Reducing Arthritis Fatigue – clinical Teams using cognitive behavioural approaches (RAFT)

Protocol Version 4: 07 September 2015

HTA grant ref: 11/112/01
UHBristol R&D ref: ME/2011/3686

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1 Summary of research

Design: A multicentre randomised controlled trial of a group cognitive-behavioural (CB) intervention for fatigue self-management in rheumatoid arthritis (RA), delivered by the rheumatology clinical team in addition to usual care; compared to usual care (Arthritis Research UK Fatigue booklet).

Setting: Outpatient secondary care where RA is usually managed; using rheumatology nurses and occupational therapists (OTs) who know how RA pain, disability and fatigue interact.

Target Population: Patients with RA and fatigue severity of ≥6/10 on a Numerical Rating Scale, that they consider recurrent/persistent. Exclusion: changed major RA medication (16 wks) or gluco-corticoids (6 wks).

Intervention: A cognitive-behavioural fatigue self-management programme, co-facilitated by two rheumatology clinicians (eg nurse and OT tutor pair), using a detailed manual. Brief training in CB approaches is given, completed by an observed practice run. Groups of 5-7 patients will attend 6 sessions (2hrs/wk x 6 wks) and a consolidation session (1hr wk 14). Topics include fatigue validation, energy management, priorities, sleep, stress, and assertiveness, underpinned by goal-setting and self-monitoring of activity, rest and fatigue. RAFT quality and homogeneity are facilitated by standardised training, programme and materials and clinical supervision. Fidelity to RAFT in the RCT will be monitored in a random session in each course.

Control arm: Usual care is the Arthritis Research UK fatigue self-management booklet, used in most rheumatology units. At the baseline visit, the research nurse provides the booklet to both arms, discussing the content for 5-6 minutes, noting it suggests patients may request support, and how this is accessed locally.

Randomisation: 300 patients will be randomized, in cohorts of 10-14 in each of 7 centres. Each centre will conduct baseline visits (consent, assessment, usual care booklet) over a 2 week period every time they have recruited 10-14 patients, giving a viable CB group of 5-7 patients and 5-7 control patients. Once all 10-14 visits are completed, BRTC randomizes individual patients in that centre's cohort, the Trial Manager informs the research nurse, who informs patients, inviting those randomized to the CB arm to the group intervention.

Outcome assessment: Primary outcome is fatigue impact at 26 weeks, with persistence evaluated over 2 years at weeks 0, 6, 26, 52, 78 and 104 (plus fatigue assessment only at 10 and 18). Secondary outcomes are fatigue severity, coping and multi-dimensional impact; pain, disability, sleep, quality of life, mood, valued life activities; the RA core set; and acceptability. Process measures are helplessness and self-efficacy. To maximise returns, primary outcome (fatigue impact) collected by telephone each time.

Analysis: Intention-to-treat analysis of covariance (adjusted for baseline values) will use multivariable linear regression models and standardised effect sizes. Sensitivity analyses will include adjustment for any variables imbalanced at baseline, multi-level mixed effects models to test group and centre effects, multiple imputation techniques to investigate the impact of missing data, and multivariable analysis of any relationship between attendance patterns and outcome. Repeated measures mixed effects ANCOVA models will examine long term outcome. Exploratory baseline predictors are demographics, co-morbidities and disease activity.

Cost effectiveness: Utilities and work disability measured, NHS costs captured in staff logs (training, delivery, supervision, group size), patient costs in a simple questionnaire (sick leave, medication, GP and community care appointments, transport) and secondary care costs via hospital computer systems. Unit costs will be derived from national estimates or local micro-costing, and cost-effectiveness calculated using fatigue impact and EQ-5D-5L for cost/QALY. Bootstrapped confidence intervals used with the Incremental Cost-Effectiveness Ratio and net monetary benefit statistic for NHS and societal perspectives, plus sensitivity analyses.

Evaluation of training in CB skills: Process and effects of teaching clinicians CB skills will be evaluated after the final CB course. Tutors will be invited to take part in a focus group and/or a one-to-one interview. The focus group and interview data sets will be analysed separately using inductive thematic analysis, however the findings will be compared and integrated to build a comprehensive account of tutors' experiences.

Sample size: The original RCT of CBT delivered by a clinical psychologist showed an adjusted statistically significant difference in fatigue impact of 1.95 units on a 0-10 VAS (SD 2.7, effect size 0.77). We have assumed clinical teams using CB approaches can achieve 75% of this, indicative of a clinically significant effect. Including design effects from group and centre/tutor clustering, an analytical sample size of 75/arm would achieve 90% power ($p<0.05$, two-sided). We have capacity to recruit 300 patients to allow for attrition and centre/tutor contingencies over a 2 year follow-up.

Project outputs: The copyrighted RAFT package will be available via a royalty-free license. Findings will be submitted to NICE for inclusion in RA guidelines, and Clinical Commissioning Groups. All UK rheumatology teams will be invited to RAFT taster sessions via interactive Road Shows.

2 Background and Rationale

RA is a systemic inflammatory condition causing synovitis in multiple joints, pain, joint destruction and disability, leading to major impact on quality of life.[1] Life-long treatment is by secondary care rheumatology teams, using medication to control inflammation and multi-disciplinary interventions to reduce symptoms and maximise self-management.[2,3] RA affects approximately 0.5 million people in the UK[4] and fatigue is present on most days for most people, with over 70% reporting fatigue as bad as pain, and as severe as Chronic Fatigue Syndrome (CFS).[5,6] People with RA experience fatigue as overwhelming and unmanageable physical exhaustion or 'wipe-out' that impacts on social and work activities, and as cognitive and emotional fatigue that disrupt concentration and memory, and cause frustration and tearfulness.[7,8] 76% of specialist nurses report that fatigue is raised by RA patients during the first appointment and people with RA identify fatigue as the main reason for work loss.[9,10] Work loss affects 66% of working people with RA, with 22% becoming work disabled within 5 years, and work production loss in the UK from RA in excess of £650 million.[11-13] Fatigue predicts and reduces quality of life,[14] and people find it as hard to cope with as they do pain,[15] and consequently rate fatigue as one of their top priorities.[16,17] The highlighting of fatigue by patients stimulated research that led to international consensus that fatigue must now be evaluated in all RA clinical trials alongside the core set.[18]

Patients feel this major and unmanageable symptom is ignored by rheumatology professionals.[7] Cochrane reviews of biologic and non-biologic interventions reporting effects on RA fatigue are underway,[19,20] meanwhile a systematic review shows biologic agents to control RA inflammation have only a small effect.[21] RA fatigue has moderate associations with inflammation, pain, disability, sleep, depression and beliefs,[22-24] therefore it has been proposed that RA fatigue has complex, multi-causal pathways comprising differing combinations of variables between and within patients.[25,26] This highlights the critical role of patient self-management in persistent fatigue, and hence the need for self-management interventions. Some rheumatology teams provide broad RA management education courses, but analysis of 11 programmes showed fatigue was never addressed.[27] A systematic review of RCTs of non-pharmacological interventions reporting RA fatigue shows that exercise has a moderate but significant effect on fatigue, as does Cognitive Behavioural Therapy.[28] CBT courses are effective for fatigue in multiple sclerosis and CFS.[29,30]

CBT helps patients make links between thoughts and feelings that drive behaviours, and uses cognitive restructuring to help them try changing their behaviour.[31] For example, a belief that tasks must be done perfectly, and feeling guilty if they are not, may drive excessive activity, leading to fatigue. In CBT, key self-management skills of problem-solving and goal-setting, can be enhanced by sharing the learning process in groups with other patients as role models (social cognition theory, SCT) to increase self-efficacy, or confidence that you can do something.[32] Systematic reviews conclude that rheumatology self-management courses using CBT and/or SCT are more effective than information alone.[33,34] Three such RCTs have reported effects on RA fatigue. Group education (16 hours SCT) for patients and partners improved fatigue in patients attending alone, but increased fatigue in those attending with partners.[35] Individual CBT (11 hours CBT) improved fatigue and depression.[36] Group CBT (22 hours SCT/CBT) improved fatigue, pain, function and mood.[37] However, participation in these interventions was restricted to those with either early disease, mild disability, psychological distress, or being in a relationship, and interventions were not aimed at improving fatigue, thus patients were not recruited because of fatigue, nor studies powered for fatigue. As RA fatigue is not strongly associated with a single clinical variable and occurs in at least 70% of patients, self-management interventions should target the broad RA population. Furthermore, as RA fatigue affects quality of life, interventions that change fatigue impact might be expected to change wider well-being. Therefore Hewlett et al tested, in an RCT with broad RA inclusion criteria, a group CBT fatigue self-management programme (13 hours SCT/CBT) led by a clinical psychologist, compared to groups receiving fatigue self-management information alone. Group CBT improved fatigue impact, severity and coping, disability, depression, sleep, helplessness and self-efficacy.[38]

These four RCTs of self-management interventions differed in size of improvement in RA fatigue, with effect sizes of 0.2 to 0.77, with those led by a clinical psychologist showing the larger effect sizes. The applicants' original RCT targeted a broad RA population (fatigue 6/10 or more), improved fatigue impact, severity and coping, as well as wider well-being, and provided the greatest effect size for fatigue impact (0.77).[38] Furthermore, findings were not altered when adjusted for age, disease duration, gender or baseline readiness

to change behaviours, suggesting a widely-applicable intervention. The intervention was co-facilitated by a CBT-trained clinical psychologist (Ambler) and specialist OT (Knops) and in the nested qualitative study, patients spontaneously raised CBT elements as key to its success.[39] However, few rheumatology units have clinical psychologists, thus the course cannot currently be routinely delivered in clinical practice.

