Remotely delivered cognitive behavioural and personalised exercise interventions for fatigue severity and impact in inflammatory rheumatic diseases: a multi-centre randomised controlled parallel open-label group trial (LIFT)

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Abstract

Background: Chronic fatigue is a poorly managed problem in inflammatory rheumatic diseases (IRD). Cognitive-behavioural approaches (CBA) and personalised exercise programmes (PEP) may be effective but are uncommonly implemented because their effectiveness across the different IRD are unknown and regular face-to-face sessions are often undesirable, especially during a pandemic.

We hypothesised that remotely delivered CBA and PEP would effectively alleviate fatigue severity and impact across IRD.

Methods: We performed a pragmatic, multi-centre, UK hospital-based, investigator-blinded, three-arm randomised controlled trial of usual care (UC) alongside telephone-delivered CBA or PEP, tested against UC alone. Patients with any stable IRD were eligible if they reported significant and persisting fatigue. Treatment allocation was assigned by a web-based randomisation system. CBA and PEP sessions were delivered over 6 months by trained health professionals in rheumatology. Co-primary outcomes were fatigue severity (Chalder Fatigue Scale, CFS) and impact (Fatigue Severity Scale, FSS) at 56 weeks. The primary analysis was by full analysis set. This study was registered at ClinicalTrials.gov, number NCT03248518.

Findings: From September 2017 to September 2019, we randomly assigned 368 participants to either PEP (n=124), CBA (n=122) or UC alone (n=122), of whom n=275 female, n=92 male were enrolled, mean (sd) age 57.0 (12.7). Analyses included for CFS, n=101, 107, 107 and for FSS n=101, 106, 107 in the PEP, CBA and UC alone groups, respectively. PEP and CBA significantly improved fatigue severity (CFS mean difference (md) -3.03, 97.5% CI -5.05 to -1·02, p=0·001 and md -2·36, 97.5% CI -4·28 to -0·44, p=0.006, respectively) and fatigue impact (FSS md -0·64, 97.5% CI -0·95 to -0·33, p<0.001 and -0·58, 97.5% CI -0·87 to -0·28, p<0.001, respectively) compared to UC alone at 56 weeks. No trial-related serious adverse events were observed.

Interpretation: Telephone-delivered CBA and PEP produced and maintained statistically and clinically significant reductions in the severity and impact of fatigue in a variety of IRD. These interventions should be considered as a key component of IRD management in routine clinical practice.

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Introduction

Inflammatory rheumatic diseases (IRD) comprise the majority of a rheumatologist's workload and include chronic immune mediated disorders such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and systemic lupus erythematosus (SLE). They are common conditions, with an overall lifetime risk of approximately 8.4% for women and 5.1% for men[1], and are major contributors to the global disability burden[2].

The symptom of fatigue is a shared burden across IRD. Despite significant advances in immune therapeutics, as many as 80% of patients report significant fatigue and over 70% consider fatigue to be as important as pain[3,4]. Moreover, fatigue is a major determinant of impaired quality of life, and a principal predictor of work disability[5].

Although there are no evidenced based pharmacological interventions for IRD related fatigue, a Cochrane review of non-pharmacological interventions has reported significant benefits for psychosocial and physical activity interventions in reducing fatigue amongst IRD patients with RA[6]. However, health care services encounter multiple barriers to their implementation. First, previously tested interventions were disease specific, varying in content and structure and so are not appropriate if the clinically diverse IRD served by a rheumatology service are to receive equitable care. There has been a recent shift towards conceptualising fatigue as a construct with shared person-specific factors across conditions rather than predominating disease specific factors [7]. However, non-pharmacological fatigue interventions have not been tested across different IRD diagnoses or any other chronic diseases. Second, specialist expertise, such as clinical psychology, is not easily accessible and does not commonly exist within speciality multi-disciplinary teams (MDT)[8]. Third, some patients find it challenging to attend regular face-to-face treatment sessions due to a combination of their health, transport issues and family/work commitments[9]. Moreover, the safety benefits of remote care delivery have been starkly highlighted during the SARS-CoV-2 pandemic. As a result, health care systems are increasingly encouraging long-term adoption of remotely delivered services. However, the effectiveness of such approaches have been poorly tested in multiple specialities, including rheumatology.

Our Lessening the Impact of Fatigue in Inflammatory Rheumatic Disease Trial (LIFT) aimed to determine whether psychosocial and physical activity interventions, telephone-delivered by the rheumatology MDT, were clinically effective and safe in improving fatigue for otherwise stable patients across the IRD spectrum. We hypothesised that up to 8 sessions (over 22 weeks) of either a

standardised cognitive behavioural approach plus usual care (CBA) or a personalised exercise programme plus usual care (PEP), would be more effective than usual care (UC) alone to reduce the impact and severity of fatigue after a 56-week follow-up period.

Methods

Study design and participants

LIFT was a multi-centre, randomised, single-blind, controlled parallel-group trial. The trial protocol has been previously published [10] and subsequent amendments reported in the appendix (p18). The consent form and statistical analysis plan are accessible online (https://clinicaltrials.gov/ct2/show/NCT03248518). The trial was approved by the Research Ethics Committee Wales REC 7 (ref 17/WA/065) and the R&D of each participating NHS health board/trust and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and UK regulations.

We recruited patients attending six UK secondary care rheumatology services. Participants were considered eligible if they were 18 years or older at the time of consent, had been diagnosed with an IRD by a consultant rheumatologist, and reported fatigue to be a problem which was both persistent (>3 months) and significant (≥6 on numeric rating 0-10 scale, NRS). Participants were excluded if they had unstable inflammatory disease (as evidenced by changed immunomodulatory therapy in the previous 3 months), a potential medically reversible explanation for fatigue (e.g. severe anaemia), or had a medical condition which would make the proposed interventions unsuitable (e.g. significant heart disease). The complete list of inclusion and exclusion criteria is listed in the appendix (p2) . Written informed consent was obtained from all patients before any study-related procedures were conducted at the baseline visit.

Randomisation and masking

Participants were allocated to receive either PEP, CBA or UC (1:1:1 ratio) using a computer-generated sequence which was accessed remotely via a web-based randomisation system. Randomisation was minimised by diagnosis (RA, SLE, or axSpA or other IRD) and the presence/absence of depressive symptoms (Hospital Anxiety and Depression Scale subscale score>10 [11]). The minimisation algorithm included a 20% random twist, i.e. 20% of all the allocated randomisations were randomly re-allocated 50:50 to the remaining two treatment options. Randomisation was carried out by research nurses in the recruiting centres employing the trial's custom built database which included the randomisation tool, electronic case report form and safety reporting . Full blinding was not possible due to the nature of the intervention, which required active

engagement of participants and therapists. All investigators, including statisticians, were blinded to treatment allocation.

