National Institute for Health and Care Excellence

Final

Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: diagnosis and management

[G] Evidence reviews for the non-pharmacological management of ME/CFS

NICE guideline NG206

Evidence reviews underpinning recommendations and research recommendations in the NICE guideline

October 2021

Final

These evidence reviews were developed by the National Guideline Centre

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Introduction

There is no known cure for ME/CFS and non-pharmacological management strategies have been developed. Previous guidance has recommended the use of Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) but these have been controversial. The use of CBT and GET has been strongly criticised by people with ME/CFS on the grounds that their use is based on a flawed model of causation involving abnormal beliefs and behaviours, and deconditioning. Some people with ME/CFS have reported worsening of symptoms with GET and no benefit from CBT. Although research on pacing is sparse, this method of activity management is preferred by many people with ME/CFS. Interventions such as counselling, meditation and yoga are sometimes used to improve mobility and/or general wellbeing. Evidence here is also lacking.

The committee evaluated evidence from clinical effectiveness studies and patient experience from a wide range of non-pharmacological management strategies to inform the recommendation in these areas.

1 Non-Pharmacological interventions

1.1 Review question

What is the clinical and cost effectiveness of non-pharmacological interventions for people with ME/CFS?

1.1.1 Summary of the protocol

For full details see the review protocol in appendices.

Table 1: PICO characteristics of review question

Population	Adults, children and young people who are diagnosed as having ME/CFS.
Interventions	Any non-pharmacological treatments including, but not restricted to: • Self-management • Aids / adaptations / OT • Occupational/school advice • Behavioural/ Psychological support/ interventions • Exercise interventions • rTMS (repetitive transcranial magnetic stimulation) • Compression socks • Hyperbaric O2 • Lifestyle advice • Relaxation techniques • Dietary supplementation • Dietary strategies • Sleep interventions • Pain management • Complementary and alternative therapies Combinations of treatments (including combinations with pharmacological treatments) are allowed.
Comparisons	• Each other • No treatment / wait list control / usual care • Sham / placebo / attention control
Outcomes	Longest follow-up available. CRITICAL OUTCOMES: • Mortality • Quality of life • General symptoms • Fatigue/fatigability • Physical functioning • Cognitive function • Psychological status • Sleep quality • Treatment-related adverse effects • Pain • Activity levels • Exercise performance measures

	• Return to school / work Any validated scales will be considered. IMPORTANT OUTCOMES: • Care needs • Impact on families and carers
Study design	RCTs and systematic reviews of RCTs. Cross-over RCTs will be considered if the washout period is deemed to be appropriate.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3 Effectiveness evidence

1.1.3.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of non-pharmacological interventions for adults, children and young people who are diagnosed as having ME/CFS.

Fifty-five studies (seventy four papers) were included in the review [2, 8, 12-18, 20-24, 26, 27, 29-33, 35, 37-43, 46, 47, 51, 52, 55, 57, 58, 60-65, 67, 72, 74, 78-80, 83, 84, 86-89, 91, 93-100, 102, 104-113] Table 20 below. Evidence from these studies is summarised in the clinical evidence summary below.

A variety of non-pharmacological interventions were identified; self-management,[31, 47, 72, 107, 112] behavioural/psychological support including cognitive behavioural therapy,[2, 18, 26, 39, 42, 46, 52, 60, 63, 64, 78, 79, 84, 87, 95, 97, 107, 109] cognitive therapy,[42] counselling,[79] buddy/mentor programmes,[41, 91] the Lightning Process,[24] pragmatic/other rehabilitation programmes,[97, 102] heart rate variability biofeedback,[110] mindfulness,[22, 80, 88] group therapy,[86] exercise interventions including GET,[12, 21, 33, 57, 74, 78, 99, 104, 107, 110] physical rehabilitation,[35] anaerobic activity therapy,[42] intermittent exercise,[12] orthostatic training,[89] yoga[65] and qigong,[30] dietary supplementation,[15, 17, 32, 55, 67, 94, 111] dietary strategies[37] and complementary therapies.[38, 43, 58, 106, 113]

The majority of the interventions were compared to usual care, which differed between the studies. The study populations were mainly adults. The severity of ME/CFS was mixed or unclear in the majority of the studies.

1.1.3.2 Excluded studies

Three potentially relevant Cochrane reviews were identified but were not included in this review due to differences in the review protocols and methodologies.

One Cochrane review of exercise interventions (Larun 2017[48]) pooled all exercise therapies irrespective of the type of exercise therapy, and also pooled all control arms considered 'passive' (including treatment as usual, relaxation and flexibility). We did not consider this methodology appropriate for decision-making. Additionally, the review did not include all

critical outcomes specified in this review protocol, including cognitive function, activity levels, return to school/work, exercise performance measures and mortality.

One Cochrane review of cognitive behavioural therapy (Price 2008[75]) included study populations where not all participants had ME/CFS. Additionally, the review did not include all critical outcomes specified in this review protocol, including cognitive function, pain, sleep quality, activity levels, exercise performance and mortality.

Another Cochrane review of Chinese medicinal herbs (Adams 2009[1]), which did not include any studies and which was later withdrawn, included people with idiopathic chronic fatigue in the review protocol.

All included studies within these reviews were cross-checked for eligibility for inclusion in this review.

See the excluded studies list in appendices.

1.1.4 Summary of studies included in the effectiveness evidence

See Appendix G in Evidence review H for details on the PEM reanalysis.

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Al-Haggar 2006[2]	CBT + biofeedback: biofeedback machines gave information about internal body functions to direct the progress of CBT; training in relaxation, identifying circumstances that trigger symptoms, avoiding or coping with symptoms, changing habits and self-control. 40-60 sessions once/twice a week then tapered gradually depending on fatigue severity. Delivered at a specifically designed CFS clinic. Duration: 18 months Versus Conservative and symptomatic treatment: Psychotherapists were responsible for arrangement and formulation of all types of therapy; sometimes they consult family doctors for medical treatment of isolated systemic symptoms. No psychotherapeutic drugs were used.	N=159 people with CFS diagnosed according to 1994 CDC criteria; evaluation included detailed history taking, clinical examination and routine laboratory investigations; functional impairment of checklist individual strength >40% Strata details: children and young people (age range 10-14); severity mixed or unclear	Fatigue/fatigability (Fatigue Assessment Scale %) Return to school or work (school attendance hours/month) at 18 months	Conducted in Egypt PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Broadbent 2016[12] 2017[13] & 2013[14]	Graded exercise therapy using spin cycle ergometer, 3x per week. All sessions supervised by accredited exercise physiologist and postgraduate clinical exercise physiology students. Workloads were determined from the baseline VO2 peak cycle test for each participant. Each exercise session consistent of a 5-min gentle warm-up of unloaded cycling,	N=24 people with CFS (1994 CDC criteria, diagnosed by their own medical practitioner); mean time since diagnosis (SD): 2.9 (2.6) years Strata details: adults (mean age (SD): 50.9 (10)); baseline self-reported fatigue severity scores	**Exercise performance** VO_2peak (ml/kg/min) Peak power (W) VE peak (not defined but probably peak expiratory	Conducted in Australia Differences in baseline fatigue severity scores may indicate different disease severity and may have influenced scores in the examined outcomes.

Study	Intervention and comparison	Population	Outcomes	Comments
	initially followed by a 10- to 15-min block of GE (load equivalent to 50% VO2peak, RPE 3). Recommended cadence was between 50 and 70 rpm. Exercise sessions were progressed by increasing the duration of the session only as tolerated for each participant. The workload was not increased until participants had achieved three consecutive exercise sessions of 30 min in total with no increase in symptoms, and the increase was 10% of the current workload. If participants reported any increase in fatigue or other symptoms during post-exercise, the exercise intensity was reduced until participants felt able to manage progression. Versus Intermittent exercise using a spin cycle ergometer, 3x per week. All sessions supervised by an accredited exercise physiologist and postgraduate clinical exercise physiology students. The workloads were determined from the baseline VO2 peak cycle test for each participant. Each exercise session consistent of a 5-min gentle warm-up of unloaded cycling, initially followed by a 10- to 15-min block of IE of 1 minute of moderate intensity cycling (60% VO2peak, RPE 4-5) alternated with 1 minute of unloaded or very low-intensity cycling (30% VO2peak, RPE 1-2). Recommended cadence was between 50 and 70 rpm. Exercise sessions were progressed by increasing the duration of the session only as tolerated for each participant. The workload was not increased until participants had achieved three consecutive exercise sessions of 30 min in total with no increase in symptoms, and the increase was	(fatigue severity scale) ranged between 15.8% (very low) to 100% (severe); mean (SD) baseline self-reported fatigue severity: Graded exercise 84.5% (16.6%); Intermittent exercise: 71.6% (23.7%); Usual care: 85.1% (10.8%); all indicating high fatigue severity	flow i.e. maximum speed expiration) Elapsed test time (min) Modified Borg scale (rated perceived exertion) Measured during exercise test, 12 weeks post intervention	ITT analysis n=8 in each group; missing/incomplete data not reported; potentially not enough power to detect a difference/clinical effect. Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: resting HR, resting sBP/dBP, respiratory exchange ratio (RERpeak), peak HR, Peak sBP/dBP. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]

Study	Intervention and comparison	Population	Outcomes	Comments
	10% of the current workload. If participants reported any increase in fatigue or other symptoms during post-exercise, the exercise intensity was reduced until participants felt able to manage progression. Versus Standard care - Participants were asked to follow the advice of their medical practitioner (rest and maintaining activity for daily activities) and not engage in any other physical activity during the study. 12 weeks			
Brouwers 2002[15]	Baseline parameters were assessed in weeks 1 and 2. Participants then received the supplement or placebo for the next 10 weeks. Nutritional poly nutrient supplement (125ml) containing several vitamins, minerals and coenzymes, specifically developed to have a high antioxidative capacity, twice daily for 10 weeks Versus Identical appearing placebo (125ml) twice daily for 10 weeks	N=53 people with CFS, diagnosed according to 1994 CDC criteria. Participants were recruited from a general internal medicine database which consisted of clinically diagnosed CFS patients. Strata details: adults; severity mixed or unclear (CIS-fatigue ≥40 and SIP8-total ≥750)	General symptom scales (Sickness Impact Profile-8; self-reported improvement) Fatigue (Checklist Individual Strength fatigue severity sub scale) Activity level (accelerometer) Adverse events (nausea) at 12 weeks	Conducted in the Netherlands Other outcomes not extracted: - CDC checklist (patients indicated which symptoms were present in the previous 6 months and mean number of symptoms reported. Not a validated 'general symptom scale'. - Daily fatigue levels (patients rated the intensity of their fatigue during a two-week period in a complaint diary. They rated the

Study	Intervention and comparison	Population	Outcomes	Comments
				Daily Observed Fatigue (DOF) four times a day on a scale of 0 (no fatigue) to 4 (severely fatigued). Not a validated measure of fatigue. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Castro-Marrero 2015[16] & 2016[17]	Coenzyme Q10 plus nicotinamide adenine dinucleotide in enteric-coated tablets (50 mg of CoQ10 and 5 mg of NADH) and excipients (20 mg of phosphatidylserine and 40 mg of vitamin C), two tablets twice daily for 8 weeks Versus Identical appearing enteric coated tablets without active ingredients and containing only excipients, two tablets twice daily for 8 weeks	N=80 people with CFS, diagnosed according to 1994 CDC criteria. Participants were enrolled from an outpatient CFS clinical unit. Strata details: adults; severity mixed or unclear	Fatigue (Fatigue Index Scale) Sleep (Global Pittsburgh Sleep Quality Index) Pain (McGill Pain Questionnaire) Adverse events Exercise performance measure (VO2 max, workload in km/h, Borg	Conducted in Spain All female participants. Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: HR, pulmonary carbon dioxide output, respiratory quotient, BP, PEM reporting: the percentage of

Study	Intervention and comparison	Population	Outcomes	Comments
			scale of perceived exertion) at 8 weeks	participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Chalder 2010[18] & Lloyd 2012[51]	Family focused CBT: 13 x 1-h sessions every 2 weeks, involving encouraging balance between activity and rest; gradually increasing activities; establishing a sleep routine; addressing beliefs such as fear, high self-expectations and all-or-nothing thinking; encouraging the family to express their own views about the illness and agreeing a way forward and paying attention to relapse prevention. Delivered by two trained and experienced cognitive behavioural psychotherapists. Versus Psycho-education: 4 sessions over a 6-month period. Content similar to CBT, but mode of delivery was didactic. Involved discussion, information giving and problem solving but specific homework assignments and cognitive restructuring not included. Families were not given a manual. Both groups included close liaison with relevant school teachers and home tutors. Key issues	N=63 people with CFS fulfilling either the Oxford or 1994 CDC criteria; participants were investigated by a paediatrician, prior to referral, to exclude alternative causes for their fatigue. A clinical assessment involving all members of the family took place to establish whether the adolescent had CFS/ME according to either the CDC or Oxford criteria. Strata details: children and young people (age range 11-18); severity mixed or unclear	<u>At 24 months:</u> General symptom scales (self-reported global improvement in fatigue and disability; Strengths and Difficulties Questionnaire) Fatigue (Chalder Fatigue Scale) Physical functioning (SF36 physical functioning) <u>At 6 months:</u> Treatment related adverse events (serious adverse events)	Conducted in UK Work and social adjustment scale reported as mean SD at 6 months and median IQR at 24 months – both extracted, but only 6-month outcome analysed. School attendance was only reported as author-dichotomised data at 12 and 24 months, so 6-month data extracted. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC/Oxford criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	were: endorsement of the reality of the condition, negotiating a graded return to school and for some reducing the number of subjects. In some cases repeat years were negotiated. Anxieties about reintegrating with peer groups were addressed and some adolescents were supported in changing academic institutions.		Return to school/work (% school attendance; Work and Social Adjustment Scale)	used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Clark 2016[20] & 2017[21] (GETSET trial)	Graded exercise therapy (n=107) – Self-help booklet describing a 6-step programme of graded exercise self-management, based on the approach of GET developed for the PACE trial and NICE recommendations. Six steps: stabilising a daily routine, starting regular stretching, deciding on a physical activity goal and choosing a type of activity with which to start, setting a physical activity baseline, increasing the duration of physical activity and finally the intensity. If symptoms increased after an incremental change in activity, participants were advised to maintain activity at the same level until symptoms had settled, before considering another incremental increase. In the first 30 minute session (face-to-face, by Skype or by phone), a physiotherapist provided guidance on following the booklet and answered any questions. Up to 3 further 20 minute appointments by skype/telephone were offered over 8 weeks by 2 experienced physiotherapists who were trained to support participants in using the booklet, but explicitly told not to provide therapy. Physiotherapists inquired about progress, answered questions, with a focus on moving forward to the next step, recognised achievements and provided feedback, with the	N=211 adults with CFS (NICE 2007 criteria); participants were recruited from secondary care clinics for CFS and had a full medical assessment (history, physical and mental state examination, laboratory tests) to rule out alternate diagnoses. Strata details: adults; severity mixed or unclear (mean age (SD): GET 38.1(11.1); control 38.7 (12.7)).	General symptom scales (Clinical global impression change in CFS and overall health: positive vs negative and minimum) Fatigue (Chalder fatigue questionnaire) Physical functioning (SF-36 physical function) Psychological status (Hospital anxiety and depression scale) Adverse events (Non-serious adverse events, Serious adverse events, Serious adverse reactions) Activity levels (International Physical activity questionnaire-high vs low/moderate)	Conducted in the UK Dichotomous reporting of continuous outcomes not extracted (improvement/deterioration of from baseline in fatigue and physical functioning scales) not extracted due to the high risk of bias associated with author-dichotomisation of continuous data. The continuous data reported for these outcomes have been extracted. PEM reporting: Only participants meeting the NICE 2007 criteria were included (has PEM as a compulsory feature).

