants will receive additional key leaflets and diaries to assist them with making changes to manage fatigue. The times and duration of keeping the diary as well as the exchange of content will be set individually for each patient following assessment and in collaboration with the allocated therapist. For example the participant may be asked to keep the rest and activity dairy for up to two weeks before a session with the therapist and they will talk about it via video call where the participant shows the diary to the therapist.

The *Personalised Exercise Programme (PEP)* is theoretically based on the premise that chronic fatigue relates to PA intolerance, supported by unhelpful illness beliefs (such as fear avoidance) and deconditioning, with a consequent increased perception of effort. PEP aims to disrupt this vicious cycle by a graded exposure behaviour therapy, which is symptom contingent, to gradually optimise patients levels of PA with view to modifying their altered perception of effort, improve their tolerance of PA, fitness and function, reverse the deconditioning and ultimately reduce the severity and impact of fatigue. Participants will receive an individually tailored graded exercise programme, initially delivered according to their physical capacity and gradually increased in duration and then intensity. The participants will receive additional information and diaries to assist

with the intervention. The times and duration of keeping the diary as well as the exchange of content will be subject to change based on the instructions of the allocated therapist. The intervention will utilise pedometers and/or heart rate monitors for goal-setting and to enhance motivation.

4.3.2 Treatment protocol

Both interventions will be delivered by trained rheumatology health care professionals, such as rheumatology nurses, occupational therapists and physiotherapists, with a pre-existing understanding of IRDs. Participants will be offered seven one-to-one telephone or internet-based audio/video call (based on patient preference) sessions (up to 45 minutes) of CBA or PEP interventions with a trained rheumatology health care professional. The first session of the PEP intervention, however, will be delivered face-to-face. PEP may be delivered by a rheumatology specialist physiotherapist and CBA may be delivered by a rheumatology nurse or alternatively an equally qualified and trained allied health professional. A booster session will be conducted at 22 weeks after start of therapy by the relevant rheumatology health care professionals.

4.3.3 Training of therapists before the study

Separate CBA and PEP training will be provided for the rheumatology nurses and physiotherapists. This will comprise an intensive 3-day group course delivered by experienced designated investigators (see delegation log in Trail Management File, TMF) supplemented with the modified therapist manuals. The course will utilise a range of methods including skills practice with specific feedback using fictitious but typical fatigued cases.

4.3.4 Supervision and support of therapists during the study

Supervision will be provided by designated investigators (see delegation log in TMF) on a fortnightly basis, as required, to the rheumatology health care professionals either face to face or by telephone depending on feasibility and preference. Some of the sessions will be recorded and used in supervision to provide feedback to rheumatology health care professionals and to ensure treatment fidelity. We aim to take a 5% sample of sessions from individuals who agree to be recorded which is based on a random sample generated from an algorithm that takes into account session number, therapist, site location, patient gender. 5% of total number of sessions for those in CBA and PEP is 89 recordings, however this will be subject to participant agreeing to be recorded and treatment adherence (no sessions completed).

In addition, support will be available in cases where a rheumatology health care professional requires assistance with respect to a particular participant. In addition to direct contact option with the supervisor, we will have a notification system incorporated in the database provided and maintained by CHaRT (see 8.2). After secure log-in, the rheumatology health care professional is able to log a report with details about the issue using the participant ID number but no further identifying details included. The database will, if requested, notify the designated investigator or nominated deputy if unavailable as summarised in the delegation log in the TMF, who will provide clinical input if necessary or identify either designated supervisor to provide support if an intervention

specific issue is raised. We will aim to arrange for the rheumatology health care professional to be contacted within 24 h (based on normal working hours) regarding the issue and agreement reached on the required action to be taken and by whom.

5 STUDY POPULATION

5.1 Number of Participants

Based on the sample size calculation (see 10.1), 100 evaluable participants per treatment are required. The data of participants are evaluable when outcomes at the 56 weeks follow-up are available. Based on our own previous studies, we estimate a dropout rate of 20% and therefore we anticipate recruiting 125 participants in each treatment group, or 375 participants previously diagnosed with IRD (e.g. RA, SLE and AxSpA, psoriatic arthritis, vasculitis or Sjogren's Syndrome).

5.2 Participant Selection and Enrolment

Local procedures at the participating study sites are different and the recruitment process may vary in order to accommodate the specific circumstances at each site. Study posters and leaflets will be available at NHS premises of study sites and displayed on websites and social media to increase awareness of the study. Patients are asked to contact their Rheumatology team if they are interested in the study as enrolment is by invitation only. All potential participants will undergo a two-step screening process consisting on a pre-study invite and an assessment of their medical notes to identify potentially eligible participants. All participants will provide written informed consent before they undergo the baseline assessment visit and randomisation to one of the three intervention groups (see 4.3.1).