Procedures

All participants were aware that the trial interventions were designed specifically to reduce fatigue. As a minimum, all participants received UC in the form of a Versus Arthritis (formerly Arthritis Research UK) education booklet for fatigue. This booklet addresses the principal domains of fatigue which may be amenable to self-management and represents UC in almost all rheumatology services in UK.

The CBA and PEP active treatments were therapist based, with accompanying manuals. They were adapted, with IRD patient involvement, from previous fatigue-specific cognitive behavioural and exercise interventions[12,13] to ensure that they were suitable for a remote delivery via telephone, and applicable to the broad spectrum of IRD. A detailed description of each intervention is available in the supplementary material, but briefly, CBA was a psychological intervention which targeted unhelpful beliefs and behaviours and aimed to replace them with more adaptive ones. PEP was an individually tailored exercise programme combined with a graded exposure behavioural therapy which aimed to normalise misperceptions of effort and enhance exercise tolerance.

Both CBA and PEP interventions were telephone delivered by health professionals in rheumatology (HPR) employed within local NHS Rheumatology departments. They received intensive training and supervision from experienced exercise therapists or a cognitive behavioural therapist and clinical psychologist with expertise in fatigue interventions. They were further supported throughout the course of the study, with therapist manuals and ongoing individual supervision. Based on previous experience[13], participants were offered a maximum of seven one-to-one sessions, each up to 45 minutes in duration, over a period of 14 weeks with a booster session conducted at 22 weeks after the start of the intervention. The final number of sessions was individually determined between subject and therapist.

Participants were separately asked to attend local clinical research facilities for assessment of outcomes on average at 10, 28 and 56 weeks after randomisation. If participants were unable to attend in person, the follow-up was conducted by telephone by research personnel at the site or centrally by trial office staff. During the SARS-CoV-2 pandemic, follow up was limited to telephone contact and 56 week were outcomes prioritised.

Outcomes

Our tested interventions were designed to reduce both the severity and impact of fatigue, distinct aspects of similar patient importance. We therefore collected two primary outcomes: Chalder Fatigue Scale (CF, 0 [low]-33 [high], Likert scale)[14], a measure of fatigue severity, and the Fatigue Severity Scale (FSS, 1 [low]-9 [high] scale)[15], an assessment of fatigue impact.

Secondary outcomes were multi-dimensional aspects of fatigue (BRAF-MD)[16], health related quality of life (Short Form 12)[17], pain intensity (NRS) [18] , sleep disturbance (Jenkins Sleep Scale)[19], anxiety and depression (Hospital Anxiety & Depression Scale)[11], impact on work and activities (WPAI) [20,21], and change in global health.

Adverse events were recorded by local and central study teams following a study specific standard operating procedure for adverse events in non-clinical trials of investigational medicinal products studies. Events were identified by members of the local research team by asking the participant during assessment visits or during telephone contact with the therapist delivering the intervention whether a potential SAE has occurred since the previous contact. In addition, participants self-reported events via direct contact with the local research team, therapist, by completion of study questionnaires (but also during phone calls with the Trial Office staff). Adverse events were then assessed for seriousness and relatedness by a designated experienced investigator with rheumatology expertise (NB) and investigators responsible for the training of therapists, as required.

Sample size

Our planned primary analysis strategy was to separately compare CBA plus UC versus UC alone, and PEP plus UC versus UC alone. In order to preserve the overall 5% error with two comparisons and two primary outcomes tested sequentially, *a priori*, we designated the CF at 56 weeks as the dominant primary outcome and only if positive would the FSS then be formally analysed.

The minimally important effect was 0.5, equating to 2 points in the Chalder Fatigue Scale (assuming SD of 4 points), based on the trials at which evaluated similar non-pharmaceutical interventions. The pre-specified alpha for these two comparisons was set at 2.5% to maintain an overall level of not more than 5%. For 90%, we required 100 evaluable participants in each of the three groups. From our own previous trials, we expected a dropout rate of 20% and inflated the target sample size to 125 participants in each treatment group, or 375 participants in all.

We used a simple t-test approach, as is standard, but planned and used repeated measures ANCOVA regression models to increase precision by adjusting for the baseline analogue of the primary outcome measure(s), using serial measures at three follow-up times points, and including baseline

predictors (used in the minimisation procedure). A factor that we anticipated deceasing power was any potential clustering due to any therapist effects (the HPRs delivering either the PEP or the CBA intervention). We expected that any such clustering would be small, especially given the primary time point of interest was at 56 weeks. Given the difficulties in specifying relevant intra-class correlation co-efficients (ICC), the methodologic difficulties in the sample size to adjust for this in two of the groups (with possibly different ICC), and not in the UC alone group, and the subsequent uneven allocation ratios to optimise power that arise from such calculations, we did not explicitly adjust for therapist ICCs in the sample size calculation. We did expect any gains in power from using baseline and repeated within-person measures to offset any small loss in power arising from potential therapist effects.

Statistical analysis

Continuous variables were summarised using mean (SD) and discrete variables and were reported as absolute numbers and percentages. The primary outcomes were analysed using a heteroscedastic partially nested repeated measures mixed effects linear model. This model included the baseline version of the score, and binary fixed effects variables for (nominal time) scoring >10 on the HADS depression subscale. Treatment effects were estimated from the treatment-by-time interaction, the main time point of interest was 56 weeks. A random effect for therapist was included in the CBA arm only to incorporate clustering due to therapist, there was no evidence of therapist effect in the PEP arm, a random effect for centre was included for the PEP and control group. Degrees of freedom were adjusted for the small number of clusters using the Kenward Rogers method. The primary approach used all follow-up data and analysed-as-randomised approach under a missing-at-random assumption, a full analysis set analysis. Imputation and pattern mixture models were used to test the robustness of intervention effect estimates under different assumptions, these are described and reported in detail in the supplementary material. Additional analyses conducted for the primary outcomes were: Complier Average Causal Effect (CACE) to estimate the intervention effect in complies; a post-hoc subgroup analysis by diagnosis (RA versus non-RA) at baseline; and the impact on those whose data may have been influenced by SARS-CoV-2 related lockdown(s). We also undertook a post-hoc comparison of PEP versus CBA. These are described in more detail in the supplementary material. The primary outcomes are reported using 97.5% confidence intervals to reflect the two comparisons with control. Secondary outcomes were analysed using similar models but reported with 95% confidence intervals, there were no multiplicity adjustments made to secondary outcomes. All analyses used Stata version 16·0. An accompanying cost-effectiveness analysis will be reported separately. This study was prospectively registered with ClinicalTrials.gov,

number NCT03248518. Analyses in the statistical analysis plan not reported here will be the subject of future manuscripts.