If the clinical team could deliver a CB intervention for fatigue, it could be embedded in usual care, delivered by clinicians who routinely support patients in self-management and understand how fatigue interacts with fluctuations in RA inflammation, pain and disability and their self-management. A manualised, group intervention for MS fatigue, led by the clinical team after training in CB approaches has been piloted.[40] A search of RCT registration databases found no similar RCTs for RA fatigue in progress. The applicants have produced and piloted their original RCT intervention[38] as a programme suitable for delivery by rheumatology health professionals who are not CB therapists, using a detailed course manual (**R**educing **A**rthritis **F**atigue - clinical **T**eams using CB approaches, RAFT).[41] The brief training for RAFT, which covers CB skills and the RAFT programme, includes running an observed practice course. Having completed this training, in our pilot a local tutor pair (rheumatology nurse and OT) ran a clinical course, which was rated by patients as 8.8/10 for both satisfaction and recommending the course to others.[41] The manual and training were then refined with the clinicians and patients (Robinson, Rooke), and are now ready for testing in an RCT.

This proposal addresses the key government target of enabling people with long-term conditions to self-manage[42,43] as well as RA-specific guidelines by NICE[44] and professional bodies[2,3] that recommend support for self-management, fatigue, and use of CB therapies. Given the success of psychological therapies but shortage of clinical psychologists, improving access to psychological therapies (IAPT) is also a government target.[45] This is being achieved through manualisation of interventions and training of non-clinical assistants to deliver them, often by telephone and under close supervision by a psychologist, adhering closely to the intervention stipulated and referring those cases that are not straightforward, onto the psychologist. Such IAPT interventions are largely delivered to people with an episode of anxiety or depression. However, in people with RA, where thoughts, feelings and behaviours interact with a complex, life-long chronic physical illness, it is crucial that psychological therapies are provided by clinicians who understand the multiple interactions between fatigue and the patient's wider self-management of medications and multiple, fluctuating symptoms. The experienced rheumatology clinicians who will deliver this CB intervention will be able to draw on their clinical expertise and skills to centre discussion around the patient's personal disease context. They will be accustomed to making clinical decisions in complex RA cases and will thus require minimal supervision and be less likely to refer patients on to a clinical psychologist. In addition, whilst IAPT-trained non-clinicians generally deliver individual telephone interventions, these rheumatology clinicians have the management skills to deliver the intervention to groups of patients, thereby enhancing the efficacy of the intervention by the use of role-models (SCT).[32] The value of learning with others in a similar condition was highlighted by patients in our original RCT,[39] and is particularly helpful for validating this invisible symptom.

This proposal addresses a clear health need for people with RA who have prioritised fatigue[16,17] as a symptom that is commonly experienced (70%), overwhelming and impacts their quality of life but which they do not know how to manage.[7,8] Furthermore, given the frequency of fatigue in a life-long condition,[5] and the limited success of pharmacological interventions on fatigue,[21] this intervention will continue to have relevance in the future, with results remaining important to patients, clinicians and thus the NHS. The information gained will be evidence on the efficacy and cost-effectiveness of a fatigue intervention that could be delivered routinely by usual clinicians, and whether (and how) training rheumatology clinicians in CB approaches affects the way they deliver care more broadly. The intervention builds on existing research into RA fatigue, much of which has been conducted by this team.[7,9,16,18-20,22,23,25,28,38,41,46,47]

3 Aims and objectives

Overall aim: to test a group cognitive-behavioural intervention for RA fatigue, that can be routinely delivered by clinical rheumatology teams across the NHS. This showed clinical efficacy when delivered by a clinical psychologist[38] but as few rheumatology teams have these, the programme has been manualised for delivery by the rheumatology team after brief training, with all supporting materials and minimal clinical supervision.[41]

Objectives:

1) To assess whether there is a clinically important difference in the impact of fatigue between patients participating in a group cognitive-behavioural self-management course for RA fatigue delivered by the

clinical rheumatology team using a detailed manual, in addition to usual care; compared to patients receiving usual care, which includes written fatigue self-management information

2) To compare differences between groups for secondary outcomes of fatigue severity, coping, mood, sleep, helplessness, pain, disability, valued activities, quality of life, work, health service use, acceptability, and cost-effectiveness for the NHS, patients and society
3) To evaluate and control for potential demographic, psychological, and clinical predictors of fatigue change
4) To evaluate persistence of effect (if any) over 2 years
5) To explore whether clinical teams trained in cognitive behavioural approaches, perceive any positive or negative outcomes, particularly on their wider clinical practice

4 Methods

4.1 Design: This is an RCT of a group CB course for the self-management of RA fatigue, delivered by the two trained members of the usual clinical team after brief training, in addition to usual care; compared to usual care alone (Arthritis Research UK patient information booklet on fatigue). After training in the lead centre (Bristol), 7 pairs of clinicians (tutors) will each run 4 courses of RAFT in their local rheumatology centre using the detailed manual and materials. The 6 month primary endpoint is fatigue impact, with a 2 year follow-up. A qualitative study after delivery of the course will evaluate the clinicians' (tutor pairs) experience of RAFT and of developing CB skills, both positive and negative, and any influence on their wider clinical practice.

The RCT design addresses objectives 1-4 and provides a rigorous test of the intervention by controlling for bias, and is supported by an accredited clinical trials unit (Bristol Randomised Trials Collaboration, BRTC), who are co-applicants. Blinding of patients and clinicians is not possible because of the need to engage patients in making cognitive and behavioural changes. However, all outcome measures are validated, and analysis will be performed blind to allocation. The intervention was previously developed by the applicants following the MRC framework for complex interventions.[48] First, development of the intervention was grounded in qualitative data about RA patients' experiences of fatigue.[7] Next, the piloted and refined CBT intervention, co-facilitated by a clinical psychologist and OT (Ambler, Knops) was tested in an RCT,[38] followed by a qualitative evaluation of underlying processes, and any outcomes not captured by questionnaires.[39] Third, the programme was manualised for delivery by the 2 members of the usual clinical team after training, then training and delivery were piloted, and RAFT refined in collaboration with clinicians and patient research partners.[41] Thus RAFT is now ready for formal testing in a pragmatic trial to evaluate use in normal clinical practice. RAFT content encapsulates the complex conceptual framework of RA fatigue, in which thoughts, feelings and behaviours interact with disease processes and consequences (eg inflammation, disability), and personal context (values, circumstances) to exacerbate or perpetuate fatigue.[25,26]

The qualitative design of the tutor evaluation addresses objective 5. There will be rigorous thematic analysis[49] of tutor focus groups and one-to-one interviews, with independent analysis by a second researcher.. The use of qualitative methods in combination with quantitative methods to unpick detailed processes and explore unanticipated outcomes is a recommended methodology in complex interventions.[48,50] In the original RCT, the qualitative evaluation with the CB patients identified that they valued key CBT processes (reflective questioning, goal-setting, self-monitoring by daily activity charts), and appreciated learning in groups, while identification of important outcomes not captured in the questionnaires (return to valued leisure activities)[39] led to the inclusion of a VLA scale in the current proposal.

4.2 Patient care group and setting: Patients with RA[51] and fatigue severity $\geq$6/10 on an NRS,[47] which they feel is a persistent or recurrent problem. The setting is outpatient secondary care as this is where RA continues to be managed throughout the UK. Testing delivery in 7 centres will evaluate the extent to which it is deliverable widely in the NHS. The intervention will be co-facilitated in each of 7 participating rheumatology units by two rheumatology clinicians (nurses/OTs, Band 6 or 7). These experienced clinicians understand how RA pain and disability interact in the self-management of a long-term, fluctuating condition that requires adaptation to an uncertain outcome.

4.3 Intervention: RAFT is a CB fatigue self-management programme, delivered to groups of 5-7 RA patients, in 6 x 2hr sessions (weeks 1-6) and a consolidation session (week 14). Sessions are co-facilitated by a rheumatology tutor pair (eg nurse and OT) after brief training in CB approaches (formulation) completed by delivering an

observed practice course. They have a standardised manual and materials, and minimal clinical supervision by a clinical psychologist. RAFT content, CB approaches, training and delivery are described below.

4.3.1 RAFT Content: The first hour of each session is a discussion facilitated by the tutors (Table 1). After a coffee break each tutor takes half the group for goal setting as smaller groups allow each patient to discuss their goals with the group. Topics related to fatigue and skills likely to improve fatigue self-management build on each other week by week (see table). For example, in week 1 the discussion topic is the struggle to self-manage fatigue, and is largely led by patients. After coffee, tutors draw ideas from patients on why they persist in boom and bust behaviours (eg the rewards of getting things done), and the discussion is steered towards helping patients generate positive strategies for energy management (eg prioritising, pacing, planning). This is built upon further by the homework, which is to self-monitor their activity, rest and fatigue patterns by colouring in a daily activity/rest chart every hour for the week. In week 2, the discussion topic is exploring personal priorities people would like to aim for in their lives if they were less fatigued, moving on into goal-setting where the small groups review each person's daily activity chart to understand patterns of behaviour and their consequences (fatigue). Then, using the personal life priorities identified before coffee, each patient is encouraged to set personal short and long-term goals. How these goals are to be achieved is linked back to the activity/rest chart, to help patients identify small changes they could make, typically reducing boom and bust behaviours. The intention is that as the charts are completed each week, they show an improving balance of rest/activity, and fewer episodes of fatigue. Review of the activity charts in week 3 is related to topics of sleep and rest, which are then linked to relaxation and stress (week 4), which in turn is linked to difficulty communicating fatigue needs (week 5). Week 6 is a review of all the skills learnt, and the tutors draw from the participants, a reflection on how far they have progressed in self-management. This is based on two metaphors of life with fatigue as being trapped on a desert island; and how to climb back out of the pit of fatigue using the skills they have learnt as the rungs of a ladder. The 7th session is in week 14, after patients have been using their new behaviours for 8 weeks without support. The aim is to consolidate the skills they have learnt, reflect on how those worked in the real world, and help them set future goals, including dealing with set-backs.