5.2.1 Identifying Participants

A nurse who is a member of the direct care team will identify potential participants using established databases and/or by searching of clinic lists at each study site. Patients with rheumatologist diagnosed IRDs (e.g. RA, SLE and AxSpA, psoriatic arthritis, vasculitis or Sjogren's Syndrome) will be selected. Each potential participant will be contacted by the direct care team on behalf of the local Principal Investigator first. They will receive a pre-study invite either by post or at the time of a rheumatology appointment consisting of a cover letter (see Appendix 1 for details on SWAT Study within a Trial), study information and a few questions to explore interest and eligibility. They will also be asked to give permission for the local research personnel to access their hospital medical notes to further screen for eligibility and for permission to be contacted by the study team (local and central).

If a participant has been identified as potentially eligible a member of the local research team will contact the potential participant within a week to invite him/her to an appointment for a baseline assessment visit at the local study site.

5.2.2 Screening for Eligibility

After return of the pre-study invite, the research personnel at each study site will assess their medical notes to determine eligibility based on the inclusion and exclusion criteria summarised in 5.2.3 and 5.2.4. A trained rheumatology research nurse will review and confirm eligibility. In addition, the local rheumatology consultant will have the opportunity to withdraw (see 6.3) or exclude participants.

5.2.3 Inclusion Criteria

In order to be considered eligible for participation in the study they must:

- be ≥ 18 years at the time of consent
- have been diagnosed by a rheumatologist with an IRD such as RA, SLE or AxSpA
- report fatigue to be a persistent problem as evidenced by answering both questions:
    - Have you had problems with fatigue for more than three months? (Yes)
    - Please circle the number that shows your average level of fatigue during the past 7 days. (≥ 6 based on a scale of 0 (no fatigue) to 10 (totally exhausted))
- have access to a telephone landline or mobile telephone and/or internet based audio/video calls
- give permission for researchers to access their hospital medical notes
- currently be under the care of a secondary care physician
- have stable disease as evidenced by no change in immunomodulatory therapy within the last three months based on the hospital medical record

5.2.4 Exclusion Criteria

Participants will be excluded if:

- there are significant abnormalities of thyroid function (TSH levels) on the most recent blood test done within the last three months
- there is evidence of severe anaemia (haemoglobin levels) on the most recent blood test done within the last three months
- there is evidence of severe renal dysfunction (eGFR) on the most recent blood test done within the last three months
- they have a medical condition which would make the proposed interventions unsuitable, e.g. significant heart disease
- they are pregnant
- they are unable to understand English sufficiently to take part in the intervention
- they are unable to provide written informed consent
- they are not willing to be randomised
- they are currently participating in an interventional clinical trial

5.3 Consenting Participants

The potential volunteers will make a decision to participate when they attend the local study site for the baseline assessment visit. An appropriately trained member of the research personnel at each site will obtain informed written consent from the participants.

During the first baseline assessment visit, a designated member of the local research team will determine interest in participating and confirm potential eligibility (including re-confirmation of fatigue state). He/she will explain the study and answer any questions, which the patient has but will also raise issues of feasibility of use of telephone and, if necessary, investigate whether they have for example a hands-free option on their telephone. If a suitable option is not available, a telephone with hands-free function (owned and maintained by the LIFT study team) will be loaned for the intervention period.

No study specific procedures will take place before written consent has been obtained. Once the participant is ready to provide informed written consent, the patient will complete the baseline assessment forms, have clinical information recorded and will be screened for other treatable causes of fatigue. Therefore, the research nurse will take a blood sample to measure thyroid function, haemoglobin and renal function, if these have not been assessed within past three months. Should the person become ineligible as result of the blood test, we will follow the procedure for ineligible participants. In addition, a blood sample is taken to measure CRP and ESR as well as blood samples (1 x PAXgene RNA, 1 x PAXgene DNA, 1 x serum) for storage for future ethically approved research. Procedures for reporting all study blood results will be in place (see also 9).

Participation in the LIFT study will be recorded by the nurse in the hospital medical records together with a copy of the signed consent form.

The research nurse will also determine whether the participant has ever met the relevant classification criteria for RA (mandatory), or other IRDs (non-mandatory):

1) RA (2010 American College of Rheumatology/European League Against Rheumatism RA criteria [50] or 1987 American College of Rheumatology RA criteria [51]),

2) SLE (1997 American College of Rheumatology SLE criteria [52]) and

3) AxSpA, (Assessment of Spondyloarthritis (ASAS) criteria for AxSpA [53]).

5.4 Procedure for ineligible and non-recruited participants

The research nurse or other member of the research team will complete the relevant section of the case report form (CRF) for each person and the reasons for ineligibility will be recorded. If the reason for ineligibility is reversible with appropriate treatment, e.g. change in immunomodulatory therapy, thyroid disorder or anaemia, the potential participant may be contacted at a later stage and, if appropriate, re-invited for assessment including re-consenting and new participant ID. Patients who selected 5 for their average level of fatigue may be re-sent an invitation after 3 months, if appropriate. The collected anonymised data will be stored in the designated database for evaluation but no further data will be collected from the participant unless the person specifically requests to destroy all collected, questionnaires and data during the formal withdrawal procedure (see 6.3).