Role of the funding source

The funder had no role in data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to the final data and had responsibility to submit for publication.

Results

We identified 1,251 potentially eligible participants of whom 381 (30%) met criteria for further assessment and were consented between September 4, 2017 and September 30, 2019. Last participant last visit was October 31, 2020. Eligibility was confirmed in 368 (97%), allocated to either PEP (n=124), CBA (n=121), or UC (n=122) (Figure 1). One participant was excluded post-randomisation as a recent change in immunosuppressive medication was discovered.

Of those randomised, 202 (55%) were diagnosed with RA, 78 (21%) with connective tissue disease, 72(18%) with spondyloarthritis and 12 (5%) with another IRD. Overall, n=275 (74.9%) were female and n=92 (25.1%) with a mean (sd) age of 57.0 (12.7), disease duration 11.4 (10.2) years and low levels of systemic inflammation (ESR: 16.2 (15.9)). The groups were balanced across baseline characteristics (Table 1).

Participants assigned to PEP received a median of 5 sessions (IQR 1–8) within the 30-week treatment window. In total, 19 (15%) elected to stop PEP within the 30-week treatment window and 20 (16%) participants did not attend any sessions. There were 14 PEP therapists who saw a median of 12 patients each (minimum 1 to maximum 23). Participants assigned to CBA received a median of 8 sessions (IQR 2–8) within the 30-week treatment window. In this group, 11 (9%) elected to stop therapy within the 30-week treatment window and 18 (15%) did not attend any CBA sessions. There were 13 CBA therapists who saw a median of 15 patients each (minimum 1 to maximum 21). At 56 weeks 25, 16 and 14 participants allocated to PEP, CBA and UC respectively declined further follow-up, and a further 9, 2 and 6 were lost to follow-up, respectively (Figure 1). The analysis of CFS included 101 in PEP, 107 in CBA, and 107 in UC. Similarly, for FSS there were 101 in PEP, 106 in CBA, and 107 in UC. The baseline demographic characteristics of the 72 whose primary outcomes were not captured were similar to the overall trial population (appendix p10).

CF and FFS scores improved over time in both intervention groups (Figure 2, Table 2). At 56 weeks, both PEP and CBA reduced fatigue severity (CF) (-3.03, 97.5% CI -5.05 to -1·02; p=0·001 and -2·36, 97.5% CI -4·28 to -0·44; p=0·006, respectively), and fatigue impact (FSS) (-0·64, 97.5% CI -0·95 to -

0·33; p<0·001 and -0·58, 95% CI -0·87 to -0·28; p<0·001, respectively) compared with UC. These differences are equivalent to a fatigue severity effect size of -0.54 and -0.44, for PEP and CBA, respectively, and a fatigue impact effect size of -0.61 and -0.56, for PEP and CBA, respectively, using the standardised mean difference scale. Multiple imputation sensitivity analyses gave similar results and remained significant even in the most conservative scenario where missing data from the active treatment groups were assumed to remain unchanged, in contrast to the UC alone comparator where the observed ITT improvements were assumed (at 56 weeks CF: PEP -1.53, CBA -1.76; FSS: PEP -0.43; CBA -0.43; appendix p11). The adjustment for receiving at least 3 sessions of active treatment enhanced the effect of PEP on fatigue severity (CF md -4·44, 95% CI -5·66 to -3·21, p<0.001), but had little impact on the treatment effect of PEP on fatigue impact or CBA effect on either primary outcome (appendix p16).

The treatment effects on secondary outcomes were mixed at 56 weeks (Table 2). Statistically significant effects were observed for both PEP and CBA on multi-dimensional fatigue scores, mental health related quality of life and sleep disturbance, while PEP additionally provided significant reductions in depression, valued life activities and work disability. In particular, the effect on overall work impairment (WPAI -15·58, 95% CI -27.41 to -3.74; p=0·010) at 56 weeks was large. In contrast, neither treatment significantly improved pain, anxiety or physical health related quality of life (Table 2). Overall, however, both treatments improved general wellbeing. At 56 weeks, when asked how their global health status had changed since the start of the trial, 24.5% and 17.4 % of PEP and CBA participants, respectively, compared to 3.9% of UC alone participants, reported feeling either 'very much better' or 'much better'. In an exploratory analysis, PEP was superior to CBA with regards to global health status (p=0·003) (appendix p14) and overall PEP consistently showed more positive effects than CBA for other outcomes, although these differences were not statistically significant (appendix p12).

We also conducted post-hoc sub-group analyses (appendix p16-17). First, differences in effects according to IRD diagnosis were examined. At 56 weeks, participants with RA reported similar PEP effects on fatigue severity and impact compared to participants with an alternative IRD diagnosis. At the same timepoint, RA participants reported superior CBA reductions in fatigue severity compared to non-RA participants, but similar reductions in fatigue impact. Second, although all participants had completed their scheduled treatment sessions prior to the onset of the SARS-CoV-2 pandemic UK lockdown (defined as 11, March 2020) 124 (34%) remained under follow-up. Although this sub-group reported similar treatment effects in terms of fatigue impact, they reported less benefit in the terms of fatigue severity at 56 weeks (CF md: PEP -2·41, 95% CI -5·32 to 0·5; CBA -1·29, 95% CI -4·00 to 1.42) compared to those who completed follow-up prior to pandemic lockdown (CF md: PEP -

3·37, 95% CI -5·66 to -1·08; CBA -2·65, 95% CI -5·16 to -0·75). Sex-disaggregated data are reported in the appendix (appendix p17-18).

A total of 425 adverse events were recorded of which 61 (14.4%) were assessed as serious adverse events (SAEs). The number of people experiencing at least one SAEs was balanced across groups (n=12, n=8 and n=14 for PEP, CBA and UC, respectively) and no SAE was related to the trial (Table 3). Of the 364 recorded AE's (Table 3), only one was related to intervention (musculoskeletal trauma due to exercise).