Study	Intervention and comparison	Population	Outcomes	Comments
	aim of increasing motivation and self-efficacy. A therapy leader trained the two physiotherapists until they were deemed competent and then provided regular individual supervision. Physiotherapists followed a manual and all participant guidance sessions were audio-recorded for supervision, feedback, and monitoring of treatment integrity. If a participant could not be contacted by telephone or Skype, an email was sent to re-engage them. Participants also had at least one specialist medical care consultation as per control group. Versus Standard medical care (n=104) – Before randomisation, all patients had at least one specialist medical care consultation, delivered by doctors with specialist experience in chronic fatigue syndrome. SMC could involve prescriptions or advice regarding medication, as indicated for symptoms or comorbid conditions such as insomnia, pain, or depressive illness. Although not routinely scheduled during the trial, further SMC sessions were available after randomisation for patients who required it, but it was not a standardised intervention. 8 weeks		Return to school or work (Work and social adjustment scale) at 12 weeks (4 weeks post-intervention)	
Collinge 1998[22]	Combined mindfulness and medical qigong group intervention – 2 hrs/week. Instruction and guided practice of two techniques: mindfulness meditation (based on traditional Buddhist practice) and medical qigong. Participants were partnered for encouragement and were encouraged to share experience in group	N=70 people with CFS diagnosed by a physician and meeting 1994 CDC criteria and no major medical conditions; independently confirmed by subjects' physician	Quality of life (SF36 health transition score – improvement) at 12 months	Conducted in the USA PEM reporting: the percentage of participants with PEM was not reported.Serious

Study	Intervention and comparison	Population	Outcomes	Comments
	discussion, with a focus on integrating self-healing practices into daily life. Not clear who delivered intervention. Duration 9 weeks. Versus Usual care (no details)	Strata details: adults (age range of participants 27-61 yrs); severity mixed or unclear (estimated global functioning level of ≤75%)		population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
Crawley 2018[24], Crawley 2013[23] & Anon 2019[62] (SMILE Trial)	Specialist medical care + Lightning Process: 3 x 4-hour group sessions on consecutive days. Theory session with taught elements on the stress response, mind - body interaction, and how thought processes can be helpful or negative, followed by group discussion. In practical sessions, participants identified goals, were given different cognitive strategies and asked to identify a goal to attempt at home. Offered at least two follow-up phone calls with an LP practitioner. Versus Specialist medical care: focused on improving sleep and using activity management. Sessions delivered by doctors, psychologists, physiotherapists and occupational therapists in family-based rehabilitation consultations. Number and timing of sessions dependant on individual needs and goals. Those with significant anxiety or low mood were offered CBT. Participants could choose physiotherapist-delivered graded exercise therapy, which focuses on an exercise programme rather than other activities.	N=100 people with CFS/ME diagnosed after a thorough assessment which included screening for other disorders associated with fatigue (NICE 2007 criteria). Strata details: children and young people (age 12-18 years); moderate (those too severely affected to attend hospital appointments were excluded)	Fatigue/fatigability (Chalder Fatigue Scale) Physical functioning (SF36 physical function) Psychological status (Spence Children's Anxiety Scale, Hospital Anxiety and Depression Scale) Pain (Visual Analogue Scale) Return to school/work (school/college attendance in the previous week) Adverse events (Serious adverse events attributable to study interventions) at 12 months	Conducted in UK. Outcomes reported at 6 months and 12 months, but only 12-month data extracted as this was the longest follow-up time point that data was available (as per review protocol). PEM reporting: Participants diagnosed according to NICE 2007 guidelines (has PEM as a compulsory feature).
Deale 1997[26] & Deale 2001[27]	CBT: Presenting problems were assessed, and patients kept diaries recording hourly details of activity, rest, and fatigue. Schedule of planned, consistent, graded activity and rest was agreed. Activity and rest divided into small, manageable portions spread across the day and patients encouraged to persevere with targets and not to reduce them on a bad day or exceed them on a	N=60 people diagnosed with CFS according to the Oxford criteria and the 1991 CDC criteria (Schluederberg 1992); patients received a standardized assessment interview with a consultant psychiatrist experienced in chronic fatigue	At 5 years: General symptom scales (Self-reported global improvement of much better or very much better)	Conducted in the UK 2001 paper is a 5 year follow up; MOS, fatigue questionnaire and general health questionnaire are reported as dichotomous outcomes

Study	Intervention and comparison	Population	Outcomes	Comments
	good day. Once a structured schedule was established, activity gradually increased and rest reduced, step by step as tolerance developed. A sleep routine was established. Cognitive strategies - unhelpful or distressing thoughts were recorded and, in discussion and as homework, participants practiced generating alternatives. Final sessions involved strategies for dealing with setbacks and "action plans". Duration 4-6 months Versus Relaxation: same session structure - first three sessions involved engagement, rationale giving, information gathering, and diary keeping. No advice about scheduling activity, reducing rest, or altering sleep patterns was given. Relaxation techniques were adapted from applied relaxation training. Progressive muscle relaxation, visualization, and rapid relaxation skills were taught during the 10 treatment sessions and were practiced twice daily as homework. Duration 4-6 months	syndrome and a full history was taken Strata details: adults; severity mixed or unclear	Return to school / work (full or part-time employment) At 6 months: Fatigue (Fatigue problem rating; Chalder fatigue questionnaire) Physical functioning (SF-36 physical functioning scale) Psychological status (Beck Depression Inventory; General health questionnaire 12 item) Return to school / work (Work and Social Adjustment Scale)	(no. with score > author defined cut-off) – not extracted. Self-reported global improvement scores were reported at 6 months and 5 years; Only 5-year data analysed as this was the longest follow-up time point available (as per review protocol). Recovery rates and relapses also reported but not in review protocol. PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1991 CDC/Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Dybwad 2007[30]	Qigong (n=15) - Qigong exercises once a week with a certified instructor during the 6 months intervention period. Participants performed	N=31 people with CFS (1994 CDC criteria); diagnosed by a	Quality of Life (SF36)	Conducted in Norway

Study	Intervention and comparison	Population	Outcomes	Comments
	Qigong exercises for two hours a week. Each session started with 30 min group session on simple principles of anatomy and physiology followed by 1 hour of Qigong. Qigong training consisted of simple exercises containing stretches, rotations and diagonal movements. The exercise was gradually progresses to more complex movements. The last 30 minutes were left to breathing exercises, relaxation and meditation as well as non-structured conversation between the participants. Versus No treatment (n=16) 6 months	medical doctor experienced with the CFS. Strata details: adults (mean age (SD): 44.3 (12.8) years); severity mixed or unclear; average years since symptom onset (SD): 8.1 (7.3)	Fatigue (Fatigue severity scale) Exercise performance (VO_2 max (ml/kg/min), Max work-load (Watt): maximal resistance on bicycle ergometer the patient was able to manage, Borg scale – rating of perceived exertion) at 6 months	Mean age and male/female ratio reported within text (36 years, range: 17-62; 5/27) differs from what is reported in demographics table; the latter has been extracted. Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: max HR, lactate threshold, respiratory exchange ratio. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Friedberg 2016[31]	2 fatigue self-management programs with slight differences (as below). They involved no face-to-face visits or clinical contacts with an	N= 137 people with CFS, meeting 1994 CDC criteria.	Fatigue (Fatigue severity scale)	2 self-management programmes combined for analysis (fatigue

Study	Intervention and comparison	Population	Outcomes	Comments
	interventionist. The program (delivered by booklet and audio CDs) educated the participant about diagnosis, possible causal factors in CFS; stress factors and behaviours that play a role in disturbed sleep patterns, post-exertional symptoms, and push-crash activity cycles. Persistent fatigue was explained as a symptoms associated with doing too much or too little. Optimal self-management intended to provide healthy balance between mental and physical exertion and rest. Daily diary used to identify baseline activities, symptoms, stress levels. Self-management text showed participants how to identify unhelpful behaviours and beliefs about illness followed by the development of more useful cognitive and behavioural coping strategies. Program encouraged individualised self-scheduling of home-based assignments, sleep-rest assignments and coping skills. The final topic was post-intervention planning for maintenance of new skills. Duration: 3 months 1. Fatigue self-management with actigraphs and web diaries (FSM:ACT). Participants received a 56 page self-management booklet and 2 audio CDs that duplicated the booklet. A relaxation audio CD was also included. Daily online web diaries were assigned to monitor fatigue and track compliance with the program. Actigraphs were worn 24/7 for 1 week at baseline, and at 3 month and 12 month follow-ups. Actigraphs were used for research purposes, and not to assist the intervention. Duration: 3 months Versus	Adults (age 18-65); severe (study author reports participants were severely affected based on SF-36 PF and fatigues scores at baseline)	Physical functioning (SF-36 physical functioning subscale) Psychological status (Beck depression inventory 2; Beck anxiety inventory) at 12 months	self-management programmes 1 & 2 versus usual care). PEM reporting: 87.8% of participants had PEM (68.7% lasting >24 hours, 19.1% lasting <24 hours); 12.2% had no PEM. Serious population indirectness – 1994 CDC criteria used; PESE is not a compulsory feature [original analysis]; <95% of participants had PEM [PEM reanalysis]. Actigraph, step counter, and 6 minute walk test results reported only as not statistically significant/p-values. Outcomes reported at 3 months and 12 months, but only 12-month data extracted as this was the longest follow-up time point that data was available (as per review protocol).

Study	Intervention and comparison	Population	Outcomes	Comments
	2. Fatigue self-management with step counters and paper diaries (FSM:CTR). Participants received the same self-management program as the FSM:ACT group but with the following differences. Daily paper diaries (converted to paper from web diary forms used in FSM:ACT) were assigned to monitor fatigue. Pedometers were worn 24/7 except when sleeping or bathing at the 1 week assessment periods (baseline, 3 month and 12 month follow-ups). Subjects recorded number of steps indicated on the step counter at the end of each assessment day. Versus Usual care/no treatment control: consisted of patient's usual care (not further specified). Participants filled out daily online web diary and wore actigraphs during 1 week assessment periods only (baseline, and 3 month and 12 month follow-ups).			
Fukuda 2016[32]	Ubiquinol-10 (CoQ10) - Capsules containing ubiquinol-10, provided by Kaneka, 50mg in each capsule. 3 capsules (150mg) taken daily after a meal. Supplementation time and methods were left to patient's discretion. Duration 12 weeks. Versus Placebo - Capsules containing placebo, provided by Kaneka (not further described). 3 capsules daily after a meal. The supplementation time and methods were left to the patient's discretion. Duration 12 weeks.	N=43 people with CFS, diagnosed according to 1994 CDC criteria. Participants were recruited from an outpatient clinic and were assessed for psychiatric diagnoses by a neuropsychiatrist. Strata details: adults (age >20 years); severity mixed or unclear	Adverse events (Serious adverse events or hospitalisations related to study intervention) Cognitive function (Uchida-Kraepelin psychodiagnostic test-number of responses and number of correct responses) at 12 weeks	Uchida-Kraepelin psychodiagnostic test – response time per question and correct rate reported only as 'not statistically significant' Sleep quality – number of awakenings >1 min and >5 mins – measured by Life Scope device not extracted as not a valid measure of

Study	Intervention and comparison	Population	Outcomes	Comments
				sleep quality; other measures of sleep quality reported only as 'not statistically significant' CES-D (depression scale) and Chalder fatigue scale results reported only as 'not statistically significant' – unable to extract. Correlation between change in these scores and change in ubiquinol levels reported – not relevant to protocol. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Fulcher 1997[33]	Graded exercise therapy (n=33) – weekly for 12 weeks; supervised treatment and the next week's exercise prescription. All sessions supervised by an exercise physiologist using	N=66 people with CFS (Oxford criteria); mental state and physical screenings performed, and when appropriate full	General symptom scales (Clinical global impression of overall change score)	Conducted in the UK Hospital anxiety and depression scale and

Study	Intervention and comparison	Population	Outcomes	Comments
	basic principles of exercise prescription, adapted for the patients' current's capacity. Home exercise was prescribed on at least five days a week, with initial sessions lasting between five and 15 minutes at an intensity of 40% of peak oxygen consumption (roughly 50% of the maximum recorded heart rate). The daily exercise prescription was increased by one or two minutes (negotiated with the patient each week) up to a minimum of 30 minutes. The intensity of the exercise was then increased to a maximum of 60% of peak oxygen consumption. Patients were given ambulatory heart rate monitors to ensure that they reached but did not exceed target heart rates. The main exercise was walking but patients but patients were encouraged to take other modes of exercise such as cycling and swimming. Patients were advised not to exceed prescribed exercise during a good phase. If patients complained of increased fatigue they were advised to continue at the same level of exercise for an extra week and increase when fatigue had lessened. Versus Flexibility treatment (n=33) – Flexibility and relaxation sessions were provided by the same exercise physiologist. Each patient was taught a stretching routine and relaxation techniques. Patients encouraged to start with 10 min sessions increasing to 30 mins a day, 5 days a week as more stretching exercises were added. They were specifically told to avoid doing any extra physical activities. Patients kept a weekly activity diary, recording the type, duration and response to exercise or stretching, which	medical records were obtained from referring doctor to ensure other disorders excluded. Strata details: adults (mean age (SD): 37.2 (10.7)); severity mixed or unclear (5 participants who were too incapacitated to attend for outpatient treatment were excluded); Mean illness duration (range): 2.7 (0.6-19) years; n=20 were taking full dose anti-depressants; n=10 were taking low dose tricyclic anti-depressants as hypnotics. All were told to continue their medication unchanged; 27 (41%) had successfully been treated for a comorbid disorder beforehand but still met criteria for 'chronic fatigue syndrome'	Fatigue (Chalder fatigue score) Physical functioning (SF-36-physical function) Exercise performance (Treadmill walking test duration) at 12 weeks	Pittsburgh sleep scale reported only as median (IQR). SF-36 general health sub scale reported. Not extracted as not validated alone. SF-36 total score also reported but not extracted, as the total score is not a validated way of reporting SF-36 data. Clinical global impression of change score was reported at 12 months follow-up, however not extracted as the majority of the control group patients (flexibility) had since gone on to receive the intervention. Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: max HR, recovery HR, post-exercise blood lactate, maximal quadriceps voluntary contraction.