Table 1: CB course design

Wk	1st hour	Supporting materials*	2nd hour
1	Course purpose and expectations Ground rules: Commitment, confidentiality, homework Validating fatigue: Share and discuss fatigue experiences (difference from flare) Self-management strategies, struggles and difficulty of changing habits	H: Arthritis Research UK booklets H: Setting our course (groups' ideas)	Energy management -Boom & bust behaviour -Rewards/pitfalls of this -Prioritise, pace, plan, choices H: Achieving balance H: Activity cycling T: Activity/rest diaries
2	What are your priorities for change, to ↑QoL? What are your drainers and energisers?	T: Wheel of life (priority areas)	Goal setting (two groups) -Short/long-term goals -Use peer group for ideas
3	Self-sabotage on the course Sleep and rest Hours needed? Quality v quantity Sleep hygiene strategies	H: Best ways of self-sabotage H: Getting a better night's sleep T: Sleep diary (if needed)	Goal-setting review Successes/barriers New goals
4	Stress and relaxation Personal stressors, bodily reactions Relaxation rationale and techniques	H: Effects of stress H: Relaxation practice guide T: Relaxation CD	Goal-setting review Successes/barriers New goals
5	Assertiveness and communication Passive, manipulative, assertive? Other people's reactions to these? Communicating your needs	M: Cartoon examples H: Saying 'No'	Goal-setting review Successes/barriers New goals
6	Review self-help tools What have you learnt? Review each topic Dealing with setbacks – what could you do? Negative self-talk, automatic thoughts, and rumination	M: Fatigue pit: Falling in/digging out H: The pit; Coping with setbacks	Goal-setting review Successes/barriers New goals
14	Review last 8 wks; skills; dealing with setbacks; new goals	M: Islands: Were on a Desert island (passive) looking to the Mainland (100% healthy, unrealistic). Now on Adaptive Coping Island (realistic)	

* H = Handouts, M = Metaphor, T = Tools

4.3.2 RAFT CB approaches: In cognitive-behavioural interventions professionals use reflective (Socratic) questioning and guided discovery to enable patients to identify links between their thoughts, feelings, behaviours and symptoms (formulation),[31] as opposed to the more traditional approach of assessing (diagnosing) the problem, then telling the patient what it is and what to do about it. A crucial feature of CB approaches is that the tutor remains non-judgemental and does not instruct the patient.[31] The use of self-monitoring (daily activity/rest charts) and goal-setting are the most effective tools in bringing about behavioural change,[52] while the use of metaphors helps turn abstract or difficult therapeutic concepts into a form that can be more easily understood and remembered.[53] In the qualitative evaluation of the original RCT, patients spontaneously raised these CB components as being critical, and in particular keeping daily activity/rest charts each week was a motivator for change as the coloured blocks gave a visual representation of the problem (and solution).[39] CBT is often delivered one-to-one to help patients explore the unique links between their thoughts, feelings and behaviours but the value of group CB courses is that fellow patients provide a credible source to legitimise or validate invisible symptoms such as fatigue, and act as role-models and peer support in the goal-setting and problem-solving processes.[32,54] The original RCT showed that individualised goal-setting can be pursued successfully in sub-groups, and still improve fatigue and well-being, while statistical adjustments for group in the analysis made no difference to the findings.[38]

4.3.3 RAFT Training and Supervision: We have standardised our original intervention for delivery by non-CB rheumatology clinicians. A RAFT manual contains detailed instructions for each of the 7 sessions, including the key points to be drawn from patients, and sample conversations.[41] Each section of the manual covers one session, and contains all the required timings, materials (handouts, diagrams to be drawn on the whiteboard, metaphors, goal-setting records, activity charts) with a clear indication of when and how they are to be used. RAFT development, content, programme, manual and training align with the recent standards for delivering self-management programmes for people with long-term conditions, as proposed by the Quality Institute for Self-Management Education and Training (QISMET),[55] an independent body working in the long-term conditions sector. Benchmarks include patient involvement in development, detailed individual session guides and handouts, structured training and support for facilitators.

The 7 tutor pairs (one pair from each centre) will be trained together in Bristol over 4 consecutive days. Training them together is cost-effective and is a better educational strategy as they will be able to practice delivering components and techniques of the programme to the whole group, mimicking the future delivery of RAFT to groups of patients. The RAFT manual and handouts will have been provided during study site visits, to read before training. On the first morning a 1 hour session covers the patient perspective of fatigue and the complex causal pathway,[7,8,25,26] and the quantitative and qualitative results of the original RCT[38,39] (Hewlett, Dures). Over the following 2.5 hours, there is an introduction to CB principles, self-efficacy and managing groups, plus practice in CB formulation (linking thoughts, feelings and behaviours) (Ambler, Hewlett).[31,32] On the subsequent 7 half-days, RAFT sessions 1-7 are explored and discussed (half a day for each), with an opportunity to practice components of these in groups, with support from patient partners (Robinson, Rooke), and observation and feedback (Ambler, Knops, Hewlett, Dures). To complete their training, tutor pairs must deliver an observed practice course locally. This is observed by either Ambler, Knops, Dures or Hewlett, with feedback and debriefing after each session.[41] This is part of the RAFT training to enable tutors to gain confidence in course delivery. Using the RCT entry criteria, the research nurses will recruit patients specifically to attend the observed practice course -they are not randomised and do not provide questionnaire data. As these are experienced rheumatology clinicians, only minimal ongoing clinical supervision/support is required for the use of CB techniques: one session will be observed in alternate courses for each pair (Ambler or Knops) with feedback and debriefing. Tutor pairs will select sessions with which they would most like support. Advice is available by telephone if needed (Ambler). These arrangements arose from the RAFT pilot[41] and in clinical practice will be provided by a trained CB Therapist within the local Trust, but for pragmatic reasons training and supervision are provided centrally in the RCT.

4.3.4 RAFT Delivery: Training is completed after the observed practice course. Tutors must have delivered observed sessions 1-6 in order to start delivering their 4 courses to randomised participants. Session 7 is a consolidation session for patients after an 8 week gap, and as no new material is presented this session can be observed when it is due, rather than causing a delay to the start of randomised course delivery. Each tutor pair will co-facilitate 4 RAFT courses, each comprising 5-7 patients. Quality and homogeneity of RAFT is facilitated by the use of standardised training for tutors, and a standardised manual containing all materials, delivered by the same tutor pairs in each centre, for every course.

4.3.4.1 Tutor unable to deliver session: Tutors have unexpected illness, and pragmatically, these instances must be catered for. In the case of a tutor being suddenly unavailable, the remaining tutor will either deliver the session alone, delay the session by 1 week, or ask another clinical team member to be present as a supporter. This clinician will not deliver any course content, and the group will not split into two sub-groups for goal-setting. If there is long term unavailability of a tutor (eg long term sickness, or they leave their clinical post), then the centre will contact the Trial Manager in Bristol to discuss training for a new staff member.

4.3.4.2 Participant unable to attend sessions: Patient will be asked to attend all 7 sessions if possible, but as RA is a fluctuating condition some patients will inevitably miss some sessions. In this event, tutors will ask the patient to come early the next time, so that they can explain some of what was missed.

4.4 Control (usual care): Unlike pain, fatigue is not routinely addressed in usual care in great detail. Patients are generally given a fatigue information leaflet by the nurse (61% of respondents in a recent survey by the applicants). Thus the control is usual care including provision of the Arthritis Research UK fatigue booklet.[56] This is the most comprehensive and recent fatigue self-management booklet for arthritis, which was written for Arthritis Research UK at their request, by Hewlett, Ambler and Dures (2011), following publication of their original RCT. It contains information on all the topics in the RAFT course, includes a pull-out sample activity/rest chart to complete, and suggests at several key points that the patient ask their rheumatology team for support to work through the booklet.

4.4.1 Usual care delivery to both arms: The Arthritis Research UK Fatigue booklet is provided to both control and intervention arms at the baseline visit, after consent and assessment but prior to randomization (section 4.9). The research nurse will spend 5-6 minutes showing patients the sections in the booklet (using a brief, standardized guideline). They will point out that the booklet suggests patients might wish to request support from the rheumatology team to help them try the activities described, and explain the local usual care arrangements for requesting help (generally the local nurse helpline). Seeking help is thus is an intended outcome of the booklet, and appointments will be captured within health economics data.