Discussion:

Our trial, the largest to evaluate fatigue specific interventions in IRD, and the first to test remote delivery or generic approaches across heterogeneous diagnoses, found that PEP and CBA, when added to UC, were safe and improved fatigue severity and impact amongst patients with a range of IRD compared to UC alone. The benefits were maintained at 6 months following treatment completion. Additional benefits of improved mental health related quality of life and sleep were observed for both interventions, whilst PEP also enhanced valued life activities and reduced levels of work disability and depression.

The effects of PEP and CBA were medium sized for the co-primary outcomes of fatigue severity and impact and more than the reported minimum clinically important reductions of the corresponding measures[22]. The effects on secondary outcomes were generally small in magnitude, though it is likely that these may have cumulatively contributed to a clinically meaningful improvement in general well-being as reflected by the important improvements in global health status. In the context of the existing literature, these effects are favourable when compared to disease specific interventions. Meta-analyses of physical activity and psychosocial interventions in RA report modest effects on fatigue reduction [6]. Similarly modest fatigue effects have been reported following meta-analyses of biologic immune therapies in RA[23] and axial spondyloarthritis [24]. Few IRD trials have targeted fatigue as their primary outcome. In RA, small (n<100) fatigue-specific trials of physical activity have found improvements in fatigue[25], however participants were not followed up after therapy completion. Physical activity adherence commonly declines after completion of therapy and its benefits can be rapidly lost[26]. The maintenance of PEP's effect, after 56 weeks of follow-up, is notable and could be explained by the integration of a behavioural component designed to disrupt unhelpful illness beliefs (such as fear avoidance) which may indirectly contribute to poor adherence. In contrast, enduring effects from psychosocial interventions are more consistently observed. The

Reducing Arthritis Fatigue Impact trial (RAFT) recently found a significant improvement in fatigue impact over 2 years. Similar to our CBA arm, otherwise stable participants received a fatigue specific psychosocial intervention which was delivered by the rheumatology MDT, under specialist supervision, and compared to UC. In the RAFT trial, although fatigue impact improved, fatigue severity did not. A direct comparison of the total BRAF scale at 1 year, the only shared fatigue outcome measure, revealed comparable fatigue reductions compared to CBA (RAFT: mean difference - 3.63; LIFT CBA: mean difference -4.86), but a less favourable fatigue reduction compared to PEP (mean difference -6.73)[13]. Moreover, RAFT was RA specific and adopted face to face, group-based delivery. While effectiveness may be reduced, there are cost benefits to group delivery. In the future, these interventions could be tested to assess the cost-effectiveness of hybrid individual and group based remote delivery.

The benefits of remote delivery to enhance therapy accessibility are recognised and are especially attractive for this patient population given the fatiguing effects of travel. Furthermore, the SARS-CoV-2 pandemic has resulted in a rapid shift towards remote delivery across indications, often with inadequate evidence. Significant supportive effectiveness data do exist for telephone delivered psychosocial interventions for mental health and physical activity promotion interventions in the general population[27 28], although long-term follow studies are generally lacking. Our study is one of the few remote delivery trials in IRD, evidencing similar positive outcomes with reassuring improvements after 56 weeks of follow-up.

The mechanisms by which PEP and CBA exact their effects on fatigue are unknown. We do not anticipate that these interventions target the primary causes of fatigue (which remain uncharacterised), but rather hypothesise that they attenuate factors which maintain the persistence and impact of the symptom. CBA, for example, aimed to replace unhelpful beliefs and behaviours which can exacerbate fatigue. This more focussed approach may explain why only specific fatigue domains (physical and emotional domains of fatigue, as measured by the BRAF) improved among CBA participants. In contrast, the established pleiotropic effects of physical activity likely explain the pan-domain fatigue improvements observed in PEP (appendix p15).

LIFT was primarily designed to be a pragmatic trial. Its major strength is its generalisability to a typical rheumatology service and its selection of a sizeable, but commonly overlooked, group of patients who report chronic fatigue despite adequate management of their inflammation. Inflammation is one of many factors which contribute to IRD-related fatigue and in real world practice, rheumatologists prioritise the treatment of inflammation in the first instance before considering alternative approaches for fatigue. External validity was enhanced further by

368 embedding the trial within several rheumatology services. The interventions were delivered by
369 members of the MDT who integrated their therapist duties within their standard clinical schedules
370 and this study indicates that psychological and physical therapy skills can be efficiently acquired by
371 relevant HPRs. In doing so, the trial was equally vulnerable to the standard challenges faced by
372 health care services, for example waiting lists and staff turnover due to illness and changing roles.

373 Despite our trial being methodologically rigorous, several limitations exist. First, full blinding was not
374 possible due to the need to engage people in behavioural change. Moreover, the comparator was
375 treatment as usual (UC) since the intention of our pragmatic trial was to determine whether our
376 interventions improved upon current practice. The potential for resultant detection bias was
377 mitigated by blinding investigators and analysts to allocation. Non-specific treatment effects, such as
378 placebo, exist in real world practice, however, we aimed to minimise such effects by designating our
379 primary endpoint at 56 weeks, 6 months post therapy. Also, the risk of nocebo effects in relation to
380 our comparator does not appear significant. As a minimum, UC participants received established
381 educational materials which have previously been associated with a positive impact[29] and within this
382 trial was related to improved outcomes and equivalent attrition rates. Second, 12% of PEP and CBA
383 participants discontinued their respective therapies due to multiple reasons. These rates are,
384 however, in line with our previous experiences[30] and 53% of these patients still contributed to the
385 primary outcome. Third, we were unable to fully assess whether or not intervention participants
386 adapted/implemented what was being prescribed.

387 The issue of missing data should be further framed within the context of the SARS-CoV-2 pandemic.
388 Although 33% of participants remained under follow-up at pandemic onset, our capacity to capture
389 several outcomes remotely enabled 77% of all primary outcomes to be recorded at 56 weeks, close
390 to our *a priori* 80% follow up estimate. The pandemic may also have biased the interventions'
391 effects. The majority of this patient population would have been classed as clinically vulnerable and
392 advised to isolate in their homes in turn potentially compromising some of the core self-
393 management aspects of CBA and PEP, e.g. physical activity. Indeed, our post-hoc sub-group analysis
394 indicates decreased PEP and CBA effects on fatigue severity among these participants. Thus, out
395 with these extraordinary pandemic conditions, the benefits of both interventions could have been
396 even larger. Third, we chose not to define adherence according to session attendance due to
397 anticipated wide variation in individual participant needs. In fact, the CACE analysis supports this
398 decision for CBA, however it seems that superior PEP outcomes are achieved if participants attend at
399 least three sessions and so a minimum attendance should be prescribed in future practice. Finally,
400 this trial was not powered to examine for consistency of intervention effects across specific IRDs.
401 Consistent with routine care, the trial population included several IRDs of varying prevalence, the

commonest being RA. While the size of effects of PEP were similar in our post-hoc sub-group analysis of RA and non-RA participants, participants with RA appeared to experience larger CBA effects compared to non-RA participants. One potential explanation is that CBA was originally informed by a RA specific psychosocial intervention.