Study	Intervention and comparison	Population	Outcomes	Comments
	determined the next week's prescription. Patients were offered the exercise intervention immediately after the flexibility treatment concluded. 12 weeks			PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. The fatigue VAS was not extracted as the mean scores reported were not consistent with the scale range reported.
Guillamo 2016[35]	Functional reconditioning programme (n=46): structured into 4 microcycles built around cardiovascular training. These were grouped into a mesocycle, which had to be repeated 3x during the programme. Each microcycle included 5 sessions: 3 of these took place in the laboratory, while the other 2 were conducted at the patient's home, with 2 rest days per week.sessions combined endurance training with the training of other physical capacities such as flexibility (Range of Motion, ROM), muscular strength and skill-related fitness such as balance or coordination.	N=68 people with CFS diagnosed according to the 1994 CDC criteria; diagnosis confirmed by consensus between 2 physicians. Strata details: adults (mean age (range): active group 46 (27-64); control group: 47 (28-60)); severity mixed or unclear; n=19 (58%) patients entering the intervention group (n=33) also had fibromyalgia; n=32 (97%) also reported pain and mood	Exercise performance (maximal workload at maximum effort inwatts, VO_2 max ml/kg/min, Borg scale (rated perceived exertion) at 24 weeks (12 weeks post-laboratory training)	Conducted in Spain Differences between functional assessment periods (FAI: baseline; FA II: post 12 weeks of lab training; FA III: post additional 12 weeks of home training) only reported selectively for the intervention (AG) group for most outcomes. Control group (CG) results

Study	Intervention and comparison	Population	Outcomes	Comments
	12 weeks of laboratory training & 12 weeks of home training Versus No treatment (n=22)	changes and had some kind of neurocognitive symptoms		available for FA II period, for physiological/exercise test related outcomes obtained in the maximum intensity stage during exercise testing; hence only these have been extracted for this study. Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: respiratory exchange ratio, HR. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Hobday 2008[37]	Low sugar low yeast diet: based on the 'Beat Candida Cook Book', adapted to ensure nutritional requirements were met and that it	N=52 people diagnosed with CFS according to 1994 CDC criteria. Participants were	Quality of life (SF36 individual sub scales)	Conducted in the UK

Study	Intervention and comparison	Population	Outcomes	Comments
	provided sufficient diversity to promote adherence. All sugar containing foods, refined carbohydrates and yeast containing foods were omitted together with alcohol and caffeine. Fruit and milk consumption were limited and participants were encouraged to have one live yogurt per day. Versus Healthy eating diet: based on Department of Health guidelines for the general population. Participants were encouraged to increase fibre, fruits and vegetables to at least 5 portions per day and reduce consumption of fat and refined carbohydrate. Increasing fish intake to twice per week (1 portion oily) was also recommended. Duration: 24 weeks.	recruited from a dedicated CFS clinic. Strata details: adults; severity mixed or unclear	Fatigue (Chalder Fatigue Scale) Psychological status (Hospital Anxiety and Depression Scale) at 24 weeks	PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Huanan 2017[38]	Abdominal tuina: step one pressing of the abdomen with the palm lasting 5 minutes, step two rotatory kneading of the abdomen lasting 5 minutes, step three pushing and pulling of the abdomen lasting 5 minutes, step four pushing the abdomen with a finger lasting 5 minutes. 20 sessions over 4 weeks - 5 sessions per week. Versus Acupuncture: Participants lay in the dorsal position. After routine sterilisation, needles 0.25mm x 40mm were inserted in to points at a depth of 50-60mm. After the sensation had been felt by the participant, the uniform reinforcing-reducing method was undertaken. Needles were	N=80 people with CFS; meeting 1994 CDC criteria Strata details: adults (18-60 years); severity mixed or unclear	<u>At 3 months:</u> Fatigue (Fatigue scale 14) Psychological status (self-rating anxiety scale; Hamilton rating scale for depression) <u>At 4 weeks:</u> Adverse events (adverse events and serious adverse events)	Conducted in China Fatigue scale-14 (FS-14) was used to assess the patient's level of physical fatigue (8 items) and mental fatigue (6 items). Each item can be scored on a 0-1 scale and a higher score indicates a greater severity of fatigue. A Chinese version of FS-14 has been validated.

Study	Intervention and comparison	Population	Outcomes	Comments
	maintained in this position for 20 minutes. 20 sessions over 4 weeks - 5 sessions per week.			Fatigue and psychological status outcomes reported at 4 weeks (post-treatment) and 3 months, but only 3-month data extracted as this was the longest follow-up time point that data was available (as per review protocol). PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Janse 2018[39] (Janse 2015)[40]	Web based CBT - protocol driven feedback. Based on face-to-face CBT for CFS protocol and consisting of 7 modules: getting started and goal setting, regulate sleep-wake cycle, helpful beliefs about fatigue, how to communicate with others about fatigue, gradually increasing activities, reaching goals step by step, evaluation and the future. Treatment tailored to patient's current activity pattern, measured by actigraphy. Patients asked by the therapist to	N=240 people with CFS according to 1994 CDC criteria; consultants assessed medical status to decide whether referrals had been sufficiently examined to rule out a medical explanation for fatigue; if medical evaluation deemed insufficient then patients seen again for anamnesis, full	General symptom scales (Sickness Impact Profile-8) Fatigue (Checklist Individual Strength fatigue severity sub scale; Chalder fatigue Questionnaire)	Conducted in the Netherlands 2 CBT arms (protocol driven feedback and support on demand) combined for analysis (CBT versus waiting list).

Study	Intervention and comparison	Population	Outcomes	Comments
	report on their progress according to a schedule set by the therapist (at least fortnightly). Therapists provided feedback and sent reminders if patients did not follow the schedule. The therapists were psychologists trained and experienced in delivering CBT for CFS. Median treatment duration 27 weeks. Versus Web based CBT - support on demand. Same CBT intervention but patients only received feedback if they ask for it. Patients did not receive any reminders from the therapist if they did not report on their progress via email. Median treatment duration 27 weeks. Versus Waiting list (median waiting time 26 weeks).	physical examination, case history evaluation and laboratory tests following national CFS guidelines; psychiatric comorbidity that could explain fatigue ruled out using Mini International Neuropsychiatric Interview Strata details: adults; severity mixed or unclear (score 35 or higher on Checklist Individual Strength fatigue sub scale and 700 or higher on the Sickness Impact Profile 8)	Physical functioning (SF36 physical functioning) Psychological status (Symptom Checklist 90 – psychological distress) Adverse events Activity level (actigraphy score) Return to school/work (Work and Social Adjustment Scale) at 6 months	Chalder fatigue questionnaire, work and social adjustment scale and actigraphy reported in supplementary material and for completers only. These outcomes were added after trial registration but before the start of the study. Adverse events were only measured from halfway through the trial. PEM reporting: 90.4% of participants had PEM. By study arm: CBT 88.8%, waitlist 93.8%. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; <95% of participants had PEM [PEM reanalysis].
Jason 2007[42]	CBT: participants evaluated the effect of gradual and consistent increases in activity and utilized strategies other than avoidance. 45 minute meetings once every 2 weeks, involved	N=114 people with CFS, according to 1994 CDC criteria; screening questionnaire to assess diagnostic criteria as	Quality of life (Quality of life scale) General symptom scales (self-reported global	Conducted in the USA Fatigue severity scale appears to be average

Study	Intervention and comparison	Population	Outcomes	Comments
	engaging participants in therapy and treatment rationale, schedule of planned graded activity developed in collaboration with the participant, discussion of and assignments related to negative automatic thoughts, encouraged to practice generating less catastrophic and more helpful alternatives, focused on fears, perfectionism, self-criticism and unrealistic performance expectations. Activity gradually increased and rest slowly reduced and sleep routine established. Duration: 26 weeks (13 sessions). Versus Anaerobic activity therapy: individualized constructive and pleasurable activities accompanied by reinforcement of progress. 45 minute meetings once every 2 weeks involving exercise prescription and monitoring and maintaining functional gains, principle of specificity in training for achieving functional gains, importance of gradually increasing anaerobic activity, completion of an exercise diary to identify goals/problems, preliminary targets set at safe, achievable level, exercise programme plus flexibility and exercise programme guidelines and an exercise diary, problems identified and dealt with, new targets established after habituation achieved to existing ones, behavioural prescriptions with scheduling modifications. Duration: 26 weeks (13 sessions). Versus Cognitive therapy: developing cognitive strategies to better tolerate and reduce stress	specified by 1994 CDC criteria; structured clinical interview for DSM-IV to establish psychiatric diagnoses; physician screening evaluation included an in-depth medical and neurological history and a general and neurological physical examination; relevant medical information gathered to exclude possible other medical causes; laboratory tests included a chemistry screen, complete blood count, ESR, arthritic profile, hep B, Lyme disease screen, HIV screen and urinalysis, tuberculin skin test; detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly etc. Strata details: adults; moderate (people who used wheelchairs, were bedridden or housebound were excluded)	impression of overall change rating) Fatigue (Fatigue Severity Scale) Physical functioning (SF36 physical functioning) Psychological status (Beck Depression Inventory; Beck Anxiety Inventory) Pain (Brief Pain Inventory – severity sub scale and interference sub scale; muscle and joint pain numeric rating scales) Return to school/work (number in employment) Exercise performance measure (6 minute walk) at 12 months	score (1-7) rather than total score Employment numbers and global impression calculated from percentages All trials armed were compared with each other PEM reporting: PEM severity was reported as a continuous outcome, but the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
	and symptoms, lessen self-criticism and treat maladaptive beliefs. Emphasizes pacing activities - increasing low effort activities and decreasing symptom producing activities. 45 minute meetings once every 2 weeks involving personal accounts of illness, stress reduction techniques for intrusive symptoms, limitations and emotional distress, relaxation exercises, cue-controlled relaxation, cognitive coping statements to counteract catastrophic thinking, self-demands and intolerance of symptoms, review of daily stress and fatigue records to identify stress/symptom associations, imagery technique, if imagery exercises succeeded in elevating mood they were incorporated into daily relaxation practice, discussion of quality of social support to identify maladaptive beliefs and generation of cognitive coping statements, identification of cognitive difficulties and exposure to memory compensation and cognitive retraining techniques, review of course of therapy. Duration: 26 weeks (13 sessions). Versus Relaxation: based on prior studies in the area of chronic illness; several types of relaxation demonstrated; 45 minute meetings once every 2 weeks involving history taking and relaxation rationale, stress/fatigue diary, progressive muscle relaxation, autogenic training , homework assignments, breathing focus techniques, yoga form stretching, thematic imagery relaxation, review of the most helpful techniques and progress made in therapy; post-treatment relaxation programme developed in			

Study	Intervention and comparison	Population	Outcomes	Comments
	collaboration with participant. Duration: 26 weeks (13 sessions).			
Jason 2010[41]	Student buddies: students with a background in psychology/social work provided support to their assigned participants (2 hours/week at participants' homes. Emotional support provided and any form of direct help provided functional support - household tasks such as organizing files, writing letters etc. and helping participants monitor their energy levels in order to help participants avoid overexertion, thereby avoiding setbacks and relapses, while increasing their tolerance for activity. Student buddies attended 4 hours of training and subsequent 1-hour weekly meetings throughout the 4-month duration of the program. Buddies were matched based on the participants' particular needs and geographical location. Versus No intervention. After post testing, they were provided a buddy intervention.	N=30 with CFS, diagnosed according to 1994 CDC criteria Strata details: adults; severity mixed or unclear	Fatigue (Fatigue Severity Scale) Physical functioning (SF36 physical functioning) Psychological status (Perceived Stress Scale) at 4 months	Conducted in the USA PEM reporting: PEM severity was reported as a continuous outcome, but the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Joung 2019[43]	Myelophil at a dose of 2 g orally per day. Myelophil is the 1:1 mixture of Astragali Radix and Salviae Miltiorrhizae Radix and was extracted using 30% ethanol for 20 h at 80°C. Duration 12 weeks. Versus Matching placebo containing a starch and lactose mixture of the same size, weight, and shape as Myelophil. Duration 12 weeks.	N=98 people with CFS, diagnosed according to the 1994 CDC criteria. Participants were recruited from 2 university hospitals and all other known causes of chronic fatigue must have been ruled out. Strata details: adults (18-65 years); severity mixed or unclear	Fatigue/fatigability (numeric rating scale; visual analogue scale; fatigue severity scale) Adverse events (adverse events; serious adverse events) at 12 weeks	Conducted in South Korea The Chalder fatigue questionnaire was translated into Korean and then modified by the NRS method to evaluate fatigue severity. The modified questionnaire was applied in previous

Study	Intervention and comparison	Population	Outcomes	Comments
				studies, but unclear whether it is validated – downgraded for measurement bias. SF36 reported as an overall score – not validated for use in this way and therefore not extracted PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Knoop 2008[46]	Guided self-instructions based on CBT. Self-instruction booklet containing information about chronic fatigue syndrome and weekly assignments. Programme took at least 16 weeks, but often more if patients formulated long-term goals such as returning to work. Patients asked to email (or telephone) at least once every 2 weeks to report their progress. A cognitive–behavioural therapist, trained in regular CBT for chronic fatigue syndrome, responded to this email or call. If patients did not	N=171 people meeting 1994 CDC criteria for CFS; no further information on diagnosis. Strata details: adults; severity mixed or unclear (participants scored ≥35 on CIS fatigue severity sub scale and >700 on SIP-8).	General symptom scales (Sickness Impact Profile 8) Fatigue (Checklist Individual Strength – fatigue severity) Physical functioning (SF36 physical functioning)	Conducted in the Netherlands PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory

Study	Intervention and comparison	Population	Outcomes	Comments
	respond every 2 weeks, a reminder was sent by email or patients were telephoned. Versus Waiting list		at mean 10 months	feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Kos 2015[47]	Activity pacing self-management (APSM) program. 3 one-on-one sessions with an occupational therapist. Coaching on performing daily life activities within individual limits. Activity duration used in program 25-50% lower than the capacity participants reported to account for overestimations. Activity blocks interspersed with breaks (rest or light activity) of equal duration. Education on fatigue/strategies to cope/fatigue/pacing. Once participants could control daily activities without excessive fatigue activity levels increased gradually. Goals set/adjusted at each session. Duration 3 weeks. Versus Relaxation techniques. 3 one-on-one sessions with a physiotherapist, 60-90 mins each. Education about the role of stress in CFS biology, and the opportunities stress management provides to handle this issue. Patients stress management techniques such as Jacobson relaxation skills, Schultz relaxation skills, visualization, and other. Therapist provided activities to improve coping in stressful events based on stress diary kept by participant. Duration 3 weeks.	N=33 people (females only) with CFS, diagnosed by an experienced internist, meeting the 1994 CDC criteria and using serial physical examination and laboratory measurements. Strata details: adults (18-65 years); severity mixed or unclear (participants had to be able to attend clinic for assessment and treatment which may have excluded those most severely affected)	Quality of life (SF36 – 8 subscales) Physical functioning (Canadian occupational performance measure – performance and satisfaction subscales) at 5 weeks	Conducted in Belgium Study also reports checklist individual strength and CFS symptom list, but data not analysable (median (IQR)) Study also reports change in health status (SF36) compared with 1 year previously – not extracted as not relevant, 3 week intervention PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
				Study only included women.
Lopez 2011[52]	Cognitive behavioural stress management: 12 weekly group meetings held in 2-hour sessions, consisting of two parts: a relaxation component (specific relaxation techniques, including progressive muscle relaxation and visualization techniques) and a didactic and discussion component (taught to better recognize how stress impacts emotionally and physically and the relationship between thoughts, feelings, and behaviours). The primary therapeutic technique used was cognitive restructuring targeting cognitive appraisals of ongoing stressors. A specific focus is on teaching general stress management skills. Also learned specific coping skills and interpersonal communication skills such as assertiveness and anger management. Homework was assigned each week and was collected and discussed in the subsequent week. Led by a post-doctoral clinical fellow and advanced psychology graduate students. Duration 12 weeks. Versus Psycho-education seminar control group. The half-day PE condition summarized many of the strategies from the 12 week CBSM group but in a condensed format. The seminar was scheduled during the 6th week of the CBSM group and was run by a clinical post-doctoral fellow.	N=69 people with CFS, diagnosed according to 1994 CDC criteria and physical exam Strata details: adults; severity mixed or unclear	Quality of life (Quality of Life Inventory) General symptom scales (CDC Symptom Inventory total) Psychological status (Perceived Stress Scale; Profile of Mood States total mood disturbance) at 12 weeks	Conducted in the USA Differences between study groups in outcomes at baseline Study also reports fatigue sub scale of Profile of Mood States but cannot use total score and sub scales for different outcomes (double counting). PEM reporting: 97.4% of participants had ‘unusual fatigue after exertion’, measured using the CDC symptom inventory which asked the question “During the past month, have you been unusually fatigued or unwell for at least one day after exerting yourself in any way?”. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; inadequate