4.4.2 Control patient requests for help with fatigue: In order to minimize the risk of contamination between the arms we will ask the local nurse specialist managing such requests, not to book a control patient in to see a clinician who is also an intervention tutor. However, this may be unavoidable in small teams therefore tutors will record any control patient appointments for fatigue support and this will be entered as a variable in the analysis. We considered using the same control as for the original RCT, a single, group didactic information session. However, we believe that the new 32-page fatigue self-help booklet is now current best practice as these are freely available in most rheumatology units (Arthritis Research UK reports 30,000/year distributed). We also considered controlling for the social effects of 6 group CB sessions, but 6 sessions of didactic information do not reflect best or current practice and would likely have high attrition. In addition, studies that have controlled for social effects by matching numbers of group sessions, still show CBT to be superior,[36] and patients in the original RCT said that whilst the group effect was helpful, it was the CB techniques and the facilitative role of the tutor that were more important.[39]

4.5 Inclusion/Exclusion criteria: Patients over 18, with confirmed RA[51] and fatigue severity of $\geq$6/10 on an NRS,[47] that they consider a persistent or recurrent problem, will be eligible. Patients will only be excluded if they have insufficient English to participate in group discussions, or lack capacity for informed consent, or have recently changed major RA medication (16 weeks) or glucocorticoids (6 weeks). For the latter, inflammation may be a key driver of fatigue and thus medication change might have some effect. Interested patients who are ineligible at screening will be offered re-screening after 3-4 months. Thus we are targeting a very broad group of RA patients who consider that they have a significant problem with which they would like help. This makes the findings potentially generalisable, reflecting the large proportion of patients experiencing fatigue.[5] In order to test generalisability of the programme, we have selected 7 participating rheumatology units that encompass a range of large and small departments, both academic and non-academic, and cover city and rural areas.

4.6 Sample size: The baseline-adjusted effect size found in the original trial of CBT delivered by a clinical psychologist (0.77) was 1.95 units on a 0-10 VAS for impact of fatigue, with a SD of 2.7. We have powered the proposed trial of CB approaches delivered by the rheumatology team, to be able to demonstrate an average effect size across all participating centres of at least 75% of the original trial (ie 1.46 units, equivalent to an effect size of 0.54). We regard this as clinically important as it is equivalent to removing one third of patients to below the fatigue criterion for trial entry, a sufficient reason to introduce a service change. There are no published data on a minimal clinically important difference for RA fatigue impact but for fatigue severity, MCID

is between 0.82 and 1.12 on a 0-10 VAS.[57] At a power of 90% and a two-sided significance of 0.05 this requires 73 patients/arm. As we are interested in the average effect across all centres we expect no loss of power as a result of randomising patients by site.[58,59]

The intervention will be delivered in 4 groups of 5-7 patients (likely mean 6), in 7 hospital outpatient rheumatology departments by a pair of trained tutors in each centre. As patient inclusion criteria are identical across centres there are two sources of clustering in the intervention arm: the CB group effects and the centre/tutor effects. In the original trial the intra-class correlation coefficient (ICC) for CBT group using the primary outcome was an estimated <0.00001. No data currently exist for centre/tutor effects of CBT on fatigue in RA patients so we are taking an ICC value of 0.01 for groups clustered within centres, which is larger than one determined in a trial of group CBT in back-pain patients.[60] The resulting design effects increase the required analytical sample size to 75/arm.

In the original RCT, most attrition occurred after patients had completed their CBT or control intervention, ie loss to completion of questionnaires, not loss to the intervention. We intend to minimise this through enhanced patient follow-up procedures (eg collecting primary outcome by telephone each time, see minimising attrition 4.10). Therefore we anticipate approximately 80% of patients will provide primary outcome data at 26 weeks. However, attrition rate over the requested 2 years is unknown, therefore we have planned capacity in this trial to recruit up to 150 consenting patients per arm, in order to maintain sufficient power for 2 year analysis (ie total n=300). Relaxing the power criterion to 80% we would still determine statistical significance ($p<0.05$) if we obtained outcome data on 55 rather than 75 patients per arm, or if we obtained an effect size of 65% rather than 75% of the original RCT, or we observed a centre/tutor ICC of up to 0.1 rather than 0.01. Our timetable and expected recruitment rates allow for delays in CB group formation and for unexpected centre delays whilst maintaining sufficient statistical power for the longer term outcomes.

4.7 Recruitment per centre: Experience shows a pragmatic approach to recruitment is needed to take account of the natural variation in group size, the need to form viable groups and the number of centres needed for timely completion of the requested 2 year follow-up. Theoretically, for 300 patients, each of 7 centres needs to randomise 42-44 participants but in clinical practice group sizes always vary, therefore a target of 7 centres each running 4 CB courses with an average of 6 participants/group (n=168) provides contingency for variation in group size (5-7 patients/group gives 140-196 CB participants), or for some centres to run fewer courses if there is staff absence. If (unexpectedly) a centre cannot participate, then one of 3 other interested UK hospitals would be approached, or existing centres asked to run an extra cohort. As recruitment for cohorts 1-28 will stop as close to 150 participants/arm as is consistent with viable group formation, the ***maximum*** number of participants (392) is unlikely to have been reached. In this instance, the possibility of one of the centres running an extra cohort will be considered.

Recruitment to research studies involving weekly attendance and lengthy follow-up is lower than for courses delivered as clinical care. In addition, in our original RCT we had to use mainly mailshots (which had a 66% non-response rate) because the single research assistant covered two hospitals and was also responsible for questionnaire mailings and data entry. However, this time these will be managed by the Trial Secretary and in addition there will be a research nurse in each centre to recruit. We anticipate that by concentrating on face-to-face recruitment we can increase identification of interested patients, and each centre should recruit sufficient patients by screening 130-200 patients. Centres have approximately 600-1200 RA patients, seen 1-2 times/year who can be screened at each visit, and data show 50% of consecutive clinic attendees have fatigue $\geq$6/10.[47] As fatigue is a chronic problem, patients who are interested but currently ineligible will be re-screened by post every 3-4 months. Recruitment posters will be displayed in rheumatology, physiotherapy and OT clinics, and mailshots used if needed. In the original RCT, recruitment was approx 4 patients/month, and we are confident we can achieve this again.

4.8 Recruitment procedures: The research nurse in each centre will target RA clinics and aim to approach all attending RA patients (introduced by the clinical team). If patients are interested in participating they will be invited to complete a screening fatigue NRS, and other eligibility criteria checked. If they are eligible the nurse will talk through the patient information sheet with them, and give them a reply slip with a reply-paid envelope to return to the research nurse. We will phone the patient after 3-4 days if there has been no response. If they wish to participate the research nurse will inform them of the dates for the next CB course, reminding them that they may or may not be randomised to receive it. The nurse will explain that as soon as 10-14 patients are recruited, they will call all the patients to arrange a visit for written consent, baseline assessment and usual care. Closure of recruitment for a cohort must be agreed with Bristol. These visits will take place over a two

week period, and when all are completed, randomisation will occur (section 4.9). To maintain engagement, the nurse will call the patient monthly to update them on recruitment rates and when baseline visits might occur. If a patient is interested but not currently eligible due to recent medication change or low fatigue levels, the nurse will ask permission to contact them for rescreening after 3-4 months. We aim to record the age and gender of those who decline, and fatigue NRS if available (anonymized).

4.9 Randomisation procedure: Whenever a centre has completed the baseline visit for 10-14 participants (all conducted over a 2 week period; comprising consent, assessment, usual care; see section 4.8), the Trial Manager in Bristol will request a randomization event for that centre's cohort. Randomisation will be managed by BRTC. Randomization is stratified by centre; and within centres it is stratified by course (courses 1-4). Allocation will be 1:1 but in the event of an odd number, the CB arm will receive an additional patient. On being informed that a cohort of 10-14 has been formed and consented, the Trial Manager will obtain the randomisation sequence from BRTC, and inform the local research nurse, who will then inform the consented patients (using a brief, standardized guideline to ensure those randomized to Usual Care alone are reminded they are receiving current best practice). Those randomised to the CB intervention will have the dates, times and venue confirmed.

4.9.1 Randomized patient unable to attend their allocated CB course: Occasionally, a patient may not after all be able to attend on the next course dates. In this instance, they will be offered a subsequent course, and a new baseline evaluation will be performed two weeks beforehand.

4.9.2 Screened patient eligibility changes at later baseline assessment: Gaps between screening and baseline assessment are inevitable as baseline assessments cannot be performed until a centre has accrued 10-14 screened patients (sufficient for randomization). Changes to eligibility at this point (eg fatigue less severe, medication changed) will be noted for sub-group analysis and the patient will proceed to randomization, reflecting the pragmatic nature in which this intervention would be delivered in practice, to a population with fluctuating, recurrent fatigue and frequently changing medication regimens.

4.10 Minimising attrition and attrition bias: Retention in research studies that require weekly attendance is often more problematic than in such interventions when they are provided as clinical care. In the original RCT, 76% of patients attended most of their 7 CBT sessions,[38] indicating the intervention is highly acceptable. However, in the proposed study, the 2 year follow-up period creates a risk of significant loss to completion of later questionnaires. In the original RCT outcome data were not returned by approximately 50% of recruited patients although there were no differences in loss between arms and no significant demographic differences between those remaining in the trial and those withdrawing or failing to complete questionnaires.[38]

In order to reduce attrition prior to starting the intervention, we will randomise as close to the dates of the CB courses as possible, assisted by faster recruitment through dedicated research nurses, who will also keep patients informed about recruitment progress. In our original RCT, those patients who could not make the course dates, (eg due to holiday) were offered subsequent courses and most were able to attend, but to improve attendance we will inform all patients who agree to be randomised, of the forthcoming CB course dates, so that they can keep them free in case they are randomised to the intervention arm. In clinical practice, not all patients will attend all 7 sessions and in our original RCT 23% of patients attended 3 or less, but an intention-to-treat effect size of 0.77 was still seen.[38]

In order to maximise questionnaire returns, this time the Trial Secretary (Celia Almeida, GCP trained research associate) will telephone each patient at each assessment point to collect the primary outcome data (fatigue impact NRS), and remind the patient that the questionnaire package is being posted. If the questionnaire pack is not returned within 2 weeks, she will phone to check it was received. This personal contact will not only increase collection of the primary outcome, but should motivate the patients to complete the full questionnaire package. Information about this phone call will be part of the recruitment process. To try and enhance feelings of community, engagement and responsibility, all RAFT study materials will include the study logo (a raft – easily memorable); mailings of the full questionnaire packs will be accompanied by a short newsletter highlighting overall questionnaire return rates; and we will send a thank you notelet upon returns. The assessments at week 10 and 18 are exploratory and will contain only the BRAF fatigue scales and patients will be informed these are only 'mini-questionnaires' to encourage returns. We will seek ethics approval for permission to write once to those who withdraw and ask if we can telephone them (or write) for a fatigue impact NRS at 6 monthly intervals. We will also send them a letter asking them why they withdrew (a list of potential reasons with tick boxes, returned anonymously) to improve ITT assumptions in analysis.