6 RANDOMISATION AND BLINDING

6.1 Randomisation Details

After the patient has provided written consent to participate in the study and eligibility has been confirmed, the member of the local research team will randomise the participant via the Clinical Trials Unit (CTU). The CTU is the Centre for Healthcare Randomised Trials (CHaRT) based within the University of Aberdeen. The CTU provides a 24 h randomisation web based service. Using a computer generated sequence, participants will be allocated to receive either of the two treatments or usual care (1:1:1 ratio). Randomisation will be minimised by diagnosis (RA, SLE, AxSpA or other IRD) and the presence/absence of depressive symptoms (Hospital Anxiety & Depression Scale (HADS) depression subscale >10) and will include a random element set at 20%. That is, 20% of all the allocated randomisations will be randomly re-allocated 50:50 to the remaining two treatment options.

Randomised participants will be contacted by the study co-ordinator (or designated deputy if unavailable) by post, email and/or telephone with information about their intervention and details of their allocated therapist, if applicable. All personal contact details will be only accessible in the password protected study database (see 8.2).

6.2 Blinding

Full blinding will not be possible due to the need to engage people in behavioural change. However, to reduce detection bias, we will aim to blind research personnel undertaking outcome assessments to participants' treatment allocation. To facilitate blinding we will remind participants to refrain from discussing (and subsequently revealing) their treatment allocation at follow-up assessments with the research personnel. Finally, data will be analysed blind to allocation.

6.3 Withdrawal Procedures

Participants will have the option to withdraw at any time during the study period of 13 months. The participant needs to request this formally and a withdrawal document will be completed and signed by the designated research staff at the local sites. They have the option to either withdraw from the study completely or from parts of it (pre-study invite, treatment or follow-up). If participants withdraw from the study completely or from follow-up assessments, they will not receive further invitations but we will use the data collected prior to the withdrawal (depending on permission). Those withdrawing from the treatment only will continue to be sent invitations to attend and complete follow-up assessment visits, unless they request to withdraw completely later on. Failure of any participant to complete a follow-up at any particular time-point will not be counted as a withdrawal unless the participant formally requests to withdraw. In addition, a participant can also be withdrawn by others, for example the local PI or primary consultant, should the need arise at any stage throughout the study period. This also includes loss of capacity for continuous consent.

7 STUDY AND SAFETY ASSESSMENTS

There are unlikely to be major safety issues with our proposed non-pharmacological interventions. However, if the rheumatology healthcare professional delivering CBA and PEP or any study personnel have any safety concerns, we will follow a specific Standard Operating Procedure (SOP) for adverse events in non-CTIMP studies. In brief, they will use a standard template after secure log-in into the study database. A designated investigator with rheumatology background and/or designated experienced investigators responsible for the training of therapists as summarised in the delegation log in the TMF will then assess and categorise events according to the SOP to determine if the event is expected, related and/or serious. There will be access to independent clinicians (both rheumatology and psychology), if required. We will make every effort to report all confirmed related serious adverse events to the sponsor within 24 working hours after the CI has been made aware of them.

8 DATA COLLECTION AND MANAGEMENT

8.1 Data Collection

Case Report Forms (CRF), including medical outcomes, and questionnaires as indicated under 3 and 3.8, respectively, are completed during the assessment visits at the local study site either on paper or online in the database. All participants will have the option to complete the questionnaires and diaries online in the database (requires a valid email address) or on paper depending on personal preference. There will be the option to complete the questionnaire at home, if the participant requests this. Paper questionnaires will then be returned via pre-paid envelopes to the study centre. If the participant opted for online entry, he/she will receive secure access limited to own data in the database via a link sent to a provided email address and/or log-in code. Paper health economic diaries which are filled by the participant throughout the study will also be returned either in person to the local study site or by pre-paid envelope to the study centre Aberdeen. If a participant is entirely unable (e.g. due to mobility issues) to attend a follow-up visit at 10, 28 or 56 weeks in person, but is still happy to continue with the follow-up, the data collection (except blood samples, step test, DAS28) will be done by phone and post. The option for remote data collection will only be used in selected cases at the discretion of the PI/CI/Co-CI if an assessment visit at the local site would be delayed for at least 3 weeks. In case of a participant unable to attend a follow-up visit, the paper questionnaire, diaries and ActivPAL will be sent out by post and will be returned via pre-paid envelopes to either the study centre or the local study site. In case of a local site unable to perform a follow-up visit, the Trial Office staff will perform the remote visit instead. Information from medical records will be taken retrospectively once the local site is in a position again to continue. Any participants who do not return a questionnaire at the 56 weeks follow-up visit will be telephoned and asked some questions over the phone about fatigue (i.e. Chalder Fatigue Scale, Fatigue Severity Scale), Patient Global Impression of Change, Disease activity and intensity of pain. Personal data, including postal address, phone numbers (landline and mobile), email addresses, and anonymised data files for study outcomes are stored in locked filing cabinets (hard copy) and in a bespoke database provided and maintained by CHaRT (see 8.2) as well as secured shared drives with access via password controlled computers (university and NHS networks) by study staff only (electronic data) (see also 13.1.1 and 13.1.2). Participants will have the option to undertake a multi-modal MRI brain scan (see Appendix 2). A

subgroup of participants and all therapists will have the option to take part in an interview as part of the Qualitative Evaluation sub-study (see Appendix 3).