In the UK and elsewhere, there are currently no formally recommended fatigue specific treatments for patients with IRDs. By supporting the prescription of expensive immune therapeutics, health care providers have afforded independence from physical disability to a new generation of IRD patients. By alleviating the ongoing invisible disability of fatigue, patients may achieve a fuller independence which in turn will enable healthcare providers to fully maximise the gains of their investment in immune therapeutics. Our results now support the prescription of both PEP and CBA for IRD related fatigue. Although these are not the first non-pharmacological interventions to be successfully tested for fatigue, in practice, few rheumatology services provide evidence-based fatigue specific therapies due to implementation challenges. The data presented herewith offer robust evidence to overcome existing implementation barriers and subsequently enable widespread access. The versatility of remote delivery is especially timely in the context of the SARS-CoV-2 pandemic, allowing both patients and therapists to interact from the safety of their homes. Moreover, the remote model offers an efficient opportunity towards centralising health care service provision across multiple sites/regions while delivery by the rheumatology MDT, rather than sparsely available specialists, will enhance accessibility further. Finally, these data support a standardised approach to fatigue management across the IRD spectrum, eliminating the operational challenges of disease specific programmes and ensuring inclusivity of care. Fatigue is a patient priority across the spectrum of chronic disease. The transdiagnostic benefits of CBA and especially PEP in IRD would support their testing in other clinical populations. However, although at least as comparable to other fatigue interventions, the effects of PEP and CBA are moderate in size with significant numbers of patients continuing to report clinically relevant fatigue. Additionally, it is unknown whether these effects will be maintained beyond 1 year. In the future, effects may be optimised by targeting those patients most likely to receive a larger benefit from either PEP or CBA, integrating clinical and biological makers to derive useful clinical decision tools. or applying a combined PEP-CBA approach. Moreover, booster sessions may be required to prolong their benefits longer term.

In conclusion, telephone delivered CBA and PEP provided statistically and clinically significant reductions in fatigue severity and impact for a wide range of otherwise stable IRD patients. The treatments were well tolerated, their benefits were maintained 6 months following treatment completion and they were successfully delivered by members of the rheumatology MDT after specialist training.

436

437 **Data sharing**

438 Anonymised individual patient data will be made available following any reasonable request made to
439 the corresponding author, subject to a data sharing agreement and UK research governance
440 regulations. The intervention manuals can be found on
441 https://www.abdn.ac.uk/iahs/research/epidemiology/lift-1286.php.

442

443 **Manuscript Contributions**

444 NB, LA and EB drafted the original manuscript and all authors contributed to its conceptualisation,
445 investigation, supervision, methodology, validation, review, final approval and accountability. EB,
446 GM and LA curated, visualised and analysed the data. KM, RE, SG, KL, PM, JN, LP, SS, AW, GMJ and
447 NB acquired funding. EB, GJM and NB administered the study.

448 **Declarations of interests**

449 The authors have no competing interests

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455 **Membership of oversight committees**

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458 Warwick); Mrs Margaret Fisken (patient partner); Mrs Shenac Knox (patient partner).

459 *Data Monitoring Committee*: Professor Richard Watts (University of East Anglia), Dr Antoni Chan
460 (Royal Berkshire Hospital) and Dr Georgia Ntani (University of Southampton).

461 Both committees met every 6-12 months during the course of the trial

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465 **References:**

1. Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum* 2011; **63**(3): 633-9.
2. Smith E, Hoy DG, Cross M, et al. The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**(8): 1462-9.
3. Repping-Wuts H, van Riel P, van Achterberg T. Fatigue in patients with rheumatoid arthritis: what is known and what is needed. *Rheumatology (Oxford)* 2009; **48**(3): 207-9.
4. van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology (Oxford)* 2010; **49**(7): 1294-302.
5. Dures E, Cramp F, Hackett K, Primdahl J. Fatigue in inflammatory arthritis. *Best Pract Res Clin Rheumatol* 2020; **34**(2): 101526.
6. Cramp F, Hewlett S, Almeida C, et al. Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev* 2013; (8): CD008322.
7. Hulme K, Safari R, Thomas S, et al. Fatigue interventions in long term, physical health conditions: A scoping review of systematic reviews. *PLoS One* 2018; **13**(10): e0203367.
8. Dures E, Almeida C, Caesley J, et al. A survey of psychological support provision for people with inflammatory arthritis in secondary care in England. *Musculoskeletal Care* 2014; **12**(3): 173-81.
9. Brenes GA, Ingram CW, Danhauer SC. Benefits and Challenges of Conducting Psychotherapy by Telephone. *Prof Psychol Res Pr* 2011; **42**(6): 543-9.
10. Martin KR, Bachmair EM, Aucott L, et al. Protocol for a multicentre randomised controlled parallel-group trial to compare the effectiveness of remotely delivered cognitive-behavioural and graded exercise interventions with usual care alone to lessen the impact of fatigue in inflammatory rheumatic diseases (LIFT). *BMJ Open* 2019; **9**(1): e026793.
11. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6): 361-70.
12. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; **377**(9768): 823-36.
13. Hewlett S, Almeida C, Ambler N, et al. Group cognitive-behavioural programme to reduce the impact of rheumatoid arthritis fatigue: the RAFT RCT with economic and qualitative evaluations. *Health Technol Assess* 2019; **23**(57): 1-130.
14. Cella M, Chalder T. Measuring fatigue in clinical and community settings. *J Psychosom Res* 2010; **69**(1): 17-22.
15. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; **46**(10): 1121-3.
16. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S. Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. *Arthritis Care Res (Hoboken)* 2010; **62**(11): 1559-68.
17. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**(3): 220-33.
18. Pain: clinical manual for nursing practice Pain: clinical manual for nursing practice Margo McCaffery Alexander Beebe Mosby Yearbook UK pound17.25 0 7234 1992 2. *Nurs Stand* 1994; **9**(11): 55.
19. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol* 1988; **41**(4): 313-21.
20. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; **4**(5): 353-65.