5 Evaluation

5.1 Data collection time points: Outcomes will be measured at Weeks 0, 6, 10, 18, 26, 52, 78, and 104 using measures validated in RA. The 6 week assessment (posted 2 days after session 6 for each cohort) will reflect the intense support of the weekly sessions. At weeks 10 and 18, only fatigue data will be collected (Bristol RA Fatigue scales, BRAFS),[46,47,61] to capture outcomes 1 month before and 1 month after the week 14 consolidation session. The primary outcome is fatigue impact at 26 weeks (ideally collected within weeks 25-27), by which time patients should have become skilled at utilising fatigue self-management techniques. The commissioning brief was for 2 year follow-up, and by assessing this 6 monthly (weeks 52, 78, 104), we should capture any loss of efficacy if self-management skills start to be forgotten or lost, and when this starts to occur. This in turn, would inform the timing of any booster sessions to be tested in future research.

5.2 Clinical and social participation data: Fatigue impact (primary outcome) will be measured by a single numerical rating scale (BRAF-NRS Impact).[46,47,61] The secondary fatigue outcomes are fatigue severity and coping (BRAF-NRS Severity, BRAF-NRS Coping), which will clarify the relationships between changes in fatigue severity, impact and coping; and an RA fatigue multi-dimensional questionnaire (BRAF-MDQ) with component subscales (physical fatigue, living with fatigue, emotional fatigue, cognitive fatigue),[46,47,61] which for the first time will allow exploratory analysis of different fatigue types for predicting response to therapy. Only one other validated fatigue outcome measure was developed specifically for RA (Multi-dimensional Assessment of Fatigue scale, MAF) but it has a 15% non-completion rate and only provides a global fatigue score.[62]

The commissioning brief stipulates secondary outcomes of mood (Hospital Anxiety and Depression scale, HAD),[63] pain (VAS), and quality of life (EQ-5D-5L part 1; global question from Arthritis Impact Measurement Scale),[64,65] which all fit with the conceptual model of fatigue.[25,26] Two additional secondary outcomes are based on important issues generated by patients in the original RCT: sleep quality (single question from the Pittsburgh Sleep Quality Index),[66] and returning to important leisure activities that had been lost to fatigue[39] (discretionary activity subscale of the Valued Life Activities scale for RA, VLA).[67] Social contact with other RA patients for support will be measured at weeks 52 and 104 as group work may enhance seeking of social support (unvalidated question). The commissioning brief also stipulated assessment of the RA Core Set.[68] Beyond pain and fatigue, disability is an additional core set item (Modified Health Assessment Questionnaire, MHAQ),[69] as are professional assessment of painful joints and swollen joints, an inflammatory marker (C-Reactive Protein) and patient global opinion (VAS). These last four form a single disease activity score (DAS28),[70] through a weighted algorithm (patient global VAS will be as specified in the Arthritis Impact Measurement Scale).[71] DAS28 will be measured at 0 and 26 weeks only as it requires an additional hospital visit for assessment and venepuncture, and is a potential predictor not an outcome; a patient self-report version (PDAS2)[72] will be used in addition to avoid repeated hospital visits. The two remaining core set items, physician's opinion and x-ray damage, are unlikely to be altered by CB approaches and will not be measured.

5.3 Cost effectiveness data: Utility scores will be measured using the EQ-5D-5L[64] and work disability, presenteeism and absenteeism by the Work Productivity and Activity Impairment scale (WPAI).[73] Time logs and expense forms will be used to track all resources used in the delivery of the 4 day training programme including trainee and trainer time (and preparation time), travel costs and course materials to calculate the fixed cost of training (including support during the observed practice course). Similarly for the delivery of the CB sessions, NHS resources will be captured in staff time logs (recording session preparation, delivery, de-briefing, supervision time and materials). We will record group size at each practice and CB session so that these costs can be allocated on a per patient level. Subsequent NHS primary care and patient personal resource use during the 2 year follow-up will be captured in a short questionnaire asking about events related to arthritis or arthritis fatigue (GP or community physiotherapy, OT or nursing appointments, sick leave and changes in RA medication). Medications will be recorded by the research nurse at the baseline visit, then listed in the patient's subsequent questionnaires (updated with the most recent data at each mailing) and the patient asked to indicate changes from the previous date. Secondary care costs for events related to arthritis or arthritis fatigue will be obtained by the research nurses from the hospital computer system, including rheumatology and orthopaedic in-patient stays, and out-patient appointments in rheumatology (medical, nursing, physiotherapy, OT) and orthopaedics. Monthly blood monitoring visits will be excluded, whether primary or secondary care based. At the baseline visit the research nurse will document the patient's normal transport method for

hospital, GP or other NHS appointments and the cost of that transport, to use as a multiplier for calculating costs.

5.4 Process data: To understand what key processes prompt behavioural change in complex interventions,[48] helplessness (Arthritis Helplessness Index, AHI)[74] and self-efficacy (RA Self-Efficacy, RASE)[75] will be measured. RASE contains questions on beliefs about RA self-management topics covered in RAFT and the Arthritis Research UK Fatigue booklet.

5.5 Acceptability and feasibility data: RAFT and the booklet acceptability will be assessed at week 26 by satisfaction and recommending the course to others.[41] Information on whether either led to a request for further appointments for help with fatigue also collected at week 26. Feasibility of delivery in the NHS will be captured through monitoring of course scheduling and delivery, and the tutor evaluation groups.

5.6 Data collection for self-report questionnaires (Table 2): At all time points except 0 and 26, questionnaire packs will be sent out from Bristol by the Trial Secretary. In order to maximise questionnaire returns, the Trial Secretary (GCP trained research associate) will telephone each patient at each assessment point to collect the primary outcome data (fatigue impact NRS), remind the patient that the questionnaire package is being posted, with a check phone call if not returned within 2 weeks.

At weeks 0 and 26 the patient has a visit to the research nurse (Table 2) and will complete the self-report questionnaire packs during the visit. Thus at weeks 0 and 26, the research nurses, not the Trial Secretary, will collect the fatigue impact NRS (primary outcome) by phone, when they ring to arrange the face-to-face visit.

Table 2: Study assessments for patients (Intervention delivered weeks 1-6 and 14)

Week	**0[a,b]**		**6[c]**	**10**	**18**	**26[b]**	**52**	**78**	**104**
Event	**Visit**		**Post**	**Post**	**Post**	**Visit**	**Post**	**Post**	**Post**
Consent then allocate next study number from the centre's list	**X**								
Nurse-led questionnaires:									
Demographics	**X**								
Medications	**X**								
Travel costs	**X**								
Self-report questionnaire:									
Fatigue impact (BRAF-NRS Impact)	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Fatigue severity (BRAF-NRS Severity)	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Fatigue coping (BRAF-NRS Coping)	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Fatigue impact dimensions (BRAF-MDQ)	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Disability (MHAQ)	**X**		**X**			**X**	**X**	**X**	**X**
Disease activity (PDAS2) inc pain & global	**X**		**X**			**X**	**X**	**X**	**X**
Anxiety and Depression (HAD)	**X**		**X**			**X**	**X**	**X**	**X**
Sleep (Pittsburgh question)	**X**		**X**			**X**	**X**	**X**	**X**
Valued Life Activities (VLA)	**X**		**X**			**X**	**X**	**X**	**X**
Quality of life (EQ-5D-5L)	**X**		**X**			**X**	**X**	**X**	**X**
Helplessness (AHI)	**X**		**X**			**X**	**X**	**X**	**X**
Self-Efficacy (RASE)	**X**		**X**			**X**	**X**	**X**	**X**
Work Productivity (WPAI) and sick leave	**X**		**X**			**X**	**X**	**X**	**X**
1^{o} care appointments for RA& helpline	**X**		**X**			**X**	**X**	**X**	**X**
Social Support							**X**		**X**
Medications	**(by nurse)**		**X**			**X**	**X**	**X**	**X**
Satisfaction and acceptability						**X**			
DAS28: Joint count, VAS, blood for CRP	**X**					**X**			
Usual care booklet	**X**								
Inform GP by letter	**X**								
2^{o} care appointments for RA									
Research nurse via hospital computer	**X**					**X**	**X**	**X**	**X**

Request randomization from Bristol, then ring patients and inform them

[a] When 10-14 potential participants accrued, conduct their baseline visits over 2 weeks