8.2 Data Management System

A study specific database will be established and maintained by CHaRT. The access to the database is password controlled with personal access rights (see also 13.1.1 and 13.1.2). The structure and content of the database will be individualised based on the protocol, the study outcome questionnaires and CRF. Individual requirements such as screening log and report functions for continuous monitoring of recruitment, randomisation and follow-up will also be incorporated. There will be a read-only role which allows access to the system for audit and monitoring.

8.3 Transfer of Data

Personal data including signed consent forms (original hard copy) will be held at to local study site for the duration of the study before they are transferred by tracked surface mail service to the study centre/study team in Aberdeen for archiving or destroyed. Copies of signed consent forms and anonymised study outcomes (hard copy) will be transferred to the study centre/study team in Aberdeen by tracked surface mail service for monitoring purposes and data input, respectively. All electronic data is password protected and accessible via the secure database by the study staff from each study site as described in 8.2.

9 LABS AND SAMPLE ANALYSIS

This multi-centre study involves a number of standard blood investigations, i.e. TSH, haemoglobin, serum creatinine, CRP and ESR, routinely processed by local NHS laboratories. Blood samples for CRP and ESR analysis and sample storage for future ethically approved research will be taken at each assessment as specified in the study matrix by trained personnel only following established procedures. Blood samples for TSH, haemoglobin and serum creatinine analysis will only be taken at baseline to confirm eligibility, if required. Sample coding, preparation, storage, analysis and transfer of results and optional blood samples for long-term storage at the trial centre will be performed according to the analytical protocol based on national laboratory guidelines. The exact logistic and procedure will be agreed on with each site before the start of the study and we will make every effort to standardise the workflow across sites to reduce bias. Additional optional blood samples will be stored for future ethically approved research). All study blood results (abnormal or otherwise) will also be directed towards the local PI who can determine locally how these will be handled.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample Size Calculation

Our planned primary intention to treat analyses will compare PEP + usual care versus usual care alone, and CBA + usual care versus usual care alone separately. We base our calculations on a standardised effect size of 0.50 (considered credible in other pragmatic effectiveness studies), which would equate to being powered to detect a minimal important clinical difference of 2 units in the CF Scale, assuming a common standard deviation across the randomised groups of 4 units. Assuming an overall significance level of 5% (by calculating the two pre-specified randomised groups comparisons, PEP + usual care vs. usual care alone and CBA + usual care vs usual care alone, at 2.5%, to maintain an overall level of not more than 5%) and a power of 90%, we require 100 evaluable participants in each of the three groups.

10.2 Proposed Analysis

All statistical analyses will be governed by a comprehensive Statistical Analysis Plan, which will be authored by the study statistician and approved by the Trial Steering Committee and the Data Monitoring Committee before the main study outcome data are examined. All analyses will be carried out using Stata. In accordance with CONSORT guidelines, we will report all participant flow. Descriptive statistics of recruitment, drop-out and completeness of interventions will be provided.

Effectiveness Analysis: The main effectiveness analysis will be via intention-to-treat including all participants, with no planned interim analysis for early termination for either overwhelming evidence of effectiveness or abandoning for futility. Baseline characteristics will be presented by randomised group without formal statistical tests. We will test the primary hypothesis for between-group change in the primary outcome for each of the two pre-specified comparisons (CBA + usual care vs usual care alone and PEP + usual care vs usual care alone) using repeated measures mixed model, with subject as a random effect, and a suitably specified covariance structure (e.g. Autoregressive [1] (AR[1]), rheumatology healthcare professional as a random effect (to adjust for any clustering by rheumatology healthcare professional), with baseline outcome measure, and any other strongly predictive baseline measures, including the minimisation factors of presence/absence of depression and centre, and diagnosis. Treatment and its interaction with time will be fitted as fixed effects, and we apply standard regression diagnostics. The analysis will use statistical techniques for handling missing outcome data using multiple imputation under a missing at random (MAR) assumption. The secondary outcomes will be analysed using an analogous method. The main estimate of treatment effect will focus on the 56 weeks after baseline.

Mediation analysis: We will use modern causal inference methods to investigate the set of mediator measures. If the effectiveness analysis shows significant between group differences in the mediators then we will use parametric regression models to test for effect of mediator on outcome, and the residual direct effect of treatment on outcome. Since all the measures are continuous, the indirect effects are calculated by multiplying relevant pathways and bootstrapping is used to produce valid standard errors for the

indirect effects. All analyses will adjust for baseline measures of the mediators, outcome and putative measured confounders, and be tested for moderation by diagnosis. Mediation analyses are potentially biased by measurement error in mediators and hidden confounding between mediators and outcomes; we will build on our previous methodological and applied work in this context to include repeated measurement of mediators and outcomes to account for classical measurement error and baseline confounding. We will investigate the sensitivity of the estimates to these problems and that of unmeasured confounding using instrumental variable (IV) methods with baseline covariate by randomisation interactions as potential instruments.

Moderation analysis: We will examine differential treatment effects using the set of moderator measures by extending the intention to treat analysis models to include an interaction term between treatment and each of the moderators separately. We will use bias correction/cross-validation methods to identify robust evidence for individual moderation and for a moderation index, both on the overall effect and also along the steps of the mediation pathway.