21. Katz PP, Radvanski DC, Allen D, et al. Development and validation of a short form of the valued life activities disability questionnaire for rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011; **63**(12): 1664-71.
22. Nordin A, Taft C, Lundgren-Nilsson A, Dencker A. Minimal important differences for fatigue patient reported outcome measures-a systematic review. *BMC Med Res Methodol* 2016; **16**: 62.
23. Almeida C, Choy EH, Hewlett S, et al. Biologic interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev* 2016; (6): CD008334.
24. Shim J, Dean LE, Karabayas M, Jones GT, Macfarlane GJ, Basu N. Quantifying and predicting the effect of anti-TNF therapy on axSpA-related fatigue: results from the BSRBR-AS registry and meta-analysis. *Rheumatology (Oxford)* 2020; **59**(11): 3408-14.
25. Katz P, Margaretten M, Gregorich S, Trupin L. Physical Activity to Reduce Fatigue in Rheumatoid Arthritis: A Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* 2018; **70**(1): 1-10.
26. Marcus BH, Dubbert PM, Forsyth LH, et al. Physical activity behavior change: issues in adoption and maintenance. *Health Psychol* 2000; **19**(1S): 32-41.
27. Efron G, Wootton BM. Remote cognitive behavioral therapy for panic disorder: A meta-analysis. *J Anxiety Disord* 2021; **79**: 102385.
28. Foster C, Richards J, Thorogood M, Hillsdon M. Remote and web 2.0 interventions for promoting physical activity. *Cochrane Database Syst Rev* 2013; **9**: CD010395.
29. Hart RI, Ng WF, Newton JL, Hackett KL, Lee RP, Thompson B. What impact does written information about fatigue have on patients with autoimmune rheumatic diseases? Findings from a qualitative study. *Musculoskeletal Care* 2017; **15**(3): 230-7.
30. McBeth J, Prescott G, Scotland G, et al. Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. *Arch Intern Med* 2012; **172**(1): 48-57.

Panel: Research in Context

Evidence before this study

Chronic fatigue is common and considered a principal burden by patients with all forms of inflammatory rheumatic disease (IRD), even those who have attained pharmacological disease remission. International clinical guidelines do not currently specify fatigue management recommendations for this large clinical population.

In March 2015, and annually since, we have searched the scientific literature, with no language restrictions for all previous publications to evaluate non-pharmacological interventions for chronic fatigue in IRD. We searched PubMed, Scopus and Cochrane Database of Systematic Reviews for clinical trials with the search terms “fatigue”, “rheumatoid arthritis”, “arthritis”, “spondyloarthritis”, “vasculitis”, “rheumatology”, “lupus”, “ ankylosing spondylitis”, “ Sjogren”, “scleroderma”, “connective tissue disease”, “psoriatic arthritis”. A 2013 Cochrane systematic review reported significant fatigue reductions by physical activity and psychosocial interventions in rheumatoid arthritis (SMD: -0.36,95% CI -0.62 to -0.10 and -0.24,95% CI, -0.40 to -0.07, respectively) but failed to identify any high-quality studies (assessed by Cochrane’s risk of bias quality component tools). Since then, a single, identically assessed, high-quality study has been reported, providing evidence that cognitive behavioural approaches reduce fatigue impact in rheumatoid arthritis when delivered face to face by trained members of the rheumatology multi-disciplinary team. Overall, however, no trials have evaluated the generic fatigue alleviating effect of non-pharmacological interventions in a mixed IRD population (representative of a typical rheumatology service client cohort) nor have they examined efficient methods of intervention delivery (e.g. remote delivery) which may facilitate implementation.

Added value of this study

This high-quality fatigue alleviation trial is the first to test non-pharmacological interventions in a range of IRDs and the first to evaluate their remote delivery of care by trained members of the rheumatology multi-disciplinary team. Both telephone delivered physical exercise and cognitive behavioural interventions provided clinically and statistically significant improvements in fatigue severity and impact across a generalisable IRD population. These effects were maintained 6 months following intervention cessation.

Implications of all the available evidence

Taken together, specifically developed physical activity and psychosocial interventions are effective in alleviating fatigue in patients with IRD and should be recommended in routine clinical practice. Their generic delivery across IRDs by trained members of the speciality team should reduce barriers to health service implementation. Moreover, their remote delivery offers opportunities for time efficiencies for both care provider and patient as well as safety during pandemic conditions.

Table 1 Baseline characteristics of all enrolledstudy participants

Variable	PEP (n 124)	CBA (n 121)	Usual Care (n 122)
Age [years][#]	56·4 (12·3)	59·3 (13·0)	56·8 (12·7)
Gender[†]			
Female	97 (78·2)	84 (69·4)	93 (76·2)
Male	26 (21·0)	37 (30·6)	29 (23·8)
Employment Group			
Working full-time (30+hrs /week)	35 (28·2)	36 (29·8)	38 (31·1)
Working part-time (<30+hrs /week)	16 (12·9)	16 (13·2)	23 (18·9)
Unemployed and looking for work	2 (1·6)	1 (0·8)	1 (0·8)
Unable to work because of illness or disability	20 (16·1)	14 (11·6)	16 (13·1)
At home and not looking for paid employment	4 (3·2)	2 (1·7)	3 (2·5)
Student	2 (1·6)	2 (1·7)	1 (0·8)
Retired	42 (33·9)	46 (38·0)	36 (29·5)
Other	2 (1·6)	3 (2·5)	2 (1·6)
Missing	1 (0·8)	1 (0·8)	2 (1·6)
Ethnic Group			
Scottish	87 (70.2)	87 (71.9)	97 (79.5)
Other British	27 (21.8)	25 (20.7)	21 (17.2)
Irish	-	1 (0.8)	-
Other White	7 (5.6)	5 (4.1)	1 (0.8)
Other Ethnic	1 (0.8)	-	-
Missing	2 (1.6)	3 (2.5)	3 (2.5)
Centre			
1	50 (40.3)	50 (41.0)	49 (40.5)
2	23 (18.5)	24 (19.7)	24 (19.8)
3	14 (11.3)	13 (10.7)	13 (10.7)
4	22 (17.7)	21 (17.2)	21 (17.4)
5	9 (7.3)	10 (8.2)	10 (8.3)
6	6(4.8)	4 (3.3)	4 (3.3)