[b] Research Nurse to collect BRAF-NRS Impact by phone when booking week visit

[c] Posted 2 days after week 6 CB session has been delivered to that cohort

5.7 Fidelity to RAFT during delivery (quality assurance): Fidelity will be monitored in a random session of each of the 4 courses run in each centre. An independent observer (Cheston, Professor of Mental Health with experience in teaching nurses CB approaches) will specifically look for CB approaches used (reflective questioning, group management, goal-setting with patient ownership), delivery of RAFT as planned (adherence to session plans) and use of RAFT materials (handouts, metaphors). These are recorded on a quality assurance template, developed in our pilot study,[41] as are unhelpful delivery styles (eg didactic teaching). If the monitor finds fidelity is weak, clinical supervision is given for the next session (Ambler), followed by a further independent observation, and those training needs/supervision costs reported in the study analysis. Unlike a pharmacological RCT, in a group CB intervention it is not possible for a rigid protocol to be adhered to in every session, as tutors will need to respond to the individual issues raised in each session by every different group of patients. Therefore these plans for fidelity evaluation are pragmatic and more helpful than insisting on and evaluating strict adherence to a rigid research protocol that cannot be used in the clinical situation

5.8 Qualitative evaluation of the impact on tutors of learning CB methods: After the end of course delivery, tutors will be invited to participate in a focus group and/or a one-to-one interview, led by an experienced qualitative researcher (Dures), who will explore their experiences of learning and using RAFT and CB approaches. For the focus groups, a guide of 4-6 neutral questions will be used to generate discussion, both negative and positive, and explore whether these approaches have altered clinicians' consultation practice outside of the intervention. Focus groups allow for discussion and reflection of a common experience, so that participants can confirm or challenge each other's experiences, helping to clarify their own thoughts and so provide a collective, consideration of the topic.[76]

For the one-to-one interviews, a semi-structured guide of 6-8 questions will be used to prompt the tutor to discuss the barriers and facilitators they encountered in learning and using CB approaches. While the focus groups will facilitate comparison across sites, one-to-one interviews are more likely to capture individual differences in tutors' experiences and are more appropriate for discussing sensitive topics.

6 Analysis

6.1 Clinical and social participation analysis: Analysis will be performed blind to allocated arm and will follow the rigorous, peer-reviewed approach used in our original RCT,[38] which reflects current recommendations.[77] Baseline characteristics will be described using means and SDs or numbers and percentages for continuous and categorical variables respectively. The primary intention-to-treat analysis will involve between-arm comparisons for fatigue impact (BRAF-NRS Impact) at 26 weeks, adjusted for respective baseline values. These analyses of covariance will be implemented using multivariable linear regression models. Standardised effect sizes for the primary outcome will be calculated (adjusted mean difference divided by pooled baseline SD), with >0.5 considered a clinically meaningful effect. Sensitivity analyses of primary outcome will be conducted by (i) additional adjustment for any variables displaying imbalance at baseline, (ii) fitting multi-level mixed effects models to investigate any clustering effect from delivery in groups and centres, and (iii) multiple imputation techniques to investigate the impact of missing data, based on 20 imputed datasets, with baseline fatigue severity, impact, pain and disease activity added to the imputation model as variables predictive of missingness.[78] Secondary outcomes will be analysed in the same way, including analysis of the 4 BRAF-MDQ fatigue subscales, including preliminary multivariable analysis of the effect of different attendance rates and patterns (to be defined as having received RAFT a patient must have attended session 1).

Further analyses using repeated measures mixed effects ANCOVA models will examine the effect of interventions over time by including up to 4 follow-up scores (26, 52, 78, 104 weeks) per participant for the primary outcome, adjusting for baseline scores. Convergence/divergence between trial arms over time will be investigated by including appropriate interaction terms in the model. Clustering effect of delivery will be again investigated by including CB group and centre identifiers as additional levels. It is possible that as CB patients have more theoretical opportunity to access clinicians, they might receive additional clinical care. This was not the case in the original trial[38] but we will examine (and, if necessary, adjust for) possible differences between arms for RA medication changes. All analyses will be conducted using the most current version of Stata. Where numbers allow, we will explore co-efficients of predictors of outcome.

6.2 Cost effectiveness analysis: Unit costs for NHS staff time to train for and deliver the intervention will be based on national estimates.[79] Actual expenses incurred for training materials, refreshments and staff travel will be recorded. The costs of medications, community, primary and secondary care during follow up will be based on national tariffs,[79-81] where available, supplemented by micro-costing or local estimates where necessary. Productivity costs due to RA and fatigue will be estimated based on average weekly earnings stratified by age.[82] Resource use will be combined with unit costs to estimate the incremental cost or savings of the group CB programme over the 2 year period. The primary analysis will be from the societal perspective, including productivity costs. Secondary analyses will restrict the perspective to NHS and personal social services costs.

EQ-5D-5L utility scores will be used to estimate Quality Adjusted Life Years (QALYs) over the 2 year period, adjusting for any imbalances in baseline scores.[83] Missing data on costs or QALYs will be multiply imputed as described in the previous section. Costs and outcomes occurring during the second year of follow up will be discounted in line with NICE guidance.[84] Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic,[85] which will indicate whether the group CB programme is cost-effective compared to NICE thresholds of £20,000–£30,000 per QALY gained. Uncertainty in the point estimate of cost per QALY will be quantified by using bootstrapping methods to calculate confidence intervals around the ICER and NMB. The probability that the group CB programme is cost-effective will be depicted using a cost effectiveness acceptability curve. One way sensitivity analyses will be used to judge the potential impact of other sources of uncertainty (e.g. the discount rate).

6.3 Qualitative analysis of tutor focus groups and interviews: An inductive thematic approach will be taken to analysis, with themes extracted that are grounded in the participants' data.[49] The focus group and interview data will be analysed separately, but using the same analytical approach and process. After reading and re-reading the focus group and interview transcripts, significant statements will be extracted, coded, explored for links, built into overarching themes, and exemplified by participants' quotations. A second qualitative researcher will independently analyse a sub-set of the transcripts and themes will be compared and agreed. The findings from the focus groups and the interviews will be integrated to provide a comprehensive account of tutors' experiences.

7 Projected outputs and dissemination

Any final, minor adjustments to the RAFT manual and training will be informed by the experiences of training the 7 tutor pairs, the observed practice runs, clinical supervision, fidelity monitoring, and the qualitative evaluation with the tutors. These will also inform the development of a trainer's guide for the local, trained CB Therapists who will provide training and supervision in future clinical practice. Like the RAFT programme, manual and training, the new trainer's guide will be aligned to QISMET standards.[55] The entire RAFT package (programme, manual, materials, training and trainer's guide) will be subject to copyright and an appropriate royalty-free licensing regimen to maintain integrity (see IP section 9).

Dissemination of knowledge to the clinical and academic community will initially be by three academic papers: the efficacy and cost-effectiveness of RAFT (target Annals Rheumatic Disease); the effects of training clinicians in CB approaches, and whether this changes their approach to other health care interactions with patients (target BMJ or Arthritis Care and Research); and the long-term effects of RAFT (target Rheumatology). Findings should stimulate research into RAFT as an intervention for fatigue in other long-term conditions; into delivery by patient tutor pairs, or a combined lay/professional pair; research into possible cognitive (rather than physical) fatigue management; and research into the application of this CB approach to self-management programmes for other symptoms (eg pain). Dissemination to the participants will be through a RAFT newsletter, and to the wider RA population through the National Rheumatoid Arthritis Society website and Newsletter, and posters in the participating rheumatology centres.

8 Impact on NHS care: Clinical engagement and roll-out

The findings should change NHS practice, either by the use of RAFT to improve patient outcomes directly, or by wider utilisation of CB approaches into healthcare consultations. After publication of the original RCT, 7 rheumatology teams across the UK, Canada, Finland and Denmark contacted the applicants, suggesting RAFT will be taken up widely. However, this needs to be pro-actively driven therefore targeted approaches will be used to change practice.

If RAFT is included in NICE guidelines, Clinical Commissioning Groups (CCGs) are required to take those recommendations in to consideration. We will therefore submit the 6 month efficacy and cost-effectiveness findings to the 3 yearly review of the NICE guidelines for the management of RA, and also to the (proposed) 2 yearly review of the British Society of Rheumatology RA guidelines (in 2015/16) followed by the two year findings to subsequent NICE and BSR reviews (in 2017/18). We will prepare information packs for CCGs (or whatever commissioning body/processes are in place in 2017) to be distributed upon publication of NICE or BSR guidelines. In addition, as NICE/BSR decisions and publications may incur a time-lag, we will approach the CCGs as soon as we have 6 month efficacy and cost-effectiveness data, initially contacting the CCGs in the 7 participating centres, as those units are ready to deliver RAFT immediately. All CB courses will finish 6 months before these data are available, thus there will be no contamination from early communication of findings. Commissioners have indicated they would find it useful to have this early information in order to evaluate it and potentially be ready to respond quickly once 2 year data are ready (personal communication, 10/7/12).

We will use Greenhalgh's approach to changing practice: 'Opinion leaders' who are considered a respected and knowledgeable authority on a topic by their community, increase the chance of innovations being put into practice.[86] The CI, Hewlett, is known internationally for her work on RA fatigue (evidenced by publications, national and international keynote lectures), and would therefore drive implementation of RAFT with Dures (Leverhulme Fellow evaluating existing training of rheumatology professionals in CB skills), who has been running rheumatology workshops on CB skills. RAFT taster sessions (see Road Shows below) will be used to engage clinicians to lead a change in their local practice (Greenhalgh's 'Change Champions').[86] The majority of Rheumatology Units have a specialist nurse, therefore the results and information about RAFT will be sent to the rheumatology specialist nurse in every NHS rheumatology unit in a concisely worded, glossy flyer (lengthy unsolicited materials tend to be discarded unread). This will also be distributed via the email alerts/electronic newsletters of the Royal College of Nursing Rheumatology Forum, and British Health Professionals in Rheumatology, which will capture the majority of UK rheumatology health professionals. The likelihood of innovations being taken up is increased by any inherent features that act as facilitators,[86] therefore the flyer will include RAFT facilitating features of advantage over current practice (efficacy, cost-effectiveness); fit with perceived need and current ways of working (supporting self-management); augmented support (detailed manual and training); and flexibility (individualised goal-setting, contextualised discussion of topics). In addition, the 2-sided flyer will include details of the Roadshows and website.