10.3 Missing Data

Every effort will be made to ensure data collection is complete. However, we will use statistical techniques for handling missing outcome data. Multiple imputation under a MAR assumption will be used in the first instance, with other methods employed if the MAR assumption is not satisfied.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 Trial Management Group

The study will be co-ordinated by a Trial Management Group, consisting of the grant holder (CI), a rheumatology consultant (Co-CI), additional members of the Epidemiology group, a study co-ordinator and a representative from CHaRT. The members of the Trial Management Group and their responsibilities are summarised in the delegation log in the TMF. In addition, the names and responsibilities of all co-investigators are also summarised in the delegation log in the TMF.

11.2 Study Management

A Study co-ordinator (or designated deputy) will be responsible for the overall day-to-day management of the study and will be accountable to the CI, the Co-CI and investigators. He/she will ensure that personal and confidential information is restricted to those entitled to know it, will assist in the compliance with research and clinical governance guidelines, data protection and ethical requirements.

A Study co-ordinator (or designated deputy) will establish and maintain procedures to ensure adherence to study protocols, SOPs and administrative requirements. He/she will be responsible for training and monitoring the study staff at the local sites involved in

recruitment and assessment of the participants. He/she will assist in monitoring the study progress to ensure compliance with and adherence to the project plan and identify, evaluate and rectify problems. He/she will be responsible for checking the outcome documents for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

11.3 Trial Steering Committee

A Trial Steering Committee (TSC) has been established to oversee the conduct and progress of the study. The TSC comprises an independent chair who has expertise in trials and other members, both independent and study investigators, with background relevant to IRD or type of interventions including user representatives, who have lived experience of IRD related fatigue, and a clinician working with people with IRD. The members of the TSC are documented in the TMF at the study centre Aberdeen.

11.4 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) has been established to oversee study progress. The members of the IDMC are summarised in the TMF at the study centre Aberdeen.

12 INSPECTION OF RECORDS

Investigators and institutions involved in the study permit study related monitoring and audits on behalf of the sponsor, NHS R&D and REC. In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation.

13 GOOD CLINICAL PRACTICE

13.1 Ethical Conduct of the Study

The study will be conducted in accordance with the principles of good clinical practice (GCP). In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study. A collaboration agreement and site agreements will be signed between The University Court Of The University Of Aberdeen and the included parties and study sites, respectively.

13.1.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified using unique participant ID numbers to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The investigators and study staff involved with this study will not disclose or use for any

purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

13.1.2 Data Protection

All Investigators and study staff involved with this study will comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The investigators and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff as needed.

Computers used to collate the data will have limited access measures via user names and passwords, and such documents will be password protected and stored on secure University or NHS servers. Published results will not contain any personal data that could allow identification of individual participants.

13.1.3 Insurance and Indemnity

Where the study involves University of Aberdeen staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Grampian Health Board, which means they will have cover under Grampian's membership of the CNORIS scheme.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 Protocol Amendments, Deviations and Breaches

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study documents will not be implemented without these approvals. It is the responsibility of the sponsor to designate amendments as substantial or non-substantial.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately using the "Breach Report Form".

14.2 Study Record Retention

All study documentation (hard copy and electronic) will be kept for a minimum of 5 years from the protocol defined end of study point in the University of Aberdeen archive. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.3 End of Study

The end of study is defined as last data collection of either the qualitative evaluation study phase or during the last follow-up visit at 56 weeks from the last participant after CBA/PEP intervention or usual care start date – whichever comes last.

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 Authorship Policy

Ownership of the data arising from this study resides with the University of Aberdeen. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH authorship guidelines.

15.2 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

15.3 Peer Review

The initial study proposal was peer reviewed extensively within the system of the University of Aberdeen, as well as experts in the field before the grant application was submitted to Arthritis Research UK. Furthermore, representatives of the National Rheumatoid Arthritis Society, the National Ankylosing Spondylitis Society and Lupus UK significantly influenced the study design. In addition, the proposal underwent review from the funding agency (Arthritis Research UK). Any documents created as part of this project will undergo peer review internally within the research team, and representatives of the National Rheumatoid Arthritis Society, the National Ankylosing Spondylitis Society or Lupus UK.

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Appendix 1 SWAT 24

Background

Recruiting and retaining participants for randomised trials can be extremely difficult. It is likely that less than 50% of trials meet their recruitment target, or meet their target without extending the length of the trial [1-3]. Moreover, poor recruitment can lead to an underpowered study, which may report clinically relevant effects to be statistically non-significant. A non-significant finding increases the risk that an effective intervention will be abandoned before its true value is established, or that there will be a delay in demonstrating this value while more studies or meta-analyses are done. Moreover, if non-responses to the study invitation differ between the patients with diagnosis of RA, SLE and AxSpA, a systematic bias may be introduced that may undermine confidence in the results of the trial. Finally, poor recruitment and subsequently retention can lead to a trial being extended, increasing costs.