Study	Intervention and comparison	Population	Outcomes	Comments
				description of 'unusual fatigue after exertion' to confirm participants had PEM [PEM reanalysis].
McDermott 2006[55]	2000mg sachets of Biobran MGN-3, containing 1000mg of active ingredient and 1000mg of excipient (500mg microcrystalline cellulose, 260mg corn starch, 200mg dextrin, 40mg tricalcium phosphate). Identical to OTC preparation sold in UK and USA. Active ingredient = arabinoxylane (a hemicellulose compound released from rice bran when it is incubated with an enzyme from the shitake mushroom). Participants took a dose of 2g dissolved in water or milk, 3x/day. Duration 8 weeks. Versus Placebo – Sachets and contents identical to Biobran in appearance and taste. Participants took a dose of 2g dissolved in water or milk, 3x/day. Duration 8 weeks.	N=71 people with CFS, diagnosis according to the 1994 CDC criteria, recruited from specialist CFS clinic. Strata details: adults (>18 years); severity mixed or unclear	Quality of life (Patient global impression of overall change – at follow-up only; WHOQOL-BREF – physical, psychological, social, and environmental wellbeing subscales) General symptom scales (Measure yourself medical outcomes profile 2 (MYMOP 2) Fatigue (11-item Chalder fatigue scale) Psychological status (Hospital anxiety and depression scale – depression and anxiety subscales) Adverse events (Serious adverse events; minor side effects leading to discontinuation) at 8 weeks	Conducted in the UK PEM reporting: the percentage of participants with PEM was not reported. Very serious population indirectness – study included only a subset of CFS population with symptoms suggestive of immune activation (≥2 of: tender lymph nodes, sore throat or poor temperature control); and 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. Chalder fatigue scale – total score (bimodal) extracted; physical and mental subscales

Study	Intervention and comparison	Population	Outcomes	Comments
				reported but not extracted (likert). Serious adverse events reported as single sentence statement; not further defined.
Moss-Morris 2005[57]	Graded exercise therapy (n=25) – the target heart rate (HR) for each participant was initially set at 40% of VO2max (approx. 50% max HR) attained on the treadmill test, to be maintained for 10-15 mins 4-5x a week; exercise goals set collaboratively between the researcher and participant. Initial exercise intensity/duration set at a level during exercise testing as achievable and unlikely to exacerbate symptoms. Participants given a polar HR monitor to assess HR during exercise sessions, which assisted them to meet but not exceed prescribed intensity levels and provided external monitoring which reduced the likelihood of focusing on and adjusting exercise intensity in response to bodily symptoms. Researchers and participants met weekly over 12 weeks to assess progress, provide encouragement and set new exercise goals. During the first 6 weeks increases focused on increasing exercise duration by 3-5 minutes per week. After 6 weeks, exercise intensity gradually increased aiming for HR increases of approx. 5 beats/min per week. The final goal was for each participant to be exercising for approx. 30 mins for 5 days a week at intensity level relating to 80 % of expected maximum heart rate (70% of VO2max). Versus	N=49 people with CFS, between 18 to 65 years meeting 1994 CDC criteria, as assessed by a CFS specialist GP. Strata details: adults (mean age (range): 40.9 years (19-60)); severity mixed or unclear; median duration of illness (range): 3.08 years (6 months to 45 years); 22.4% were unemployed or unable to work due to disability; 56% were either possible or probable cases of psychiatric disorder (30% being possible or probable cases of depression; 42% being possible or probable cases of anxiety disorder) as assessed by the HADS anxiety and depression sub-scales	<u>At 42 weeks:</u> General symptom scales (Self-rated Clinical global impression of change in CFS scale) <u>At 12 weeks:</u> Fatigue (Chalder fatigue scale) Physical functioning (SF-36 physical function) Exercise performance measure (VO_2 peak)	Conducted in New Zealand Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes:max HR PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard medical care (n=24) – provided by a 'CFS' specialist physician 12 weeks			
Ng 2013[58]	Acupuncture: 8x 30 minute sessions over 4 weeks. Each participant received the intervention in an individual room and lay on a bed. Acupuncture points were chosen in accordance with the theories of traditional Chinese medicine (TCM). Performed by experienced and registered TCM practitioner. 5 needles/plastic stands used for each session. Plastic stands used, as per the control group, however needles in experimental group were longer with sharp tips and penetrated the skin. Needle manipulation was performed at the beginning, middle, and end of the session. Versus Sham acupuncture: followed the same treatment schedule and performed by the same practitioner as for acupuncture group. The same acupuncture points were used in the experimental and control groups. Before the trial the practitioner received special training in the administration of sham acupuncture. 5 needles inside needle stands were used. Specially designed needles were used - the needles were blunt and were held in place by a specially designed needle holder and plastic stand so that the needle provided only a pricking sensation on the skin without penetrating it.	N=137 people with CFS; meeting 1994 CDC criteria Strata details: adults; severity mixed or unclear	Quality of life (SF-12 physical and mental subscales) Fatigue (Chalder fatigue scale) Psychological status (GHQ-12) Adverse events at 4 weeks	Randomisation may actually be alternation. Very high risk of selection bias. PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
Nijhof 2011[61] & 2012[60] (FITNET trial)	FITNET program: Psychoeducational section and cognitive behavioural therapy section (21 interactive modules, accessible after activation by the therapist). Patients received support from trained cognitive behavioural psychotherapists solely through e-consults. According to an individually tailored treatment, therapists responded to the e-consults on a set day once a week and thereafter every 2 weeks. Parents' portal consisted of the module's content, psychoeducation, and an e-consult application. Patients and parents had separate accounts with unique usernames and passwords. The parents of patients <15 years instructed to coach their children, those of older patients were asked to encourage their children to take responsibility for their treatment. Return to full-time education was the aim of treatment. FITNET therapist and school mentor had at least one communication about school attendance and the school's effort to encourage treatment compliance. School mentor acted as a coach, adviser, or tutor when needed. Duration: 20 internet sessions over 6 months. Versus Usual care, which included individual or group-based rehabilitation programmes, cognitive behavioural therapy face-to-face, or graded exercise treatment, or both, by a physical therapist. Adolescents assigned to usual care were given the opportunity to attend FITNET after 6 months.	N=135 people with CFS, diagnosed by a paediatrician specialising in CFS using 1994 CDC criteria Strata details: children and young people; severity mixed or unclear (severe fatigue and functional impairment defined as physical functioning on CHQ score <85 and/or school participation ≤85%, and fatigue severity subscale CIS-20 ≥40)	General symptom scale (self-reported improvement in CFS) Fatigue (Checklist Individual Strength fatigue severity) Physical functioning (child health questionnaire (CHQ-CF87) physical functioning sub scale) Adverse events (serious adverse events) Return to school/work (mean school attendance) at 6 months	Conducted in the Netherlands PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. Outcome data was reported for long-term follow-up at 12-months and mean 2.7 years, but could not be extracted as the control arm was offered the intervention at the end of the initial 6-month treatment period (50% received the intervention).

Study	Intervention and comparison	Population	Outcomes	Comments
Nunez 2011[63]	CBT + GET (in groups) + conventional symptomatic pharmacological treatment: CBT led by a clinical psychologist with the main objective to identify correct behavioural patterns and adaptive thought models and create a therapeutic link. GET involved gradual increases in aerobic exercise and complementary activities such as flexibility exercise and relaxation therapy, supervised by a qualified physiotherapist with experience in general physiotherapy for neurological disease and in a third-level CFS and fibromyalgia reference unit. Duration 2.5 to 3 months. Versus Usual CFS therapy: exercise counselling and conventional pharmacological symptomatic treatment. Exercise counselling performed by personal interview with the same physiotherapist and objective to provide activities that restored patient's ability to do sustained physical exercise as far as possible.	N=120 people with CFS according to 1994 CDC criteria; evaluation included clinical history, physical exam, analytical tests (biochemical, hematological, hormonal, and immunological profile), chest X-ray, 12-lead electrocardiogram, and psychological evaluation Strata details: severity and age mixed or unclear (mean age (SD) suggests majority were adults)	Quality of life (SF36) General symptom scales (Stanford Health Assessment Questionnaire – patient global health status) Physical functioning (Stanford Health Assessment Questionnaire) Pain (Stanford Health Assessment Questionnaire - pain intensity) at 12 months	Conducted in Spain PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
O'Dowd 2006[64]	CBT to modify thoughts and beliefs about symptoms and illness and behavioural responses to symptoms and illness, such as rest, sleep and activity. Goal of treatment to increase adaptive coping strategies and reduce distress and disability. Programme included: elucidation of core beliefs regarding illness and its management, monitoring of activity levels and introduction of appropriate timetable, introduction to exercises, a range of aerobic, strength, balance and stretching exercises, behavioural modification of sleep patterns, mood	N=153 people with CFS, according to 1994 CDC criteria. The majority of participants (94%) were diagnosed with CFS by their GP or a consultant. Strata details: adults; severity mixed or unclear	6 and 12 months (pooled): Quality of life (SF36; Health Utilities Index) Fatigue (Chalder Fatigue Scale) Psychological status (Hospital Anxiety and Depression Scale; General Health Questionnaire)	Conducted in the UK Health Technology Assessment Pooled 6 and 12 month outcome data was extracted as the analysis adjusted for baseline score and assessment set. The 12-month data reported were unadjusted and

Study	Intervention and comparison	Population	Outcomes	Comments
	management advice and goal setting. Structured incremental exercise programme following group discussion about unhelpful nature of activity cycling, following CBT principles. Instructions given about pacing up by small increments once exercise level had been achieved successfully. Advice to reduce exercise considerably should a significant increase in symptoms occur. Management of setbacks was a specific subject included. Duration 16 weeks. Versus Attention control: Education and Support group. Same therapists, setting, time, duration and frequency as CBT groups. Focus on sharing of experiences and learning basic relaxation skills. Control for the non-specific effects of therapy and controlled for the effects of therapist time and attention. A stretch programme validated the role of the physiotherapist. If further questions regarding exercise were asked, group informed that there was controversy over value of aerobic exercise, and therefore did not introduce exercise. Duration 16 weeks. Versus Standard care: managed in primary care		Cognitive function (reaction time, total words recalled, correct words) Exercise performance measure (shuttles walked, walking speed, Borg perceived fatigue scale)	variability statistics were not reported for all outcomes. All trial arms compared with each other PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Oka 2014[65]	20 min 1-to-1 sessions of isometric yoga with experienced yoga instructor, between 2-4pm on the day the patient's visited hospital every 2-3 wks. Performed in seated position, no background music. Consisted of breathing exercises and several repetitions of 6 poses performed at 50% of patient's max strength.	N = 30 people with CFS. The diagnosis of CFS was made for patients meeting the 1994 CDC criteria, and did not include patients with idiopathic chronic fatigue. Participants were	Fatigue (Chalder fatigue scale) at mean 9.2 weeks	Conducted in Japan Total and subscale scores reported for Chalder fatigue scale – only total score extracted.

Study	Intervention and comparison	Population	Outcomes	Comments
	Program was modified on a patient-to-patient basis depending on severity of fatigue and pain. Patients were asked to practice the program at home on non-class days if they could; given digital and written aids. Patients were reviewed by a study doctor before and after each yoga session to check condition and for any changes/adverse events. Conventional pharmacotherapy allowed. Duration: mean 9.2 (SD 2.5) weeks Versus Usual care/wait-list control group. Hospital visits every 2-3 weeks. Conventional pharmacotherapy allowed – e.g. antidepressants, Japanese traditional herbal medicine, coenzyme Q10. Duration: mean 9.2 (SD 2.5) weeks.	enrolled from an outpatient clinic for psychosomatic medicine. Strata details: adults (20-70 years), severity mixed or unclear (level of fatigue serious enough to cause an absence from school or work for at least several days of a month but not serious enough to require assistance with activities of daily living, n=2 excluded as too severe to participate)		SF8 data only completed by/reported for yoga group – not extracted as no comparison. PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Ostojic 2016[67]	Guanidinoacetic acid - 2.4g per day, oral administration. Dose chosen as a dose that gives an increased plasma creatine concentration with minimum side effects in men and women. 3 months. Versus Placebo - containing cellulose, oral administration. 3 months. Participants monitored daily using actigraphy throughout the study.	N=21 people with CFS; participants met the 1994 CDC criteria (no further information given). All participants female. Strata details: adults; severity mixed or unclear	Fatigue (Multidimensional fatigue inventory) Quality of life (SF-36 PCS and MCS) Pain (VAS – at rest and during activity (treadmill test)) Adverse events (Self-reported) at 3 months	Crossover trial – 2 month washout period. Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear. Exercise performance measures only reported graphically (quadriceps strength, treadmill test,

Study	Intervention and comparison	Population	Outcomes	Comments
				and actigraphy results) – not extracted. PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Pinxsterhuis 2017[72]	Group-based self-management program; 8 2.5 hr sessions, 6-14 people/group. Conducted by a peer counsellor (an experienced individual with CFS) and occupational therapist who had participated in a 3 day training program. Program based on self-efficacy theory and energy envelope theory (pacing). Focus on coping with illness, dealing with healthcare professionals/significant others, sharing experiences, self-management skills, guided mastery practice, feedback, goal setting. Educational presentations by healthcare professionals at ME/CFS centre on activity pacing, physical exercise, nutrition, economic self-sufficiency, personal relationships, treatments, relaxation exercises. Duration 15 weeks. Versus	N=146 people with CFS, diagnosed by a physician or medical specialist; meeting 1994 CDC criteria and Canadian diagnostic criteria (Carruthers 2003). Strata details: adults (>18 years); severity mixed or unclear (required that patients be physically able to attend the program)	Quality of life (SF36 physical and mental component summary scores) Fatigue (Fatigue severity scale) at 12 months	Conducted in Norway SF36 – physical functioning subscale reported, but total scores extracted as a quality of life outcome (not double-counted) Outcomes reported at 6 months and 12 months, but only 12-month data extracted as this was the longest follow-up time point that data was available (as per review protocol).PEM reporting: Participants met both the 1994 CDC