Road Shows: Road Shows will be held in the south and north of the UK, allowing representatives from 40 rheumatology teams to attend. To enhance attendance, registration will be free and funding for travel will be provided. The Road Shows will provide information on the RAFT programme, training and RCT findings (morning) and opportunities to practice general CB approaches and specific RAFT elements (afternoon). The afternoon 'taster sessions' will be based on the tutor training programme and will be fully participatory (Ambler, Hewlett and Dures and patient partners Robinson and Rooke).

Website: A RAFT website will be hosted by the CI's institution, UWE, which already hosts a BRAF scale website (http://www1.uwe.ac.uk/hls/research/healthandclinicalresearch/researchareas/longtermconditions/fatiguescales.aspx). The website will include details about RAFT, the study findings, quotations from participants and tutors, and links to papers, plus a facility to submit an expression of interest.

International conference symposia: Proposals will be submit for conference symposia/interactive workshops on RAFT for the main rheumatology conferences. The British Society for Rheumatology, European League Against Rheumatism and American College of Rheumatology (BSR, EULAR, ACR) conferences attract 3,000-20,000 rheumatologists, nurses, health professionals, patient organisations, and (at EULAR) patients. Hewlett, Dures and Ambler have previously delivered workshops on fatigue, and use of CB skills by rheumatology professionals at ACR (2011, 2012), BSR (2011, 2013) and EULAR (2013), several of which were oversubscribed.

Local implementation: The Bristol Research and Innovation Group for Health is a partnership of the two Universities and two NHS Trusts participating in this RCT, and aims to turn research into evidence-based practice through Health Integration Teams (HITs). Hewlett is co-chair of the Musculoskeletal HIT and leads the underpinning self-management theme, which also includes the wider team use of CB approaches. Local Trusts have agreed to implement HIT findings wherever possible.

9 Intellectual Property

The RAFT programme will be freely available to NHS clinical departments via a licensing regimen that will help ensure take-up whilst maintaining the material's integrity. The host institution, UHBristol, will own the IP and the applicants will work with the UWE Research, Business and Innovation Department's Technology Transfer Office (Prof Hewlett's employers) and NBT (Dr Ambler's employers) to create an appropriate royalty-free licence agreement for those wishing to deliver RAFT: clinicians will undertake not to change the materials, nor pass them on to a third party, to obtain training in the use of RAFT and clinical supervision from an appropriately CB-trained local professional, and audit their work against current QISMET standards annually.[55] As RAFT uses standard CB approaches, a CB therapist working within a Trust would have the knowledge and skills to train the local rheumatology team and provide the clinical supervision needed.

10 Timetable of investigation (Table 3)

2013											**Nov**	**Dec**
Ethics, R&D, site visits, recruit staff				X	X	X	X	X	X	X		
Recruitment											X	X
Training of tutors including Practice courses												T
Database and randomisation service set-up											X	X
2014	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**
Recruitment	X	X	X	X	X	X	X	X	X	X	X	X
Completion of training practice courses	P	P	P	P	P							
1st Courses start between May/July					1	1	1					
2nd Courses start between Sept/Nov									2	2	2	
1st Course 26w FU between Nov.Jan											1-26	1-26
Data entry			X	X	X	X	X	X	X	X	X	X
2015	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**
Recruitment	X	X	X	X	X	X	X	X	X			
1st course 26w FU between Nov/Jan	1-26											
3rd Courses start between Mar / May			3	3	3							
4th Courses start between Aug/Oct								4	4	4		
2nd Course 26w FU between Mar.May			2-26	2-26	2-26							
3rd Course 26w FU between Sept/Nov									3-26	3-26	3-26	
Data entry	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative study, CB skills paper											X	**X**
2016	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**
4th course 26w FU between Feb/Apr		4-26	4-26	4-26								
Data cleaning, analysis, 6 month paper				X	X	X	**X**	**X**				
Submit 6 month data to NICE/BSR/CCGs									X	X	X	
1st Course 104w FU between May/July					1-104	1-104	1-104					
2nd Course 104w FU between Sep/Nov									2-104	2-104	2-104	
Data entry	X	X	X	X	X	X	X	X	X	X	X	X
2017	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**
3rd Course 104w FU between Mar/May			3-104	3-104	3-104							
4th Course 104w FU between Aug/Oct								4-104	4-104	4-104		
Data entry	X	X	X	X	X	X	X	X	X	X		
Data cleaning, analysis, 2 yr FU paper										X	X	X
Roadshows, submit to NICE/BSR/CCGs												
2018	**Jan**	**Feb**	Mar	April								
Data cleaning, analysis, 2 yr FU paper	X	X	X									
Roadshows, submit to NICE/BSR/CCGs	X	X	X	X								

In the 6 months prior to starting in November 2013, ethics and R&D approvals will be obtained and the Trial Manager, Trial Secretary and research nurses appointed (see Table). The CI and Trial Manager will conduct site visits to set up each centre, check all research governance procedures are fulfilled (eg local site files, GCP

training) and that recruitment and study processes are understood so that recruitment can start in mid-November. At the training week (December 2nd), days 1-4 will comprise tutor training in RAFT, and on day 5 they will be joined by the research nurses and PIs, to explain study procedures and management, and practice the DAS28 joint evaluations. Tutors will then start their observed practice runs in January 2014 to complete the training. As soon as they have completed training, each centre will start randomising patients and running their 4 CB courses. The timing of the 4 CB courses is flexible, as shown in the table by the range of start dates, which will depend on each centre's recruitment rate/staff holidays. Course scheduling will be monitored in the monthly management meetings. All centres should have started their 4th course by October 2015. On completion of these the qualitative focus groups and interviews will be held with tutors, data analysed and the paper written. All 6 month primary endpoint data should be available by May 2016, followed by data cleaning, analysis and the effectiveness paper written. Two year data will be returned by October 2017, followed by the paper on persistence. Road Shows and dissemination will be held in the final months. Key milestones are ethics and R&D, sites set up and the training event held (December 2013); Practice courses completed (May 2014); 1st courses started (July 2014); 4th courses started (October 2015); Qualitative study analysed (April 2016); Primary outcome data analysed (Sept 2016) and 2 year analysis (March 2018); Submission to NICE, and Road Shows by April 2018.

11 Project management and research governance

This study will be conducted in accordance with the Research Governance Framework for Health and Social Care and Good Clinical Practice.

11.1 Day-to-day management: The project is managed and co-ordinated centrally, with all outcome assessments being sent out by and returned to Bristol thereby enabling careful monitoring of timelines and returns. The CI (Hewlett), Trial Manager (TBA) and Trial Secretary (Almeida) will manage the trial from the Academic Rheumatology Unit at the Bristol Royal Infirmary. BRTC co-applicants, collaborators, and local PI Kirwan are onsite or within a 5 minute walk. The Trial Manager will maintain the overall site documentation and a local study file for each site, liaise with all sites and with the BRTC randomisation service. They will discuss local progress and any concerns with each research nurse by phone at least monthly, and send a 6 monthly RAFT newsletter on study progress. The Trial Secretary will obtain primary outcome data by phone, post questionnaires and enter all data, with supervision from the Trial Manager. The CI will hold weekly business meetings with the Trial Manager and Trial Secretary to review trial progress against the monthly time-plan, including each centre's progress and needs. Minutes will be kept to ensure action points are dealt with and reviewed the following week. The CI will meet 3 monthly with University Hospitals Bristol Finance to review finances.

11.2 Trial Management Group (Core) (TMGC): A TMGC will manage the details and conduct of the trial. The TMGC comprises core co-applicants and support staff: CI (Hewlett), Trial Manager, Trial Secretary (Almeida), psychologists (Ambler, Dures), trialists (Pollock, Blair, Hollingworth), local PI (Kirwan) and research nurse, and patient partners (Robinson, Rooke). Initial meetings will be monthly, reducing to 2 monthly as the trial progresses, and 3 monthly after sites are closed down in year 3. Depending on the phase of the trial collaborators will be invited (eg to discuss database cleaning).

11.3 Trial Management Group (Wider) (TMGW): The TMGW is the wider group of co-applicants Hammond (clinical academic OT), and local PIs (Choy, Creamer, Viner, Green, Thompson, Hughes), who will join the TMGC at 6 monthly meetings (conference calling available) to review the wider perspective of the project, any local concerns, and the progress of the project against the predicted time-plan. If a local PI cannot be present, their research nurse or a tutor will attend.

11.4 Trial Steering Committee (TSC): A TSC comprising a Chair (trialist), rheumatologist, CB therapist, and statistician (all independent) and a patient will meet annually to advise the team, oversee adherence to research governance and the protocol, and review progress, patient safety and any proposed protocol amendments. Observers from the sponsoring institution (UH Bristol) and the main Research Network (WCLRN) may be invited at the discretion of the Chair. Meetings will be preceded by a written report from the CI on the progress of the trial (eg milestones reached, recruitment). A Data Monitoring and Ethics Committee will review and approve the statistical analysis plan and if necessary, review unblinded data for adverse events and whether it is necessary to discontinue the trial. As no data are collected until the 6 week intense intervention has been completed, monitoring here is to protect future participants. Sufficient data (18 or 26 weeks) will have

accumulated from courses 1 and 2, for interim analysis by an independent statistician to be reported to the DMEC prior to the start of courses 3 and 4.