Trialists recognise the challenge and use many interventions to improve recruitment and retention but it is generally difficult to predict their effect. The Cochrane systematic review of strategies to improve recruitment [4] and the Cochrane review of strategies it improve retention [5] both found only a handful of interventions with high quality evidence of benefit. Given how central recruitment and retention are to all trials, it is crucial that more rigorous evaluations of recruitment and retention interventions are done.

Rationale for SWAT

One way of doing this is to do a Study Within a Trial (SWAT) [6]. A SWAT provides a protocol for the evaluation of an intervention to improve some part of the trial process, such as recruitment or retention. This evaluation is then embedded within a host trial, such as LIFT. Several teams can follow the same SWAT protocol, meaning the results can be combined in a meta-analysis. This coordinated and collaborative approach means trialists will have faster access to high-quality evidence to inform their trial design, conduct, analysis and reporting decisions.

The SWAT 24 which describes the use of a theory-based cover letter was initially developed to increase response rates of questionnaires sent during follow-up to collect outcome data direct from participants. A low response rate to these questionnaires puts the validity and generalisability of the trial results in jeopardy. Since returning the questionnaire is a behaviour, this opens up the possibility of designing a behaviour change intervention to influence the willingness of participants to do that behaviour. We propose to use SWAT 24 in LIFT to improve response rates to the pre-study invitation letter used to make initial contact with potential participants identified as described in the main protocol (see 5.2.1) to explore interest and eligibility. The SWAT 24 study is part of the Trial Forge initiative to improve trial efficiency [7].

Objective for SWAT 24

To assess the effects of a theory-based cover letter on response rate to a pre-study invite to explore interest and eligibility

Outcome

Primary outcome:

Response rate

Secondary outcomes:

Response time

Consent rate

Study retention

Intervention adherence

Intervention

The Theoretical Domains Framework (TDF) is a tool for identifying theoretical targets for behaviour change interventions [8]. The TDF and behaviour change techniques were used by the IQuaD trial team [9] to produce a template that trial teams can use to structure a theory-informed cover letter.

Comparator

A standard cover letter

Method for allocating to intervention or comparator

Participating study centres will be randomly allocated to send the standard letter or the theory-informed letter.

Analysis plan

The primary analysis is the difference in primary and secondary outcomes between those receiving the theory-based cover letter and those receiving the standard cover letter.

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Appendix 2: Delineating the neural mediators of inflammatory rheumatic disease (An optional LIFT sub-study)

Background

One of the objectives of the LIFT trial is to understand the mediators of treatment effect which will enable optimising of interventions and inferences to be made regarding the mechanisms of fatigue. We are collecting putative patient reported, clinical and physical activity profile mediator data. In addition we would like to provide the option for participants to provide their neuroimaging data by undertaking additional MRI scans of their brain.Neuroimaging has provided consistent mechanistic insights into fatigue, reinforcing our epidemiological investigations of RA related fatigue which have identified strong associations with central factors such as mental health and cognitive dysfunctions but not peripheral measures of inflammation[4,5]. We were the first to test these methods in a fatigued chronic inflammatory disease cohort. We identified multiple neural correlates of fatigue in patients with vasculitis using different structural and functional magnetic resonance imaging (MRI) modes [6,7] and we have since observed similar fatigue specific findings in RA.

Our original studies were small (n=12) and cross-sectional but did implicate a potential role for a striato-thalamo-frontal network. Among fatigued vasculitis patients, we observed an apparent overuse of the cingulum and fornix white matter tracts, as identified by Diffusion Tensor Imaging (DTI), which coincided with the high functional activity within some of their source and destination grey matter structures, specifically the thalamus, medial globus pallidus, medial frontal and cingulate gyri and paracentral lobule.

Our most recent pilot was larger and although uncontrolled included a repeat multi-modal scan at 6 months that enabled the longitudinal evaluation of fatigue in the context of standard care (which did not include fatigue specific therapy). Of those n=54 completing follow up, n=22 reported modest, albeit clinically relevant, improvements in their fatigue. Interestingly, widespread reductions in cortical grey matter volumes were measured, using voxel-based morphometry (VBM), among the non-improvers at follow-up however no such volume changes were observed among improvers. In contrast, sub-cortical grey matter volumes exhibited large significant increases in non-improvers. The sub-cortical grey matter volumes of improvers also increased, although the changes were small in comparison.

In terms of white matter integrity, as measured by DTI, widespread abnormalities were observed among improvers. Within this group, significantly reduced fractional anisotropy (FA) was measured at follow-up compared to baseline in major white matter tracts. Strikingly, no significant longitudinal FA changes were measured within the non-improvers group. Similarly, improvers- and not non-improvers- evidenced widespread imbalances in functional connectivity imbalance over time.

Overall, these data strongly associate central neural pathways in RA related fatigue. Although the different MRI metrics provide complementary evidence which implicate frontal networks, a targeted approach (e.g. with non-invasive neuromodulation devices)

will demand much greater knowledge of the precise culprit frontal regions, moreover several non-frontal regions seem also to be relevant. Until now, no studies have been adequately designed to pin-point those brain regions which mediate changes in fatigue (and so demonstrate causal potential).