Study	Intervention and comparison	Population	Outcomes	Comments
	Usual care – participants were allowed to receive treatment as usual (not standardised), but they were excluded from participation in the regular patients education program at the study hospital.			criteria and the Canadian criteria (Carruthers 2003) – the Canadian criteria has PEM as a compulsory feature.
Powell 2001[74]	Graded exercise therapy and patient education (n=114) – 3 groups. All patients received a medical assessment followed by evidence-based explanations of symptoms that encouraged graded activity. Explanation of symptoms focused on circadian dysrhythmia, physical deconditioning and sleep abnormalities. A graded exercise program was designed in collaboration with each patient and tailored their functional abilities. Once patients were successfully engaged in treatment, the role of predisposing and perpetuating psychosocial factors was discussed. Patients received an educational information pack that reiterated the verbal explanations. 2 face-to-face sessions (total 3 hrs) in which symptoms were explained and graded exercise programme was designed (minimum intervention group, n=37); In addition to the minimum intervention patients (n=39) received 7 planned phone contacts, each about 30 mins over 3 months, during which explanations for symptoms and the treatment rationale were reiterated and problems associated with graded exercise were discussed with the use of motivational interviewing techniques (telephone intervention); or in addition to the minimum intervention, patients (n=38) received 7 one hour face-to-face treatment sessions over 3 months (maximum intervention), which had the same function as	N=148; patients with CFS (Oxford criteria); all participants were assessed by a consultant physician to confirm diagnosis. Strata details: age and severity mixed or unclear (likely majority adults – inclusion criteria age rage 15-55; mean age (SD): intervention group 32.98 (10.34) years, control group 36.82 (10.51) years); severity mixed or unclear	Fatigue (Chalder fatigue scale) Physical functioning (SF-36 physical function) Psychological status (Hospital anxiety and depression scale) Sleep quality (Jenkins 4-item sleep problem questionnaire) at 12 months	Conducted in the UK GET group scores were combined from three intervention groups; All SDs calculated since 95% CIs were reported. Serious indirectness relevant to the control group since it included an element of the intervention in that graded activity was encouraged. Powell 2004 reports 2 year follow-up for the 3 intervention groups, and the original control group, who had since completed a similar intervention. This data has not been extracted as there is no appropriate comparator. PEM reporting: the percentage of

Study	Intervention and comparison	Population	Outcomes	Comments
	the telephone sessions in the telephone intervention group. Versus Standard medical care (n=34) – patients received standardised medical care. This comprised a medical assessment, advice and an information booklet that encouraged graded activity and positive thinking but gave no explanations to for the symptoms. 12 months			participants with PEM was not reported. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Ridsdale 2001[79]	CBT: 6 x up to one hour sessions led by qualified CBT therapists with experience in primary care and supervised by the study authors (total duration of treatment unclear). CBT included providing a treatment rationale, activity planning, homework, establishing a sleep routine and other cognitive interventions. Based on a model of understanding fatigue that makes a distinction between precipitating and perpetuating factors. Perpetuating factors were the focus of the intervention. The four main areas focused on were: the fatigue was managed by insuring that levels of activity and rest were both consistent and realistic given the patient's responsibilities; sleep disturbance was addressed using conventional methods; negative beliefs regarding the symptom of fatigue, self-expectations or self-esteem were identified and patients were encouraged to challenge them in the conventional way; specific	N=37 people with CFS according to 1994 CDC criteria; prior to study entry all participants were required to have had blood tests performed by a doctor, and a doctors assessment of physical health problems to ensure they were not the cause of fatigue. Strata details: age and severity mixed or unclear (age 16-75 years, but mean (SD) suggests mainly adults)	Fatigue (Chalder fatigue scale) Psychological status (Hospital Anxiety and Depression Scale) at 6 months	Conducted in the UK Total study population n=160. Results reported separately for those meeting CDC criteria for CFS. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM

Study	Intervention and comparison	Population	Outcomes	Comments
	lifestyle changes were encouraged if deemed appropriate. Versus Counselling: 6 x up to one hour sessions led by qualified counsellors with experience in primary care and supervised by the study authors (total duration of treatment unclear). Based on a manual that was originally devised for a trial of counselling for patients with depression and mixed anxiety and depression in primary care. This model of counselling is non-directive and client-centred; it offers the patient an opportunity to talk through their concerns and difficulties in a non-judgmental and supportive environment. The aim of such counselling is to help patients to understand themselves better, to suggest alternative understandings, to uncover the links between current distress and past experience, and to provide the conditions for growth and healing.			unclear [PEM reanalysis].
Ridsdale 2004[78]	CBT: 6 x 45-min sessions over 12 weeks by cognitive behavioural therapists. After an assessment, a rationale for treatment is provided. The treatment involves activity planning, homework, establishing a sleep routine and other cognitive interventions (Chalder et al. 1999). It is based on a model that distinguishes between precipitating and perpetuating factors, with the perpetuating factors becoming the focus of the intervention. The treatment ensures levels of activity and rest are both consistent and realistic given the patients' responsibilities. Sleep disturbance and negative beliefs regarding the symptom of	N=36 people with CFS according to 1994 CDC criteria; those with concurrent physical problems, which in the judgement of the doctor have caused the fatigue symptoms were excluded Strata details: age and severity mixed or unclear (age 16-75 years, but mean (SD) suggests mainly adults)	Fatigue (Chalder fatigue scale) at 8 months	Conducted in the UK Total study population n=123. Results reported separately for those meeting CDC criteria for CFS. Main outcomes in study were reported as pooled 3- and 8-month data. Unclear if extracted outcome was at 8

Study	Intervention and comparison	Population	Outcomes	Comments
	fatigue, self-expectations or self-esteem are identified and patients are encouraged to challenge them in the conventional way. Specific lifestyle changes are encouraged if deemed appropriate and relapse prevention is addressed in the last two sessions. Versus GET: 6 x 45-min sessions over 12 weeks by physiotherapists. Based on the principles of exercise prescription devised by the American College of Sports Medicine (American College of Sports Medicine, 2000), adapted to each patient's current physical capacity. It was developed from a GET protocol designed for patients with chronic fatigue syndrome in a specialist context (Fulcher & White, 1998). GET is structured and supervised activity management that aims for a gradual but progressive increase in aerobic activities, usually walking. Home exercise is programmed, with initial sessions lasting between 5 and 15 min at an intensity of 50% of the age-related estimated maximum heart rate. Patients are advised not to exceed the recommended exercise duration or intensity.			months or if it was also pooled data. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Rimes 2013[84]	Mindfulness based cognitive course (MBCT). Intro session + 8 weekly sessions, 2.25hrs each. Classes included mindfulness meditation practices which were also undertaken at home, with support of CDs. Patients talked about their experiences with mindfulness practice, issues/ how to deal with them. Each class was organised around a theme that was explored. Programme adapted so that psycho-	N=37 people with CFS, diagnosed as having CFS according to 1994 CDC or Oxford criteria at initial assessments. All participants had already completed a CBT program at a NHS CFS unit but still reported excessive fatigue.	Fatigue (Chalder fatigue scale 11-item) Psychological status (Hospital anxiety and depression scale – depression and anxiety subscales)	Conducted in the UK 6 month post-treatment follow-up data reported only for intervention group, as waitlist control group had started the intervention by that point (pre-specified).

Study	Intervention and comparison	Population	Outcomes	Comments
	educative/cognitive components consistent with cognitive-behavioural model of CFS rather than depression. Intervention aimed at helping participants to become more aware of and relate differently to thoughts, feelings, bodily sensation and self, including development of metacognitive awareness and a more accepting, non-judgmental compassionate attitude, and to help individuals disengage from unhelpful cognitive and behavioural reactions that may be maintaining symptoms. Impairment, distress, and develop new ways of coping. Participants offered a 2 month follow-up class. Classes led by 2 clinical psychologists. Versus Wait-list control group. Participants were informed that their own MBCT group with start at the 2 month follow-up (4 months from start of study).	Strata details: adults; severity mixed or unclear (score of ≥4 on Chalder fatigue scale (bimodal scoring)	Physical functioning (SF36 Physical functioning) Adverse events ('Substantive' adverse events) Return to school or work (Work and social adjustment scale) at 4 months (2 months post-treatment)	Post-treatment follow-up data also reported, but 2 month post-treatment data extracted (longest follow-up time point that data is available for both groups, as per review protocol). All participants completed a CBT program in past year. AEs – reported as single sentence statement; 'substantive' not defined PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC/Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
Sharpe 1996[84]	CBT in addition to the medical care: 16 x1 hr individual treatment sessions over four months. Treatment had a cognitive emphasis and was tailored for patients with CFS. Administered by three experienced therapists and supervised by an experienced cognitive therapist. Patients encouraged to question a simple disease explanation of the illness, to consider the role of psychological and social factors and invited to evaluate the effect of gradual and consistent increases in activity and to try strategies other than avoidance. Additional components included strategies to reduce excessive perfectionism and self-criticism and an active problem-solving approach to interpersonal and occupational difficulties. Versus Usual care: medical care alone and reassured that there was no evidence of serious organic disease. Patients told that they had CFS and advised to increase their level of activity by as much as they felt able. No further specific explanation or advice was given. Follow up by their general practitioners in the usual way.	N=60 people with CFS, according to Oxford criteria; full history and psychiatric diagnostic interview completed to determine eligibility for inclusion Strata details: adults; severity mixed or unclear	Fatigue (0-10 scale) Psychological status (Hospital Anxiety and Depression Scale) Exercise performance measure (6 minute walk distance) Activity levels (number of days in bed; percentage interference with activities measured using the pain disability index) at 12 months	Conducted in the UK Score on Karnofsky scale dichotomised (number with >80 and number with >10 point improvement from baseline) – not extracted as there is a high risk of bias with author dichotomisation of continuous outcomes. PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. Outcomes reported at 5, 8, and 12 months, but only 12-month data extracted as this was the longest follow-up time point that data was

Study	Intervention and comparison	Population	Outcomes	Comments
				available (as per review protocol).
Soderberg 2001[86]	Focused group therapy: supportive and goal-oriented short-term therapy, 10 sessions of 1.5 hours each (interval between sessions not clear). Goal to promote ability to deal with sickness and life situation by working with issues such as acceptance of the new life situation, setting realistic levels of ambition and reflecting on connection between achievement/self-esteem and activity/rest. Led by a psychologist Versus Waiting list (started group therapy after 5 months).	N=14 people with CFS, diagnosed at an infectious diseases clinic according to 1994 CDC criteria. Patients who also had fibromyalgia were excluded. Strata details: adults; severity mixed or unclear	Quality of life (Gothenburg Quality of Life Scale; VAS) at 5 months	Conducted in Sweden Fatigue (WESS) was measured but results not analysed or reported in the paper due to problems in the interpretation of 'as usual'. All female participants. Timepoint outcome measured is not explicitly stated for intervention group ('after group') but assumed to be the same as for waiting list participants (5 months). PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
Stulemeijer 2005[87] (Knoop 2007[44], Knoop 2007[45])	CBT: 10 individual sessions over 5 months. 2 treatment protocols adapted for 2 different patterns of physical activity: active and passive. Active patients learned to recognise and accept their current state of fatigue and impairment. Subsequently, they reduced their levels of activity and learnt to respect the limitations. Then the patient built up activity levels. Passive patients started a systematic programme of activity building. Beliefs that activity would aggravate symptoms were addressed and challenged. Parents were actively involved in supporting their child. Return to full time education was a goal and a plan for returning to school was discussed early with everyone involved. Four child therapists who were trained and supervised by an experienced cognitive behavioural therapist administered all therapy. Versus Waiting list - free to have other examinations or treatments and informed beforehand that, if desired, they could start therapy directly after the second assessment	N=71 people with CFS, according to 1994 CDC criteria, assessed by means of a detailed history and physical and laboratory examinations Strata details: children and young people (age range 10-17 years); severity mixed or unclear severity mixed or unclear (severe fatigue and severe functional impairment defined as a score of 40 or more on the fatigue severity subscale of the checklist individual strength)	General symptom scales (self-rated improvement in CFS) Fatigue (Checklist Individual Strength - fatigue severity sub scale) Physical functioning (SF36 physical functioning) Return to school/work (school attendance - hours attended/total hours) Pain (pain, joint & muscle pain) Cognitive function (Checklist Individual Strength concentration sub scale, reaction time tests) at 5 months	Conducted in the Netherlands PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Surawy 2005[88]	Group mindfulness training programme based on mindfulness-based stress reduction and mindfulness based cognitive therapy each week. Duration: 8 weeks. Versus	N=18 people diagnosed with CFS and meeting the Oxford criteria. Participants were diagnosed with CFS after a thorough initial screening for infectious and physical diseases.	Fatigue (Chalder Fatigue Scale) Physical functioning (SF36 physical functioning)	Conducted in the UK PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness

Study	Intervention and comparison	Population	Outcomes	Comments
	Waiting list - received standard care that may have included visits to the GP and complementary and alternative such as homeopathy or acupuncture, but not CBT or mindfulness.	Strata details: adults; severity mixed or unclear	Psychological status (Hospital Anxiety and Depression Scale) at 8 weeks	– Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Sutcliffe 2010[89]	Home orthostatic training (n=19) - Participants were asked to stand with their upper back against a wall and their heels approximately 15cm from the wall with a cushioned 'drop zone'. They were asked to maintain this position without movement for up to 40 mins or until they experienced symptoms. Versus Placebo/sham (n=19) - Participants were asked to stand against a wall with their upper back against the wall and their heels approximately 15 cm from the wall with a cushioned 'drop zone'. They were also taught to perform gentle flexion and extension exercises with their calf muscles while standing against the wall, to enhance believability counter venous pooling and prevent any possible orthostatic training effect. Participants were asked to continue training daily at home for 6 months	N=38; people with CFS (1994 CDC criteria), attending a CFS/ME clinical service. Subjects were not selected positively or negatively by presence of autonomic symptoms or history of loss of consciousness. Strata details: adults (mean age (SD): 48 (12) years); severity mixed or unclear	Fatigue (fatigue Impact scale) 4 weeks	Conducted in the UK Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: sBP, HR, sBP drop with active stand, cardiac index, (total peripheral resistance in response to active stand). PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM

Study	Intervention and comparison	Population	Outcomes	Comments
				unclear [PEM reanalysis]. Results of the fatigue impact scale at 6-month time point were not reported.
Taylor 2004[91] 2006[92]	2 part programme – illness-management group and peer counselling. Part 1: 8 sessions of illness-management group, biweekly over a period of 4 months, co-led by a peer counsellor and the author, consisting of individual check-in and reporting on self-monitored goal attainment educational lecture and discussion of self-selected, chronic fatigue syndrome-relevant topics (e.g. activity pacing, cognitive coping skills, employment issues etc.) Part 2: 7 months of peer counselling, consisting of self-advocacy training, continued monitoring of goal attainment, and ongoing case coordination services by one of the peer counsellors. Resource funds of $300 per participant were provided to support goal attainment, service acquisition, and local travel needs. Participants were required to state how the financial expenditure would facilitate goal attainment and independent living. Duration 12 months. Versus Delayed programme (waiting list)	N=47 people diagnosed with CFS according to 1994 CDC criteria; Chronic Fatigue Syndrome Screening Questionnaire to evaluate presence, frequency, and severity of chronic fatigue syndrome symptoms according to 1994 CDC criteria; Structured Clinical Interview for the DSM-IV administered by a licensed clinical psychologist to rule out psychiatric conditions that would exclude an individual from a chronic fatigue syndrome diagnosis; collection of past medical records documenting a diagnosis of CFS by a physician; and independent physician review of results from the Chronic Fatigue Syndrome Screening Questionnaire, the psychiatric interview, and the medical records to determine whether the potential participants met CFS criteria Strata details: adults; severity mixed or unclear	Quality of life (Quality of Life Index) General symptom scales (Chronic fatigue Syndrome Symptom Rating Form) Psychological status (CORE-E – overall resource gains and overall resource loss domains) at 12 months	Conducted in USA Outcomes reported after part 1 and after part 2 of the programme – only final time point (after both parts of intervention) extracted. Chronic Fatigue Syndrome Symptom Rating Form measured fatigue severity and severity of 8 Fukuda symptoms on a Likert scale 0-100 – study reports retest reliability but doesn't seem to have been validated – downgraded for measurement bias Study reports overall Quality of life index (a valid measure of QoL) and individual sub scales: health and functioning, social and economic,

Study	Intervention and comparison	Population	Outcomes	Comments
				psychological and spiritual. Overall measure extracted. CORE-E reported in Taylor 2006. Subdomains also reported. Only primary domains extracted. PEM reporting: the percentage of participants with PEM was not reported.Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
The 2007[94]	Acclydine capsules, containing 250mg of the alkaloid. Single daily dose on empty stomach, Decreasing dosage schedule: weeks 1–2, 1,000mg/day; weeks 3–6, 750mg/day; weeks 7–8, 500mg/day; weeks 9–10, 500mg every 2 days; weeks 11–12, 250mg/day; and weeks 13–14, 250mg every 2 days. Acclydine treatment combined with amino acid supplements to provide sufficient essential and nonessential amino acid intake during treatment. Versus	N=57 patients with CFS, meeting 1994 CDC criteria; psychiatric comorbidity excluded by structured interview; no mention of physician diagnosis/physical examination, etc. 26% recruited from outpatient dept; 74% from ME patient organisation newsletter. Strata details: adults (age 18-65 years); severity mixed or unclear	Activity levels (Actometer – average score over 12 days) Adverse events ('Important' side effects) Fatigue (Checklist individual strength – fatigue severity subscale)	Conducted in the Netherlands. Daily fatigue levels (patients rated the intensity of their fatigue during a 12 day period. They rated the Daily Observed Fatigue (DOF) 4x/day on a scale of 0 (no fatigue) to 4 (severely fatigued).

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients in the placebo group received placebo Acclydine and placebo amino acid supplements. There was no difference in taste, appearance, or packaging between the active supplements and the placebo capsules. Duration 14 weeks.	(adults age 18-65 years; patients with substantial functional impairment included - score >800 on SIP-8; score >35 on fatigue scale)	General symptom scales (Sickness impact profile-8) at 14 weeks	Not a validated measure of fatigue, not extracted. Side effects reported as single sentence; 'important' not defined. PEM reporting: the percentage of participants with PEM was not reported. Very serious population indirectness – study only included subset of patients with CFS who had a IGFBP3/IGF1 (blood test) ratio greater than 2.5; and 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Tummers 2012[95]	Guided self-instruction: information booklet about CFS and assignments. 20 week CBT programme for CFS described in the booklet. Patients challenged to establish goals, explains the precipitating and perpetuating factors, challenges fatigue-related cognitions and encourages to develop a sense of control over symptoms. Patients learn to reduce the focus on fatigue and establish a sleep routine. Relatively	N=123 people with CFS, diagnosed according to 1994 CDC criteria; if diagnosis was doubtful, based on baseline assessment and/or referral letter, a CFS expert contacted the referring GP or consultant for additional information to evaluate whether the diagnosis	Fatigue (Checklist Individual Strength fatigue sub scale) Physical functioning (SF36 physical functioning) Psychological status (Brief Symptom Inventory)	Conducted in the Netherlands PEM reporting: the percentage of participants with PEM was not reported. Very serious population indirectness: not all

Study	Intervention and comparison	Population	Outcomes	Comments
	active patients first have to learn to divide their activities more evenly, then gradually increase physical activity level, by walking or riding a bicycle. Patients with a low-active physical activity pattern start immediately with gradually increasing their physical activity level. Beliefs that activity would exacerbate symptoms are challenged. Patients make a plan for work resumption, containing the date when a patient will resume work, and how they will increase the hours worked. Excessive expectations regarding the response of their social environment to their symptoms are modified and patients learn how to communicate about CFS. Patients gradually increase mental and social activities, attain the goals as formulated earlier on step by step, including resumption of work. Patients learn how to prevent a relapse and further improve self-control. Patients email once every 2 weeks to ask questions and nurses monitor the progress. Intervention carried out by 8 psychiatric nurses trained in coaching patients with the minimal intervention. Nurses received supervision by a cognitive behavioural therapist experienced in CBT for CFS. Versus Waiting list (received the minimal intervention after 6-month delay).	CFS was justified. Eligibility was examined again during the 30-min intake session with the psychiatric nurse, who asked the patient about the presence of somatic or psychiatric conditions other than CFS. If they were present, the nurse contacted the researcher who informed the CFS expert. If necessary, the expert contacted the GP or consultant for additional information. If the diagnosis of CFS could be confirmed, the patient was included in the study. Strata details: adults; severity mixed or unclear (severe fatigue defined as >35 on the sub-scale fatigue severity of the Checklist Individual Strength, severely disabled operationalized as scoring <70 on the physical and/or social functioning subscale of the Medical Outcomes Survey Short Form-36)	at 6 months	patients turned out to have CFS; and 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Vos-Vromans 2016[97] (2012[98] and 2017[96])	Multidisciplinary rehabilitation: involved thorough assessment by an interdisciplinary team (physical therapist, occupational therapist, psychologist and social worker), a 10- week treatment phase (individual sessions, total contact time 33 h), including CBT, elements of	N=122 people with CFS according to 1994 CDC criteria; consultant confirmed inclusion and exclusion criteria and verified whether an extensive physical examination and	Quality of life (SF36) General symptom scales (Sickness Impact profile 8)	Conducted in the Netherlands 'Improvement and Satisfaction Questionnaire' – five

Study	Intervention and comparison	Population	Outcomes	Comments
(FatiGo trial)	body awareness therapy, gradual reactivation, pacing, mindfulness, gradual normalization of sleep/wake rhythm and social reintegration. Therapists followed principles of CBT and incorporated them with mindfulness principles. Interdisciplinary team meetings scheduled to discuss progress. Follow up with the social worker and 2 therapists of patients' choice to discuss issues of social reintegration and participation. Most therapists had experience in treating patients with chronic pain and/or chronic fatigue, were familiar with CBT, received training for each discipline (3–5 day) and attended team meetings and supervision meetings for each discipline during the trial. Duration 6 months. Versus CBT: Through dialogue with the psychologist or behavioural therapist and implementation during home exercises, patients taught to change negative beliefs regarding symptoms of fatigue, self-expectation and self-esteem. Patients also encouraged to adopt a regular sleep/wake rhythm. Time-contingent schedules made to gradually increase physical activity at home. 16 x 45-60 min sessions. Protocol specifically tailored for relatively active or passive patients. Therapists were experienced in treating patients with complaints of chronic pain and/or chronic fatigue, familiar with CBT and attended a 3-day course to familiarize themselves with the CBT protocol for CFS. Five supervision meetings were held and therapists were able to contact the supervisor as needed. Duration 6 months.	laboratory research tests had been performed to exclude any underlying illness. An interview with a psychologist was scheduled if the HADS depression subscale score was 11 or more (to exclude a major or bipolar depressive disorder) or if the consultant suspected another psychiatric illness or motivational problem. Strata details: adults; severity mixed or unclear	Fatigue (Checklist individual strength – fatigue severity) Psychological status (Symptom Checklist 90) Activity levels (accelerometer) at 12 months	questions (e.g. achieving personal goals, difference in dealing with problems), with different response categories, but categories unclear and questionnaire is not referenced/validated so not extracted. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. Outcomes reported at 6 months and 12 months, but only 12-month data extracted as this was the longest follow-up time point that data was available (as per review protocol).

Study	Intervention and comparison	Population	Outcomes	Comments
Wallman 2004[99]	Graded exercise therapy (n=34) - Initial exercise duration 5-15 mins; intensity based on the mean HR value achieved mid-point during the sub-maximal exercise tests. Graded exercise consisted of an aerobic activity that used the major large muscles of the body, of either walking, cycling or swimming. Subjects were instructed to exercise every second day unless they had a relapse. If this occurred or if symptoms became worse, the next exercise session was shortened or cancelled and subsequent sessions were reduced to a length that subjects felt was manageable (pacing). Each subject was supplied with a small laminated Borg scale, and an HR monitor to help them reach and maintain their required HR goals. Subjects rated the effort of each exercise session and recorded their exercise details in a diary. They were contacted by phone every second week over the 12 weeks to review their progress and to determine their exercise regimen for the following fortnight. Versus Relaxation/flexibility programme (n=34) - Subjects were required to listen to a relaxation tape, and perform selected stretching exercises every second day for 12 weeks. All subjects kept a diary recording their relaxation/flexibility sessions. They were contacted by phone every second week to review their progress and to discuss the flexibility regimen for the following fortnight. They had been specifically requested not to participate in any extra physical activity while they were enrolled in the study. The	N=68 people with CFS (1994 CDC criteria); diagnosis was confirmed in writing by each participant's physician. Strata details: age and severity mixed or unclear (age range 16-74 years, mean age not reported);	Quality of Life (Self-rated Clinical global impression change) Fatigue (Chalder fatigue scale) Cognitive function (Stroop test (82 questions), Stroop test (95 questions)) Psychological status (Hospital anxiety and depression scale) Exercise performance measures (Oxygen uptake/VO2 peak) at 16 weeks (4 weeks post-intervention)	Conducted in Australia Oxygen uptake assumed to be maximal oxygen uptake (VO2 max or peak), but not clearly described. Physiological measures reported in paper but not extracted for analysis as not meeting any protocol outcomes: resting sBP/dBP, resting HR, net blood lactate production, respiratory exchange ratio. Borg scale of perceived exertion reported as p-value only. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].

Study	Intervention and comparison	Population	Outcomes	Comments
	exercise physiologist attempted to spend the same amount of time on the phone with all subjects in both therapy groups. 12 weeks			
Wearden 1998[104]	This four-arm study compared an antidepressant, graded exercise and placebos of both: 1. Fluoxetine & exercise control 2. Graded exercise & drug placebo 3. Fluoxetine & graded exercise 4. Drug placebo & exercise control Graded exercise & drug placebo versus Exercise control and drug placebo included in this review (the remainder of the comparisons have been included in pharmacological interventions review). Graded exercise Subjects were instructed to carry out their preferred aerobic activity (usually walking/ jogging, swimming or cycling), for 20 minutes, at least three times per week. The intensity of the activity was initially set at a level which utilised oxygen at approximately 75% of the subject's tested functional maximum. Exercise intensity was increased when there was a consistent recorded reduction of 10 beats per minute in post-exercise heart rate for one week and two points on the perceived exertion scale. This group also received a placebo fluoxetine capsule of similar taste and appearance, taken daily. Duration: 6 months. Versus	N=136 people with CFS, diagnosed according to Oxford Criteria (Sharpe 1991). Strata details: adults (18-65 years); severity mixed or unclear.	Fatigue (14-item Chalder fatigue scale) Psychological status (depression on the Hospital Anxiety and Depression Scale) Exercise performance measure (functional work capacity/VO2 peak) at 6 months	Conducted in United Kingdom. Functional work capacity assumed to be VO2 peak – described in study as the amount of oxygen consumed in the final minute of exercise per kg bodyweight. Most subjects reached subjective exhaustion prior to reaching predicted max heart rate, and before a plateau in oxygen consumption, hence not extrapolated to theoretical max oxygen intake. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original

Study	Intervention and comparison	Population	Outcomes	Comments
	Exercise control (activity diaries) Exercise control consisted of a placebo exercise programme in which participant activity diaries were reviewed by a physiotherapist. Subjects were not offered any specific advice on how much exercise they should be taking but were told to do what they could when they felt capable and to rest when they felt they needed to. Drug placebo: Fluoxetine placebo: a capsule of similar taste and appearance, taken by participants in both study arms daily for 6 months.			analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Wearden 2006[105], 2010[102]& 2013[103] (FINE trial)	Pragmatic rehabilitation, 10 sessions delivered in patients homes/phone calls by registered, adult specialty, general nurses who had worked in primary care but no previous ME/CFS experience. Programme of graded return to activity designed by patient and the therapist on the basis of a physiological dysregulation model of ME/CFS. Focus on sleep, relaxation, concentration, memory problems, education on CFS symptoms, goal setting. Patients were allowed to consult their GP. Duration 18 weeks. Versus Supportive listening, 10 sessions. Therapy based on non-directive counselling, therapist aims to provide an empathic and validating environment in which the patient can discuss his or her concerns and work towards resolution of problems. Standard counselling techniques of active listening, reflection and summarising	N = 296 people with CFS, meeting Oxford diagnostic criteria. GP referred in accordance with a brief diagnostic protocol and checklist which included a list of exclusionary tests. Strata details: adults (age ≥18 years); severity mixed or unclear (score ≤ 70% on SF-36 physical functional scale and ≥ 4 on Chalder fatigue scale; 11% of participants non-ambulatory at baseline (used mobility aid on most days))	Physical functioning (SF36 physical functioning subscale) Fatigue (Chalder fatigue scale) Psychological status (Hospital anxiety and depression scale) Sleep quality (Jenkins sleep scale) Exercise performance measure (Step-test, Borg rating of perceived exertion) at 70 weeks	Conducted in the UK. Outcomes reported at 20 weeks and 70 weeks, but only 70-week data extracted as this was the longest follow-up time point that data was available (as per reviprotocol).Step-test: Patients asked to step on and off a 20cm step "at a normal pace". In the event the patient reached subjective exhaustion before completing 20 steps, the time taken, and number of steps completed was recorded.