Disease Group n(%)	124	121	122
RA	67 (54.0)	67 (55.4)	68 (55.7)
SpA	25 (20.2)	24 (19.8)	23 (18.9)
CTD	26 (21.0)	27 (22.3)	25 (20.5)
Other	5 (4.0)	3 (2.5)	6 (4.9)
Missing	1 (0.8)	-	
Disease duration [years] †	8.5 (3.6,14.9)	8.7 (2.7,15.9)	9.3 (3.2-17.5)
Missing	33	24	31
Other co-morbidities (Charlson Index)†	1.00 (1.0, 2.0)	1.00 (1.0, 2.0)	1.00 (1.0, 2.0)
Missing	1		
Erythrocyte Sedimentation Rate [mm] †	13.0 (17.0-22.0)	12.0 (6.0-23.0)	10.0 (5.0-17.0)
Missing	3 (2·4)	4 (3·3)	1 (0·8)
Disease Activity self-report (NRS 0-10)†	5·6 (2·4)	5·7 (2·2)	5·6 (2·2)
Missing	1 (0·8)	1 (0·8)	1 (0·8)
Physical Activity self-report (days/week)†	3.00 (1.0, 5.0)	3.00 (1.0, 5.0)	2.00 (0.0, 4.0)
Missing	1	4	2
Fatigue Average Score self-report (NRS 0-10)#	7·4 (1·1)	7·3 (1·0)	7·3 (1·1)

All as n (%) unless marked as #Continuous data: mean (sd); or †Continuous data : Median(IQR)

RA Rheumatoid artritis; CTD Connective tissue disease; SpA Spondyloarthritis

Table 2 Primary and secondary outcomes of study participants (Full Analysis Set)

Outcome	PEP	CBA	UC	PEP vs UC adjusted mean diff (97.5% CI)	p value	CBA vs UC adjusted mean diff (97.5% CI)	p value
Chalder fatigue scale							
Baseline	21·4 (5·6); 122	20·4 (5·8); 120	20·7 (5·2); 120				
10 weeks	16·5 (7·5); 91	17·2 (6·4); 95	17·9 (6·2); 94	-1.70 (-3.72 to 0.32)	0.059	-0.68 (-2.66 to 1.29)	0.437
28 weeks	14·9 (8·2); 79	15·7 (6·7); 88	18·4 (5·7); 82	-3.89 (-6.03 to -1.75)	<0.001	-2.73 (-4.79 to -0.68)	0.003
56 weeks	16·5 (7·3); 88	16·7 (6·0); 103	19·2 (5·9); 100	-3.03 (-5.05 to -1.02)	0.001	-2.36 (-4.28 to -0.44)	0.006
Fatigue Severity Scale							
Baseline	5·5 (1·1); 121	5·4 (1·0); 117	5·5 (0·9); 119				
10 weeks	5·0 (1·2); 91	5·1 (1·1); 93	5·3 (1·1); 95	-0.26 (-0.57 to 0.04)	0.054	-0.11 (-0.41 to 0.20)	0.437
28 weeks	4·7 (1·4); 78	5·0 (1·1); 88	5·3 (1·1); 83	-0.54 (-0.87 to -0.22)	<0.001	-0.24 (-0.55 to 0.08)	0.090
56 weeks	4·7 (1·5); 85	4·8 (1·3); 100	5·4 (1·1); 99	-0.64 (-0.95 to -0.33)	<0.001	-0.58 (-0.87 to -0.28)	<0.001
Outcome	PEP	CBA	UC	PEP vs UC adjusted mean diff (95% CI)	p value	CBA vs UC adjusted mean diff (95% CI)	p value
HADS Anxiety							
Baseline	8·9 (4·4); 123	8·7 (4·5); 121	8·3 (4·2); 122				
10 weeks	8·6 (4·4); 89	8·6 (4·7); 92	7·9 (4·3); 95	0.13 (-0.74 to 0.99)	0.771	0.31 (-0.55 to 1.18)	0.476
28 weeks	7·5 (5·0); 77	7·9 (4·6); 88	7·8 (4·2); 83	-0.56 (-1.46 to 0.35)	0.228	-0.16 (-1.05 to 0.73)	0.727
56 weeks	7·6 (4·9); 73	7·8 (4·4); 86	7·8 (4·6); 85	-0.74 (-1.65 to 0.17)	0.113	-0.34 (-1.23 to 0.55)	0.453
HADS Depression							