The problem with our existing studies is that they were either cross-sectional, or longitudinally followed individuals who had spontaneous changes in their fatigue (thus the changes in fatigue from one time point to the next were modest). We propose that the best way to identify which of these brain regions are most important in mediating fatigue is to perform controlled longitudinal imaging studies in individuals prior to and then following an intervention that reliably improves fatigue in most individuals.

This Lessening the Impact of Fatigue Trial (LIFT) sub-study provides a timely opportunity to address this research void.

Sub-study objective

- Which functional and structural brain mediators best explain fatigue improvement and are they potentially trans-cranially accessible?

Study design

An optional nested mechanistic observational sub-study within the Lessening the Impact of Fatigue Trial (LIFT).

Participants

All consenting LIFT participants will be invited to participate in this optional sub-study which involves an additional MRI brain scan prior to and 26 weeks after their first treatment session (if CBA or PEP) or within 8 weeks of randomisation and 6 months thereafter if usual care. The only additional exclusion criteria is any contra-indications to MRI scanning (e.g. pacemaker).

Participant selection

At the baseline visit, all participants will be provided an information sheet on this sub-study. The research team will then contact the participants a few days later to establish interest and the absence of MRI contraindications. If suitable and interested, the participant will be offered an appointment to attend their nearest participating MRI research facility (Edinburgh, Aberdeen or Glasgow) within a month. A research team member, recorded in the Delegation Log and with GCP training, will be responsible for taking additional full written informed consent (specific to this sub-study) on attendance at the imaging centre prior to the MRI assessment and then conduct a final MRI safety screen.

Participant withdrawal

All participants will be free to withdraw at any time from the MRI sub-study, without giving reasons and without prejudicing further treatment or their participation in the LIFT trial.

MRI assessment

Prior to entering the scanner, subjects will have the opportunity to practice a cognitive task required for the standard fMRI aspect of analysis. As with our previous work[6], the validated PASAT will be employed to transiently fatigue the subject. The task is a measure of cognitive function; specifically auditory processing, calculation, working memory and attention. Participants will be asked to listen to a series of numbers ranging from 1 to 9. They are required to sum consecutive numbers (i.e. the first to the second, the second to the third etc.) and to record, via a button press, every occasion two consecutive numbers sum to the number 10. Concurrently, they will be asked to focus on a computer screen displaying three boxes containing random, rapidly changing numbers. This visual stimulus is intended to distract the participants from the auditory task and hence increase difficulty. They will be instructed not to process the visual numbers in any way.

Participants will then be asked to lie supine in the 3T Phillips Achieva X-series MRI scanner in Aberdeen or the equivalent scanner in Edinburgh. The multi-modal MR will consist of structural and functional sequences:

Structural- We will collect images to allow volumetric analysis. We will also acquire images to allow determination of white matter hyperintensity lesion load and measures of white matter structural integrity (e.g. DTI).

Functional Imaging- Images sensitive to BOLD contrast will be acquired during rest to investigate metrics such as intrinsic network connectivity as well as during the PASAT task (3x3minute periods interspersed by 30s rest periods).

In total these can will take approximately 45 minutes to conduct and will be repeated at approx. 6 months (when we predict to observe the greatest effect from the interventions).

Analysis

Following pre-processing of the MRI data the following analysis will be undertaken which will integrate data which will have been collected as part of the parent trial:

Longitudinal comparisons (paired t-tests as implemented by SPSS for ROI based variables and Freesurfer for voxel based variables) of structural and functional change indices in relation to subjects' change in fatigue will be performed. Putative confounders will be individually introduced as co-variates of interest. The individual analyses will focus upon those regions of interest previously identified by our studies, but since we recognise that these are not comprehensive we will also conduct agnostic (data-driven) whole brain analyses. All analyses will be adjusted for multiple testing.

Having identified and validated key neural areas, group differences in mediators of treatment effects on outcomes will be assessed via mediation analysis methods in order to tackle the secondary objective. These involve causal inference methods, such as structural equation modelling, to account for measurement error in the imaging data, and repeated measures to allow for the inclusion of all available data. Those resultant neural mediators which are common to both interventions and accessible to non-invasive neuromodulation will serve as our future therapeutic targets.

Finally we will be using whole brain statistical pattern recognition techniques on the neuroimaging data and mediation effects identified in answer to the previous objective. In the Pattern Recognition for Neuroimaging Toolbox (PRoNTo) brain scans are treated as spatial patterns and statistical learning models are used to identify statistical properties of the data that can be used to discriminate between, or classify, experimental groups of subjects.

Sample size

We aim to recruit 120 participants (who will have been randomised to receive either usual care alone, CBA in addition to usual care or PEP in addition to usual care in the parent trial).

Data handling

MRI scan data will be stored in an anonymised format in the University of Aberdeen, Edinburgh and Glasgow imaging archive system on the university drive, with a back-up disc stored in a fireproof safe. The code for the images will be held on a separate computer relating the patient information to the participant ID. The participant ID will be used on the MRI images. Images may be stored on disc in anonymised format for research team discussions out-with the imaging department.

Safety assessments

The MRI scanner is very safe and does not expose participants to any harmful radiation. Given its reliance on a strong magnetic field, it is essential that certain metallic instruments/objects are not taken into the scan room.