Study	Intervention and comparison	Population	Outcomes	Comments
	used. Therapists did not provide explanation for symptoms. Content of sessions determined by patients and therapists avoided giving advice or leading patients. Same nurses as for pragmatic rehab. Patients were allowed to consult their GP. Duration 18 weeks. Versus Usual care – GPs were asked to manage their cases as they saw fit, but not to refer for systematic psychological therapies for CFS/ME during the 18 week treatment period.			Author defined improvement/resolution of fatigue (defined as scores of <4 on Chalder fatigue scale) and significant improvement in physical function (defined as scores of >70% or 50% improvement from baseline on SF36 sub scale) not extracted due to the high risk of bias associated with author dichotomisation of continuous outcomes. Continuous data for these scales have been extracted. Step-test only reported for pragmatic rehabilitation vs usual care comparison. Included economic evaluation paper Richardson 2013 reported EQ5D scores only graphically; unable to extract. PEM reporting: the percentage of

Study	Intervention and comparison	Population	Outcomes	Comments
				participants with PEM was not reported. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Weatherley-Jones 2004[106]	Monthly consultations with a registered homeopath (9 homeopaths from 2 clinics) over 6 months; 90 mins initial consultation and 45 mins subsequent consultations. Homeopaths prescribed remedies according to their usual practice, generally a single remedy per consultation; remedy prepared/dispensed by single homeopathic pharmacy. Versus Placebo; the same as intervention, except no indicated source material in placebo.	N= 103 people with CFS, meeting Oxford criteria for CFS diagnosis. Physical examination, blood tests, and a psychiatric assessment performed as part of assessment for eligibility. Strata details: adults (age >18 years); severity mixed or unclear	Fatigue (Fatigue impact scale; Multidimensional fatigue inventory) General symptoms scale (Functional limitations profile) at 7 months	Conducted in the UK. Functional limitations profile and Fatigue impact scale extractions – unclear if data is mean percentage change or absolute change. All change scores assumed to be representing improvement but not clearly reported for all outcomes. Author defined clinical improvement in MFI not extracted due to the high risk of bias associated with author dichotomisation of continuous outcomes.

Study	Intervention and comparison	Population	Outcomes	Comments
				Continuous data for this scale has been extracted. Functional limitations profile is British version of Sickness impact profile. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
White 2011[107] (White 2007[108] , Walwyn 2013[100] , Bourke 2014[8], Dougall 2014[29] , Sharpe 2015[83])	Standard medical care + CBT. CBT was done on the basis of the fear avoidance theory of chronic fatigue syndrome. Therapeutic strategies guided participants to address unhelpful cognitions, including fears about symptoms or activity by testing them in behavioural experiments (establishing a baseline of activity and rest and a regular sleep pattern, and then making collaboratively planned gradual increases in both physical and mental activity). Participants were helped to address social and emotional obstacles to improvement through problem-solving. Therapy manuals were	N=641 people with CFS, according to Oxford criteria; medically assessed by specialist clinic doctors to exclude alternative diagnoses. Strata details: adults; severity mixed or unclear (score of 6 or more on Chalder Fatigue scale and a score of 60 or less on SF36 physical, changed to <65 11 months post randomization to increase recruitment)	<u>At 52 weeks:</u> Quality of life (EQ5D) Psychological status (Hospital Anxiety and Depression Scale) Pain (muscle and joint pain numeric rating scale) Sleep (Jenkins Sleep Scale)	Conducted in the UK White 2013 excluded due to no relevant outcomes: reported the number of people in each trial arm who met author defined criteria for recovery. PEM reporting: 84.2% of participants had PEM. By study arm: APT 84%, CBT 84%,

Study	Intervention and comparison	Population	Outcomes	Comments
(PACE trial)	based on manuals used in previous trials. CBT was delivered mainly by clinical psychologists and nurse therapists. Duration 24 weeks. Versus Standard medical care + GET. GET was done on the basis of deconditioning and exercise intolerance theories of chronic fatigue syndrome. Establishment of a baseline of achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active. Target heart rate ranges were set when necessary to avoid overexertion, which aimed at 30 min of light exercise five times a week. When this was achieved, the intensity and aerobic nature of the exercise was gradually increased, with participant feedback and mutual planning. Therapy manual based on that used in previous trials. GET was delivered by physiotherapists and one exercise physiologist. Duration 24 weeks. Versus Standard medical care + adaptive pacing therapy. Based on the envelope theory of chronic fatigue syndrome. Identifying links between activity and fatigue by use of a daily diary, with corresponding encouragement to plan activity to avoid exacerbations, developing awareness of early warnings of exacerbation, limiting demands and stress, regularly planning rest and relaxation, and alternating different types of activities, with advice not to undertake activities that demanded more than 70% of		Adverse events (serious and non-serious adverse events, adverse reactions) Exercise performance measure (6 minute walk) <u>At 134 weeks:</u> General symptom scales (Self-rated Clinical Global Impression change in overall health Scale) Fatigue (Chalder Fatigue Questionnaire) Physical functioning (SF36 physical functioning) Return to school/work (Work and Social Adjustment Scale)	GET 82%, SMC 87%. Some outcome data was available for participants meeting the London ME criteria, but the London ME criteria does not clearly described PEM as a compulsory feature. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; <95% of participants had PEM [PEM reanalysis]. Long-term follow-up was available for some outcomes. This data was preferentially extracted for these outcomes as this was the longest time point that data was available (as per review protocol). For the remaining outcomes, 52 weeks was the longest time point that data was available, and this data was extracted. 24-week outcome data was also available but

Study	Intervention and comparison	Population	Outcomes	Comments
	participants' perceived energy limits. Increased activities were encouraged, if the participant felt able, and as long as they did not exacerbate symptoms. Manuals were created for therapists and patients. Westcare and Action for ME helped in the design of the therapy and endorsed the final manuals. APT was provided by occupational therapists. Duration 24 weeks. Versus Standard medical care provided by doctors with specialist experience in CFS. Participants given a leaflet explaining the illness and the nature of this treatment. The manual was consistent with good medical practice, as presently recommended. Treatment consisted of an explanation of chronic fatigue syndrome, generic advice, such as to avoid extremes of activity and rest, specific advice on self-help, according to the particular approach chosen by the participant (if receiving SMC alone), and symptomatic pharmacotherapy (especially for insomnia, pain, and mood). Duration 24 weeks.			this was not extracted for any outcomes.
Wiborg 2015[109]	14 group sessions of 2 h within a period of 6 months. Included personal goal setting, fixing sleep-wake cycles, reducing the focus on bodily symptoms, a systematic challenge of fatigue-related beliefs, regulation and gradual increase in activities, and accomplishment of personal goals. Patients received a workbook with the content of the therapy. During sessions, patients were explicitly invited to give feedback about fatigue-related cognitions and behaviours to fellow patients. Group therapists (n=12) held degrees in psychology with the exception of a	N=204 people with CFS, according to 1994 CDC criteria; Department of Internal Medicine assessed the medical examination status of all patients and decided whether patients had been sufficiently examined by a medical doctor to rule out relevant medical explanations. If patients had not been sufficiently examined, they were seen for standard medical tests	General symptom scales (Sickness Impact Profile) Fatigue (Checklist Individual strength fatigue severity) Physical functioning (SF36 physical functioning) Psychological status (Symptom Checklist 90)	Conducted in the Netherlands Large CBT group and small CBT group combined PEM reporting: the percentage of participants with PEM was not reported.Serious

Study	Intervention and comparison	Population	Outcomes	Comments
	therapist who held a degree in pedagogy and a social worker with experience in group therapy, who also coordinated the group programme. All therapists were trained in manualised CBT for individual CFS patients. Versus Waiting list	prior to referral to the outpatient clinic. In accordance with CDC recommendations, sufficient medical examination included evaluation of somatic parameters that may provide evidence for a plausible somatic explanation for prolonged fatigue. When abnormalities were detected in these tests, additional tests were made based on the judgement of the clinician of the Department of Internal Medicine who ultimately decided about the appropriateness of referral. Trained therapists ruled out psychiatric comorbidity as potential explanation for the complaints in unstructured clinical interviews. Strata details: adults; severity mixed or unclear (severe fatigue defined as a score of 35 or higher on the fatigue severity subscale of the Checklist Individual Strength and substantial impairment as a weighted total score of 700 or higher on the Sickness Impact Profile)	at 6 months	population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Windthorst 2017[110]	Heart rate variability biofeedback therapy- HRV-BF (n=13) – 8 individual training sessions, 50 mins, weekly. Carried out by a trained clinical psychologist. Aim of the 1st session was to	N=28 people with CFS (1994 CDC criteria). Participants underwent 2 structured clinical interviews (for DSM-IV axis	Quality of life (SF-36) Fatigue (Multidimensional Fatigue Inventory)	Conducted in Germany All female participants

Study	Intervention and comparison	Population	Outcomes	Comments
	become familiar with the setting, equipment and therapist. Subsequent sessions started with a 10-min review of the diary, followed by a 20-30 min HRV-BF practice. The HRV-BF training included practicing slow inspiration and expiration with 6-10 breaths/min, visualised on a monitor as two separate lines (breathing curve, heart rate) and meant to alter the individual stress reaction and to induce individual alleviation of tension. Period of exploring the body's reactions to the breathing and discussing these experiences alternated. After the practice interval, the therapist and patient reviewed the session records showing breathing, heart rate, skin conductance response and skin temperature. Interactions of physiology and emotion/cognition were discussed. By gaining experience with HRV-BF, patients were successively instructed to improve their RSA under real-life conditions such as imagining actual situations of stress. In addition to self-monitoring (diary keeping), homework was given in the form of daily practice exercises without the biofeedback device 2x per day 5-10 min each time. Versus Graded exercise therapy (n=15) - 8 individual training sessions, 50 mins, weekly. Carried out by a sports therapist and expert in sports medicine. The individual anaerobic threshold (IAS), collected by spirometry, was the individual training baseline. Patients were instructed in slow walking training on a treadmill adapted to their heart rate which equates about 70% of heart rate IAS. Duration and intensity set at a	disorders and somatoform disorder schedule) with an experienced psychologist, and underwent physical examination and, if necessary, laboratory testing. Strata details: adults; severity mixed or unclear	Psychological status (Depression -Patient Health questionnaire)	PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. Outcomes reported at 8 weeks (post-treatment) and 5 months, but only 5-month data extracted as this was the longest follow-up time point that data was available (as per review protocol).

Study	Intervention and comparison	Population	Outcomes	Comments
	level identified as achievable under spirometry testing and unlikely to exacerbate the patients' symptoms. Aim of 1st session was to familiarise the patient with the setting, equipment, treadmill and therapist. Subsequent sessions subdivided to 3 parts comparable to the HRV-BF training. Sessions began with a review and discussion of diary entries and the experience created by doing the exercises at home, followed by 20-30 min of waking training adapted to a moderate heart rate. At the end of the session, the sports therapist and patient reviewed the course of the session in regard to heart rate and physical reactions. Patients were encouraged to reduce resting and avoiding behaviour but simultaneously to watch carefully for symptoms and feelings of overload. In addition to continuing to keep a diary, homework consisted of 2-3 walking sessions per week at home (20-30 min), controlled by a pulse watch. All participants in both groups kept a fatigue/activity diary which was discussed at each session. 8 weeks			
Witham 2015[111]	A single dose of 100,000 units of oral vit D3 (Vigantol oil), 20,000 units vit D3 per ml, administered at baseline, 2 months, and 4 months. Medication ingested in presence of study team. Versus A single dose of placebo (Mygliol oil), administered at baseline, 2 months, and 4	N=50 people diagnosed with CFS, fulfilling 1994 CDC criteria and Canadian criteria. Participants were recruited from a connective tissue disease clinic. Strata details: adults (age ≥18 years); severity mixed or unclear	Fatigue (Piper fatigue scale) Psychological status (Hospital anxiety and depression scale – anxiety and depression sub scales)	Conducted in the UK For fatigue and psychological status outcomes – results reported as 'symptom scores' (SD) – assumed to be mean as other outcomes (not relevant to protocol) are reported

Study	Intervention and comparison	Population	Outcomes	Comments
	months. Medication ingested in presence of study team.		Adverse events (all – number of events, deaths, hospitalisations) at 6 months	as means (SD). Time point measured unclear. Participants met both the 1994 CDC criteria and the Canadian Criteria (Carruthers 2003) – the Canadian criteria has PEM as a compulsory feature. Serious population indirectness – study only included subset of CFS population who also had 25OHD (serum vit D) level <75nmol/L. Piper fatigue scale – subscale scores reported, only total score extracted.
Wright 2005[112]	Pacing – focus on pacing activity to the point of tolerance, avoiding overexertion, managing energy within overall limit, resting when needed but avoiding total rest, avoiding physically/emotional stressful situations. Duration 1 year. Versus The stairway to health programme – a structured tailored incremental rehabilitation programme. Focus on providing holistic understanding of CFS that moved away from an exclusively physical or psychological understanding of the illness; explaining vicious cycles that exacerbate	N=13 people with CFS, assessed by a paediatrician prior to entry into the study, Oxford criteria for diagnosis used (with modification for children of 3 months fatigue). Strata details: children and young people (age range 8.9-16.9 years (breakdown: 0-11: n=1; 12-14: n=7; 15-19: n=5)); severe (in mainstream schools; incapacitated by CFS to the point of not being able to attend	<u>At 12 months:</u> Quality of life (Child health questionnaire – global health subscale) Fatigue (14-item Chalder's fatigue scale) Psychological status (Birleson depression rating scale; Hospital anxiety and depression scale – anxiety subscale)	Conducted in the UK. Participants are children and young people – 1 participant was <12 years old. The Child Health Questionnaire is a family of generic person-reported outcomes measures to assess health-related quality of life for children

Study	Intervention and comparison	Population	Outcomes	Comments
	illness (including nutrition, sleep patterns, physical deconditioning, social isolation, educational estrangement, and emotional cycles); adaptive coping strategies and re-evaluating negative attributions about the illness and the future. Duration 1 year. Both interventions involved clinic appointments weekly for 1 month, 2 weekly for 3 months, 3 weekly for 2 months, and 4 weekly for 6 months. Sessions delivered by 3 clinicians. Emphasis on collaboration with patient and family and between mental health team/paediatricians, healthy diet and sleep patterns. Collaboratively agreed targets set around nutrition, activity, sleep, social activity, emotional factors and school reintegration. Constructive discussion around how lifestyles, temperaments and approaches to life may impact on illness or recovery. A tailored gradual return to school and social activity was planned where possible.	school; markedly restricted in their ability to walk from the house, but not permanently bed or wheelchair bound).	General symptoms scales (Young person functional ability scale) <u>6-month post-study period (12-18 months) :</u> Return to school or work (School attendance – percentage of half days attended in 6 month period)	and adolescents from 5-to-18 years of age. PEM reporting: the percentage of participants with PEM was not reported. Serious population indirectness – Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis].
Zhang 2015[113]	Participants were required to listen to music from the Five Element Music CD for 5 days/week, 2 days rest; 45 mins sessions starting at either 12pm or 7pm each day; volume 55-65 dB in quiet environment; tape recorders, intensity of music, patient's location kept constant throughout study; the importance of music therapy was emphasized in the first treatment. Participants also given Lixujieyu recipe (Chinese medicine); recipe prepared by study hospital pharmacy department; 300ml = 1 dose; ½ a dose administered in the morning, the other ½ in the evening. Duration 4 weeks. Versus	N= 90 people with CFS, meeting the 1994 CDC diagnostic criteria); hospitalized patients or outpatients of a CFS specialist outpatient unit. Had undergone medical examination to exclude other causes of chronic fatigue. Strata details: severity and age mixed or unclear (inclusion criteria age range 15-60, but mean age suggests mostly adults), inpatients and outpatients)	Fatigue (Fatigue scale based on Chalder fatigue scale) Psychological status (Hamilton depression scale; Hamilton anxiety scale) at 4 weeks	Conducted in China. PEM reporting: the percentage of participants with PEM was not reported. Very serious population indirectness – subset of CFS population who also met TCM definition for liver stagnation and spleen deficiency syndrome; and 1994 CDC criteria used; PEM

Study	Intervention and comparison	Population	Outcomes	Comments
	Participants were given Lixujieyu recipe (Chinese medicine); the same as for the intervention arm. Duration 4 weeks.			is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]. 5 intervention arms, data combined – different type of music + traditional Chinese medicine.