Baseline	7.3 (3.8); 123	7.1 (3.8); 121	6.8 (3.7); 122				
10 weeks	7.2 (4.2); 91	6.9 (4.2); 93	6.5 (3.7); 95	0.26 (-0.50 to 1.03)	0.497	0.09 (-0.66 to 0.84)	0.822
28 weeks	5.8 (4.1); 78	6.4 (3.6); 88	6.3 (3.5); 83	-0.70 (-1.51 to 0.10)	0.086	-0.28 (-1.05 to 0.50)	0.485
56 weeks	5.9 (3.9); 75	6.5 (3.8); 88	6.8 (4.0); 85	-1.03 (-1.84 to -0.23)	0.012	-0.47 (-1.24 to 0.30)	0.228
SF-12 PCS							
Baseline	34·7 (9·8); 117	34·1 (10·3); 116	33·4 (10·1); 117				
10 weeks	36·8 (9·7); 88	35·0 (10·0); 92	33·9 (10·9); 95	1.09 (-0.89 to 3.06)	0.280	0.82 (-1.18 to 2.82)	0.423
28 weeks	36·3 (10·6); 73	34·6 (9·8); 85	34·1 (10·5); 81	0.68 (-1.43 to 2.80)	0.526	0.72 (-1.37 to 2.81)	0.500
56 weeks	36·5 (10·6); 73	34·8 (10·6); 87	33·2 (10·8); 79	1.33 (-0.80 to 3.45)	0.221	0.06 (-2.03 to 2.15)	0.952
SF-12 MCS							
Baseline	40·8 (11·3); 117	41·6 (11·2); 116	42·9 (11·2); 117				
10 weeks	42·3 (11·1); 88	44·3 (11·0); 92	44·9 (9·5); 95	-1.16 (-3.48 to 1.15)	0.325	0.15 (-2.17 to 2.47)	0.897
28 weeks	45·3 (12·3); 73	45·0 (11·2); 85	44·7 (10·2); 81	1.82 (-0.66 to 4.29)	0.150	0.39 (-2.03 to 2.82)	0.750
56 weeks	44·8 (10·5); 73	45·3 (10·7); 87	43·2 (11·2); 79	2.79 (0.31 to 5.28)	0.027	2.47 (0.04 to 4.89)	0.046
BRAF MDQ total score							
Baseline	41·3 (14·2); 122	38·9 (13·2); 119	40·0 (12·2); 120				
10 weeks	34·4 (16·6); 91	34·8 (13·8); 94	35·4 (14·2); 95	-2.14 (-5.64 to 1.36)	0.231	0.39 (-3.16 to 3.94)	0.830
28 weeks	31·1 (17·4); 76	33·4 (14·2); 89	34·5 (13·8); 81	-5.07 (-8.76 to -1.38)	0.007	-0.76 (-4.42 to 2.89)	0.683
56 weeks	31·2 (18·4); 78	30·8 (14·9); 92	36·9 (14·2); 87	-6.99 (-10.63 to -3.34)	<0.001	-4.93 (-8.53 to -1.33)	0.007
Pain (NRS)							
Baseline	5·9 (2·5); 121	5·7 (2·3); 119	5·8 (2·3); 120				
10 weeks	5·1 (2·7); 91	5·4 (2·4); 93	5·3 (2·6); 94	-0.27 (-0.83 to 0.29)	0.349	0.02 (-0.65 to 0.69)	0.951
28 weeks	4·8 (2·9); 77	5·3 (2·2); 87	5·2 (2·3); 83	-0.57 (-1.16 to 0.03)	0.063	-0.07 (-0.76 to 0.61)	0.832
56 weeks	5·2 (2·7); 79	5·3 (2·4); 93	5·3 (2·79); 92	-0.26 (-0.84 to 0.32)	0.386	0.15 (-0.52 to 0.82)	0.663
Sleep							
Baseline	13·0 (5·3); 120	13·4 (4·9); 115	12·8 (5·3); 119				
10 weeks	12·1 (5·2); 89	11·8 (5·3); 91	11·8 (5·7); 95	0.05 (-1.08 to 1.19)	0.926	0.13 (-1.16 to 1.42)	0.840
28 weeks	10·6 (5·6); 78	11·0 (5·3); 87	11·7 (5·5); 83	-1.51 (-2.70 to -0.32)	0.013	-0.74 (-2.06 to 0.59)	0.276

56 weeks	11·6 (5·9); 75	10·8 (5·8); 89	12·9 (5·7); 81	-1.36 (-2.57 to -0.16)	0.027	-1.71 (-3.03 to -0.39)	0.011
WPAI (overall work impairment)							
Baseline	46·7 (26·8); 47	47·6 (26·0); 46	46·7 (25·0); 54				
10 weeks	44·0 (25·4); 37	46·3 (27·4); 30	46·3 (27·1); 39	-3.82 (-13.80 to 6.16)	0.453	2.78 (-7.62 to 13.19)	0.600
28 weeks	38·0 (31·1); 33	46·5 (29·3); 29	40·7 (23·8); 33	-4.99 (-15.65 to 5.66)	0.359	5.19 (-5.63 to 16.02)	0.347
56 weeks	31·0 (21·6); 21	42·7 (23·9); 29	49·8 (25·0); 31	-15.58 (-27.41 to -3.74)	0.010	-4.01 (-15.08 to 7.05)	0.477
Value Life Activities							
Baseline	1·5 (0·8); 122	1·5 (0·8); 120	1·6 (0·8); 120				
10 weeks	1·3 (0·8); 90	1·4 (0·9); 93	1·5 (0·8); 94	-0.05 (-0.21 to 0.10)	0.496	0.04 (-0.11 to 0.19)	0.615
28 weeks	1·2 (0·8); 78	1·4 (0·9); 88	1·5 (0·9); 84	-0.21 (-0.37 to -0.05)	0.012	-0.01 (-0.17 to 0.15)	0.896
56 weeks	1·3 (0·9); 76	1·3 (0·9); 88	1·5 (0·9); 85	-0.18 (-0.35 to -0.02)	0.028	-0.08 (-0.24 to 0.08)	0.328

Data are shown as means (sd); n. Results are expressed as adjusted mean difference (md) with 97.5% confidence intervals for the primary outcomes and (95% CI) and p-value for all other outcomes. PEP, personalised exercise programme; CBA, cognitive-behavioural approach; UC, usual care; HADS, Hospital Anxiety and Depression Scale; SF-12 PCS, Short Form-12 physical component summary; SF-12 MCS, Short Form-12 mental component summary; WPAI, Work Productivity and Activity Impairment (overall work impairment domain); #a negative difference favours the intervention for all outcomes except SF-12 MCS, SF-12 PCS

Table 3 Safety outcomes of all enrolled study participants

	PEP (n 124)	CBA (n 121)	Usual Care (n 122)
Participants with at least 1 SAE	**12 (5.6)**	**8 (6.6)**	**14 (11.5)**
Number of events	**17**	**19**	**25**
SAEs criteria			
Hospitalisation	13	17	20
Medically significant	4	2	5
SAEs categories[†]			
Accident incl. fractures and head injures	1	1	2
Cancer	1	2	2
Cardiovascular disease	1	0	1
Infection (severe)	0	2	6
Inflammatory disease relapse (severe)	2	1	0
Pregnancy / birth	0	0	2
Surgery (incl. hospitalisation)	9	6	6
Other	3	7	6
Participants with at least 1 AE	**56 (45.2)**	**62 (51.2)**	**59 (48.3)**
Number of events	**136**	**117**	**111**
AEs categories			
Accident	10	11	14
Cancer (suspected)	0	2	2
Gastro-intestinal	1	2	2
Cardiovascular disease	6	5	1
Flare-up of IRD	26	27	26
Infection (bacterial, viral, fungal) incl. COVID	25	23	21
Light headed/ loss of consciousness	2	2	2
Mental health	4	1	0

Pain incl. MSK related pain	14	11	9
Respiratory	2	1	1
Surgery (day case)	9	6	10
Worsening of fatigue	1	0	1
Other	36	26	22

Figure 1: Trial Profile

CFS: Chalder fatigue scale; FSS: Fatigue Severity score

Figure 2: Primary outcomes across follow-up points

CFS Chalder Fatigue Scale; FSS Fatigue Severity Scale; PEP Personalised Exercise Programme; CBA Cognitive Behavioural Approaches; UC Usual Care