This is avoided by:

1) All participants are clothed in 'theatre greens' so to avoid the danger of concealed metal objects within clothes.

2) Patients will be screened for absolute exclusion to MRI scanning.

In addition, all participants must undertake a strict and comprehensive checklist prior to scanning. This includes questions about heart valves, pacemakers and other potential metallic implants.

If a participant becomes distressed during the MRI scan, he/she will be able to access to a "panic button" which will immediately terminate the procedure.

Sub-study matrix

The study connects to the 1-year LIFT recruitment phase which will begin in August 2017 (month 0).

Study steps	-3-0 m	0-6 m	6-12 m	12-18 m	18-24 m	24-30 m
Governance approvals						
RA Subject recruitment						
MRI scan #1 (pre-intervention)						
MRI scan #2 (post-intervention)						
Data processing, analysis & report						

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Appendix 3: Qualitative Evaluation (LIFT sub-study)

Background

Qualitative studies nested within trials offer the opportunity to investigate the views and experiences of participants. They can generate insights into unexpected or unanticipated outcomes of the trial, as well as provide detailed, personal accounts that can aid understanding and implementation of the research.

Sub-study Objectives

To understand patients' experiences and views of taking part in the CBA and PEP interventions as part of the LIFT trial.

To explore patients' experiences and views that may have led to participants not engaging with the allocated intervention.

To understand rheumatology health care professionals' (therapists') experiences and views of being trained in and delivering the CBA and PEP interventions as part of the LIFT trial.

Study design

An optional nested qualitative process evaluation sub-study with participants and therapists who have taken part in the Lessening the Impact of Fatigue Trial (LIFT).

Participants

A subgroup of LIFT study participants randomised to either CBA or PEP will be invited if they have given consent to be contacted after they have completed or stopped their treatment.

All therapists (both PEP and CBA) who were trained and delivered the interventions will receive additional information.

To ensure integrity, participants will be invited to take part once they have left or completed the intervention phase (see Figure 1 main protocol).

Participant identification and sample size

We will use a maximum variation sampling strategy [1] to identify participants with a range of IRDs, gender, age, disease duration and primary outcomes in the main RCT. To achieve this, a minimum of 40 interviews (20 per intervention arm) is required. We will aim to invite all study therapists from both intervention arms across all study sites. They will be invited once they have delivered the intervention to their last allocated study participant or once they are suitably experienced based on how long they have been delivering the intervention at the time of interview – whichever comes first.

The study team at the Trial Office will send an invitation consisting of a cover letter, study information, copy of the consent form and reply slip to each potential participant who has

given permission to be contacted after the LIFT study. Participants will be invited after they attended assessment visit 4 at 56 weeks or if they have withdrawn during the follow-up phase. The study team at the Trial Office will also send invitations to all study therapists.

Participants willing to take part can return the completed Participant Reply Slip sent with the invitation letter directly to the designated study site at the Bristol Royal Infirmary. Therapists willing to take part will get in touch with the designated member of the local study team as per site delegation log by phone or email.

A designated member of the local study team as per site delegation log at the designated study site will contact the potential participant/therapist to discuss the study and arrange a date and time for the interview.

Consenting participants and therapists

Once contacted for the interview, at the beginning of the call, the purpose and process of the interview will be explained again, before potential participants are asked to consent. Verbal consent will only considered to have been given at this point and will be recorded on a digital voice recorder. Participants and therapists will have received the wording of the consent as part of their invitation to take part.

Interviews and data collection

Data will be collected through semi-structured interviews conducted by telephone or by internet-based audio/video calls. In addition to the practical considerations of offering these options, this approach acknowledges that both participants and therapists will have been involved in a remotely delivered intervention. All interviews will be audio recorded, anonymised during transcription, and checked for accuracy.

Participant/therapist withdrawal

Participants/therapists are free to withdraw at any time, and with no explanation. If they withdraw before the findings are written up, we will not include any of their data.

Analysis

Participant experiences and views of the interventions will be analysed using a framework analysis [2] to assess the content, mode of delivery, acceptability, barriers and facilitators, helpfulness and subsequent impact of the interventions on their daily lives.

Experiences and views of the therapists of intervention training and delivery, including challenges and benefits of learning and using new skills, and barriers and facilitators to supporting patients remotely will be analysed using inductive thematic analysis [3].

Data handling

The study specific database (see 8.2 in main protocol) will be used. Personal contact details will be made available to the designated member of the local study team as per site delegation log at the study site only when the participants have given their permission to be contacted.

Recorded consent will be stored as essential digital documents in a bespoke database provided and maintained by CHaRT (see 8.2 in main protocol) as well as secured shared drives with access via password controlled computers (university) by study staff only (electronic data). At the end of the project, they will be archived in the University of Aberdeen archive (see 14.2 in main protocol).

Safety assessments

We do not anticipate any side-effects of taking part in an interview. However, if the interview makes participants feel worried about their fatigue or health, the designated member of the local study team as per site delegation log will arrange for them to see their clinical nurse specialist or rheumatologist.

Sub-study matrix

See Figure 1 GANTT chart

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