11.5 Trial sponsorship, registration and ethics: The trial sponsor will be University Hospitals Bristol NHS Foundation Trust. The trial will be registered with ISRCTN, and the UKCRN portfolio. Monthly accrual data will be uploaded for UKRCN, and local R&D systems where operational. The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval. Permission will be sought to recruit 5-6 patients in each centre for the practice course (using the RCT criteria, but patients are not randomised and there is no data collection). Thereafter patients will be recruited for the RCT. Patients will receive an information sheet giving full study details and those who agree to participate will be invited for a baseline visit, at which the local research nurse, GCP trained, will ensure they understand the information, and take written informed consent before performing the baseline assessments. For the CI, University ethics approval (UWE) will also be required. Each centre will require their own local Trust R&D approval, including a Site Specific Assessment, obtained via the Central Permissions Service and IRAS as this is a UKCRN Portfolio study. The Trial Manager will manage and monitor this and will maintain a central copy of all site approvals, and centre study files.

Data will be collected and retained in accordance with the Data Protection Act 1998. All data will be anonymised at the point of data entry in Bristol, and all questionnaires and patient identifiable data kept in locked filing cabinets in the Academic Rheumatology Unit at the Bristol Royal Infirmary. Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of five years following the end of the study. Password-protected computerised data will be stored on University of Bristol computers in the Academic Rheumatology Unit at the Bristol Royal Infirmary, and are backed-up automatically on the mainframe every night. The sponsors will audit the trial in accordance with Trust policy. All trial related documents will be made available on request for monitoring and audit by UH Bristol and the relevant Research Ethics Committee.

Based on the original RCT, we do not anticipate any serious adverse events (SAE) to occur related to the intervention, but any events will be recorded in accordance with UH Bristol's Research Related Adverse Event Reporting Policy and reported to the CI, R&D departments, ethics committee, and TSC as appropriate. It is possible that tutors might become aware of a patient's significant underlying anxiety, depression, psychological/behavioural difficulties, or uncontrolled RA inflammation. As they are clinicians already providing a rheumatology service they will be able to refer these patients for appropriate support (eg rheumatologist, GP, psychologist). These few instances will be recorded and analysed, but not considered SAE. In the original RCT only 2 CB participants were offered further psychological support at the end of their fatigue course.[38] This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.6 Risks to the proposed research and plans to protect against them:

Slow recruitment: Projected recruitment rates are based on our original RCT and our local PIs are all senior rheumatologists with RCT experience, with research time funded to facilitate recruitment. A research nurse in each centre will target RA clinics and if appropriate, arrange for a mailshot. We will display posters in RA clinics, Physiotherapy and OT departments. Recruitment will be reviewed against projected targets at the monthly TMGC meetings. There is flexibility for centres in organising course dates to fit recruitment.

Inability to run courses: Our project plan assumes 7 centres delivering 4 courses with an average 6 participants. The flexibility in the number of participants that could attend each course (5-7) gives a range of 140-196 CB participants for a required sample size of 150/arm, thus providing contingency if some of the centres cannot run all 4 courses (eg due to tutor sickness). Numbers attending CB courses will be reviewed against projected targets at the monthly TMGC meetings.

High attrition: We anticipate collecting 80% of data for the primary outcome at 26 weeks. We have allowed capacity for up to 50% attrition at 2 years but aim to have substantially less than that by devoting more time to collecting follow-up data in all patients originally randomised, and by collecting all primary data (fatigue impact NRS) by telephone, plus a check phone call after 2 weeks if main questionnaires have not been returned. This

personal contact should also enhance overall questionnaire package completions. The possibility of one of the centres running an extra cohort (and thus maximising the number of participants recruited) will be considered after reviewing recruitment for the 28 planned cohorts.

Tutors requiring additional support to deliver RAFT: In the RAFT pilot the tutors felt confident to deliver the course after the training, which included an observed practice run.[2] Tutors are experienced rheumatology clinicians, accustomed to learning new skills, and as part of normal clinical supervision, one session in alternate courses will be observed and debriefing given (Ambler, Knops). If any additional clinical supervision is required it will be recorded in the staff logs and health economic evaluation as this reflects a training need and service cost.

12 Patient and Public Involvement

Patient involvement has been extensive in the development of this proposal and will continue in the RCT. Two patient research partners[87] (Robinson, Rooke) were participants in the original RCT, then became research partners on the project to manualise and pilot RAFT. They provided significant input into advising the tutors, clarifying the patient handouts, and the layout of the RAFT manual.[41] They are co-applicants on the grant, attended the team meetings developing the proposal and played a particular part in elucidating the appropriate outcomes to assess, and the scales to do so. They contributed to the lay abstract, and obtained review by a larger lay group. During the RCT they are part of the TMGC and will provide the patient perspective into the questionnaire packages, information sheets, practical arrangements and their acceptability to potential participants and will help deliver tutor training. Hewlett and Kirwan have collaborated with patient research partners on all their research studies and PhD supervisory teams since 2005,[87] have over 20 partners in the department, and provide annual training days.

13 Expertise

Team expertise and roles: The team of co-applicants has been brought together to cover the range of skills and expertise required for this trial and includes members of the Bristol Randomised Trials Collaboration (BRTC). The CI and Lead Applicant (Hewlett) is an academic nurse with a clinical rheumatology practice supporting patients with psychological distress or fatigue, using CB approaches, and was CI on the original RCT, RAFT manualisation and pilot. As CI, she takes overall responsibility for the trial and oversees its management and will contribute to tutor training and monitoring fidelity to the RAFT programme. Ambler (clinical psychologist) delivered the original CBT intervention, and supported the RAFT manualisation and pilot; he will be responsible for tutor training, including observation of the practice courses, and then clinical supervision thereafter. Pollock (trialist on the original RCT) and Blair (statistician, BRTC) are providing trial design and supervision expertise, and supervision of the analyses. Hollingworth (health economist) will be responsible for economic evaluation and analyses. Dures (psychologist and qualitative researcher) analysed the original RCT qualitative data, managed the RAFT pilot study, has had RCT training; and will conduct the qualitative study with tutors at the end of the trial. Hammond (academic OT, CB therapist) has experience of training OTs to deliver a manualised joint protection programme to RA patients using CB approaches, and advised on trial design in the original RCT; she will provide pragmatic advice on trials using CB interventions delivered by clinical teams, and recruitment strategies. Patient research partners Robinson and Rooke were participants in our original RCT, and provided input as research partners into the RAFT pilot; they will provide a patient perspective on recruitment processes, questionnaires, patient information, contribute to tutor training, help interpret the findings in patient terms, and advise on dissemination. Each of our Principal Investigators in the participating rheumatology centres is a Co-applicant and will take responsibility for ensuring the release of clinical staff to be tutors and conduct the RAFT courses, and facilitating timely recruitment. Kirwan (Bristol) and Choy (Cardiff) are academic rheumatologists and trialists with extensive RCT experience, and are providing trial design advice. Viner (Torbay), Green (Weston), Thompson (Poole) and Hughes (Chertsey) are all clinical rheumatologists accustomed to supporting RCTs, as is Creamer (NBT) who also recruited patients for our original RCT.

Collaborators: Carmichael (randomisation service/database manager, BRTC) will provide the randomisation service, set-up the database, and clean the database prior to analyses. Knops (OT, NBT Pain Management) co-led the CB courses in the original RCT, and will support tutor training, observation of practice runs, and fidelity monitoring. Thorn (BRTC) will conduct health economic analysis supervised by Hollingworth. Simons (Project Management Advisor, BRTC) will provide set-up advice and support for approvals. A statistician at BRTC (to be appointed) will analyse the RCT data, supported by Pollock and Blair.

Previous team collaboration on fatigue research: Members of this team have been collaborating on RA fatigue research for some years, for which they have an international reputation. The lead applicant (Hewlett) identified that people with RA consider fatigue an important issue that is ignored by professionals.[7] Further research (Hewlett, Kirwan, Choy) led to international consensus that fatigue must now be measured in the core set of disease outcome measures in all RA studies.[18] We have explored fatigue mechanisms (Choy),[23] are conducting Cochrane reviews of fatigue interventions (Kirwan, Choy, Hewlett, Pollock),[19,20,28] and have developed the conceptual RA fatigue model that underpins this research (Hewlett, Choy, Dures, Kirwan).[25] The team developed and validated the Bristol RA Fatigue Scales (Hewlett, Kirwan, Dures).[46,47,62] We have expertise in psychological interventions (Ambler, Hammond, Hewlett, Knops),[37,38], and ongoing research into current UK psychological support for RA patients and team training needs (Dures, Ambler, Hewlett). A natural development from this cohesive body of research was the original CBT intervention for RA fatigue (Hewlett, Ambler, Dures, Hammond, Knops, Pollock),[38,39,41] leading to this proposal for a more widely deliverable format. The Bristol Randomised Trials Collaboration has expertise in trial design, statistics and health economics (Blair, Hollingworth).

14 Potential benefits to the NHS

RA fatigue affects 70% of patients and reduces quality of life substantially.[5,14] 76% of UK rheumatology nurses say that fatigue is raised by RA patients during a first appointment, implying a lot of NHS time may be spent helping patients manage fatigue.[9] People with RA identify fatigue as the main reason for work loss, which affects 66% of working people with RA each year, with 22% becoming work disabled within 5 years, and work production loss over £650 million.[10,13] This proposal therefore includes a full health economic analysis of costs and savings.

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16 Flow diagram