See appendices for full evidence tables.

1.1.5 Quality assessment of clinical studies included in the evidence review

1.1.5.1 Self-management

Table 3: Clinical evidence summary: Self-management (activity pacing) versus Relaxation: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95 % CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Self-management versus Relaxation in adults (95% CI)
Quality of life (SF36 sub scales) - Physical functioning Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - physical functioning in the control groups was 45	The mean quality of life (sf36 sub scales) - physical functioning in the intervention groups was 8.2 higher (5.37 lower to 21.77 higher)
Quality of life (SF36 sub scales) - Role physical Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - role physical in the control groups was 11.5	The mean quality of life (sf36 sub scales) - role physical in the intervention groups was 24.9 higher (1.8 lower to 51.6 higher)
Quality of life (SF36 sub scales) - Bodily pain Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - bodily pain in the control groups was 40.4	The mean quality of life (sf36 sub scales) - bodily pain in the intervention groups was 7.6 higher (8.61 lower to 23.81 higher)
Quality of life (SF36 sub scales) - General health Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3		The mean quality of life (sf36 sub scales) - general health in the	The mean quality of life (sf36 sub scales) - general health in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95 % CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Self-management versus Relaxation in adults (95% CI)
		due to risk of bias, indirectness, imprecision		control groups was 39	3.5 higher (11.55 lower to 18.55 higher)
Quality of life (SF36 sub scales) - Vitality Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - vitality in the control groups was 35	The mean quality of life (sf36 sub scales) - vitality in the intervention groups was 3.6 higher (7.67 lower to 14.87 higher)
Quality of life (SF36 sub scales) - Social functioning Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - social functioning in the control groups was 43.1	The mean quality of life (sf36 sub scales) - social functioning in the intervention groups was 10.3 higher (5.5 lower to 26.1 higher)
Quality of life (SF36 sub scales) - Role emotional Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - role emotional in the control groups was 51.3	The mean quality of life (sf36 sub scales) - role emotional in the intervention groups was 42.6 higher (15.77 to 69.43 higher)
Quality of life (SF36 sub scales) - Mental health Scale from: 0 to 100.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,		The mean quality of life (sf36 sub scales) - mental health in the control groups was 58.2	The mean quality of life (sf36 sub scales) - mental health in the intervention groups was 11.3 higher (1.64 lower to 24.24 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95 % CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Self-management versus Relaxation in adults (95% CI)
		indirectness, imprecision			
Physical function (Canadian Occupational Performance Measure) - Performance Scale from: 1 to 10.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical function (Canadian occupational performance measure) - performance in the control groups was 5.1	The mean physical function (Canadian occupational performance measure) - performance in the intervention groups was 0.5 higher (0.62 lower to 1.62 higher)
Physical function (Canadian Occupational Performance Measure) - Satisfaction Scale from: 1 to 10.	26 (1 study) 5 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical function (Canadian occupational performance measure) - satisfaction in the control groups was 4.5	The mean physical function (Canadian occupational performance measure) - satisfaction in the intervention groups was 1.2 higher (0.13 lower to 2.53 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Kos 2015

Table 4: Clinical evidence summary: Self-management (group-based programme) versus Usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Self-management versus Usual care in adults (95% CI)
Quality of life (SF36) - Mental component Scale from: 0 to 100.	117 (1 study) 12 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias		The mean quality of life (sf36) - mental component in the control groups was 40.5	The mean quality of life (sf36) - mental component in the intervention groups was 1.4 lower (4.93 lower to 2.13 higher)
Quality of life (SF36) - Physical component Scale from: 0 to 100.	117 (1 study) 12 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias		The mean quality of life (sf36) - physical component in the control groups was 24.2	The mean quality of life (sf36) - physical component in the intervention groups was 0.5 higher (2.49 lower to 3.49 higher)
Fatigue (Fatigue Severity Scale) Scale from: 9 to 63.	118 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 57.1	The mean fatigue (fatigue severity scale) in the intervention groups was 0.7 lower (3.15 lower to 1.75 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Pinxsterhuis 2017

Table 5: Clinical evidence summary: Self-management (adaptive pacing therapy) versus usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Adaptive pacing therapy (95% CI)
Quality of life (EQ5D) Scale from: -0.594 to 1.	299 (1 study) 52 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean quality of life (eq5d) in the control groups was 0.53	The mean quality of life (eq5d) in the intervention groups was 0.01 higher (0.06 lower to 0.08 higher)
General symptom scales (proportion with positive change (very much better or much better)	233 (1 study) 134 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	OR 0.8 (0.4 to 1.6)	Moderate	
				417 per 1000	53 fewer per 1000 (from 195 fewer to 117 more)
Fatigue/fatigability (Chalder fatigue scale) Scale from: 0 to 33.	235 (1 study) 134 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatiguability (chalder fatigue scale) in the control groups was 20.2	The mean fatigue/fatigability (chalder fatigue scale) in the intervention groups was 0.3 higher (1.7 lower to 2.3 higher)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	233 (1 study) 134 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 57.4	The mean physical functioning (sf36 physical function) in the intervention groups was 3.6 lower (9.6 lower to 2.4 higher)
Psychological status (HADS anxiety) Scale from: 0 to 21.	298 (1 study) 52 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads anxiety) in the control groups was 8.0	The mean psychological status (hads anxiety) in the intervention groups was 0.7 lower (1.46 lower to 0.06 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Adaptive pacing therapy (95% CI)
Psychological status (HADS depression) Scale from: 0 to 21.	300 (1 study) 52 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean psychological status (hads depression) in the control groups was 7.2	The mean psychological status (hads depression) in the intervention groups was 0.6 lower (1.34 lower to 0.14 higher)
Pain (numeric rating scale) - muscle pain Scale from: 0 to 4.	300 (1 study) 52 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, indirectness		The mean pain (numeric rating scale) - muscle pain in the control groups was 2.11	The mean pain (numeric rating scale) - muscle pain in the intervention groups was 0.04 lower (0.35 lower to 0.27 higher)
Pain (numeric rating scale) - joint pain Scale from: 0 to 4.	300 (1 study) 52 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, indirectness		The mean pain (numeric rating scale) - joint pain in the control groups was 1.54	The mean pain (numeric rating scale) - joint pain in the intervention groups was 0.1 higher (0.24 lower to 0.44 higher)
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	301 (1 study) 52 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean sleep quality (jenkins sleep scale) in the control groups was 11.0	The mean sleep quality (jenkins sleep scale) in the intervention groups was 0.1 lower (0.75 lower to 0.55 higher)
Return to work (Work and social adjustment scale) Scale from: 0 to 40.	235 (1 study) 134 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean return to work (work and social adjustment scale) in the control groups was 21.1	The mean return to work (work and social adjustment scale) in the intervention groups was 1.3 higher (1.2 lower to 3.8 higher)
Adverse events (non-serious)	319 (1 study) 52 weeks	⨁⨀⨀⨀ VERY LOW[1,2,4] due to risk of bias, indirectness	RR 1.03 (0.97 to 1.08)	Moderate 931 per 1000	28 more per 1000 (from 28 fewer to 74 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Adaptive pacing therapy (95% CI)
Adverse events (serious)	319 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 2.16 (0.9 to 5.15)	Moderate	
				44 per 1000	51 more per 1000 (from 4 fewer to 183 more)
Adverse events (adverse reactions)	319 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.01 (0.14 to 7.06)	Moderate	
				13 per 1000	0 more per 1000 (from 11 fewer to 79 more)
Exercise performance measure (6 minute walk test)	229 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (6 minute walk test) in the control groups was 348 m	The mean exercise performance measure (6 minute walk test) in the intervention groups was 5.7 lower (24.44 lower to 13.04 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment).: Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is <95% [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 Downgraded 1 increment if the majority of the evidence had an indirect outcome (adverse events not necessarily treatment-related)..

*Studies contributing to comparison: PACE trial

Table 6: Clinical evidence summary: Self-management (programme delivered by booklet/CDs with step counter or actigraphy) versus Usual care: adults; severe

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Self-management (95% CI)
Fatigue (fatigue severity scale) Scale from: 9 to 63.	124 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 6.42	The mean fatigue (fatigue severity scale) in the intervention groups was 0.37 lower (0.66 to 0.08 lower)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	125 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 44.07	The mean physical functioning (sf36 physical function) in the intervention groups was 2.06 higher (6.45 lower to 10.57 higher)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	125 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) in the control groups was 18.64	The mean psychological status (beck depression inventory) in the intervention groups was 4.89 lower (8.3 to 1.48 lower)
Psychological status (Beck anxiety inventory) Scale from: 0 to 63.	121 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck anxiety inventory) in the control groups was 18.3	The mean psychological status (beck anxiety inventory) in the intervention groups was 2.5 lower (6.34 lower to 1.34 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is <95% [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Friedberg 2016

Table 7: Clinical evidence summary: Self-management (activity pacing) versus Stairway to health programme (structured incremental rehabilitation programme): children and young people; severe

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Self-management versus Stairway to health programme in children/young people (95% CI)
Quality of life (Child Health Questionnaire) Scale from: 1 to 5.	11 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean quality of life (child health questionnaire) in the control groups was 2.2	The mean quality of life (child health questionnaire) in the intervention groups was 2 higher (1.18 to 2.82 higher)
General symptom scales (Young person functional ability scale) Scale from: 0 to 100.	11 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean general symptom scales (young person functional ability scale) in the control groups was 81.25	The mean general symptom scales (young person functional ability scale) in the intervention groups was 12.75 lower (40.3 lower to 14.8 higher)
Fatigue (Chalder fatigue scale) Scale from: 0 to 42.	11 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue scale) in the control groups was 14	The mean fatigue (chalder fatigue scale) in the intervention groups was 4 higher (5.56 lower to 13.56 higher)
Psychological status (Birleson depression scale) Scale from: 0 to 36.	11 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (birleson depression scale) in the control groups was 10.67	The mean psychological status (birleson depression scale) in the intervention groups was 1.93 higher (5.02 lower to 8.88 higher)
Psychological status (Hospital anxiety and depression scale -	11 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Self-management versus Stairway to health programme in children/young people (95% CI)
anxiety) Scale from: 0 to 21.		due to risk of bias, indirectness, imprecision		was 6	groups was 0.6 higher (4.46 lower to 5.66 higher)
Return to school/work (% school attendance) Scale from: 0 to 100.	11 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school/work (% school attendance) in the control groups was 84.6	The mean return to school/work (% school attendance) in the intervention groups was 55.9 lower (98.14 to 13.66 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Wright 2005

1.1.5.2 Psychological/behavioural interventions

1.1.5.2.1 Cognitive behavioural therapy

Table 8: Clinical evidence summary: CBT versus usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
Quality of life (EQ5D) - individual face-to-face CBT Scale from: -0.594 to 1.	294 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (eq5d) in the control groups was 0.53	The mean quality of life (eq5d) in the intervention groups was 0.1 higher (0.03 to 0.17 higher)
Quality of life: SF-36 mental score - group based CBT SF-36 mental score. Pooled 6 and 12 months data. Scale from: 1 to 100.	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life: sf-36 mental score in the control groups was 39.07	The mean quality of life: sf-36 mental score in the intervention groups was 4.35 higher (0.72 to 7.98 higher)
Quality of life: SF-36 physical score - group based CBT SF-36 physical score. Pooled 6 and 12 months data. Scale from: 0 to 100.	103 (1 study) 6- 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life: sf-36 physical score in the control groups was 34.70	The mean quality of life: sf-36 physical score in the intervention groups was 1.63 lower (4.05 lower to 0.79 higher)
Quality of life: Health status - group based CBT Health status (HUI3). Pooled 6 and 12 month data. Scale from: -0.36 to 1.	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean quality of life: health status in the control groups was 0.39	The mean quality of life: health status in the intervention groups was 0.03 higher (0.05 lower to 0.11 higher)
				Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
General symptom scales: Clinical Global Impression Scale Proportion with change (very much better or much better) - individual face-to-face CBT	234 (1 study) 134 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	OR 0.9 (0.5 to 1.62)	417 per 1000	25 fewer per 1000(from 154 fewer to 120 more)
General symptom scales: Sickness Impact profile 8 (SIP8) - web/written CBT Scale from: 0 to 5799.	409 (2 studies) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision		The mean general symptom scales: sickness impact profile 8 in the control groups was 1320.75	The mean general symptom scales: sickness impact profile 8 in the intervention groups was 409.81 lower (531.36 to 288.25 lower)
General symptom scales: sickness Impact profile 8 - group-based CBT Scale from: 0 to 5799.	204 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness		The mean general symptom scales: sickness impact profile 8 in the control groups was 1389	The mean general symptom scales: sickness impact profile 8 in the intervention groups was 589 lower (762.88 to 415.12 lower)
Fatigue/fatigability (Checklist Individual strength - fatigue severity) - web/written CBT Scale from: 8 to 56.	520 (3 studies) 6-12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean fatigue/fatigability (checklist individual strength - fatigue severity) in the control groups was 46.4	The mean fatigue/fatigability (checklist individual strength - fatigue severity) in the intervention groups was 7.19 lower (9.13 to 5.25 lower)
Fatigue/fatigability (Checklist Individual strength - fatigue severity) - group-based CBT Scale from: 8 to 56.	204 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean fatigue/fatigability (checklist individual strength - fatigue severity) in the control groups was 46.6	The mean fatigue/fatigability (checklist individual strength - fatigue severity) in the intervention groups was 13.1 lower (16.15 to 10.05 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
Fatigue/fatigability (Chalder Fatigue Questionnaire) - web/written CBT Scale from: 0 to 33	228 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue questionnaire) in the control groups was 20.8	The mean fatigue (chalder fatigue questionnaire) in the intervention groups was 3.69 lower (5.77 to 1.61 lower)
Fatigue/fatigability (Chalder Fatigue Questionnaire) - group-based CBT Pooled 6 and 12 month data. Scale from: 0 to 33.	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (chalder fatigue questionnaire) - group-based cbt in the control groups was 20.64	The mean fatigue/fatigability (chalder fatigue questionnaire) - group-based cbt in the intervention groups was 2.61 lower (4.92 to 0.3 lower)
Fatigue/fatigability (Chalder fatigue questionnaire) - individual face-to-face CBT Scale from: 0 to 33.	234 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue questionnaire) in the control groups was 20.2	The mean fatigue (chalder fatigue questionnaire) in the intervention groups was 1.4 lower (3.4 lower to 0.6 higher)
Fatigue (fatigue severity 0-10 scale) - change scores - face-to-face CBT Scale from: 0 to 10.	60 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity 0-10 scale) - change scores in the control groups was -1.6	The mean fatigue (fatigue severity 0-10 scale) - change scores in the intervention groups was 1.9 lower (3.3 to 0.5 lower)
Physical functioning (SF36 physical functioning sub-scale) - web/written CBT Scale from: 0 to 100.	520 (3 studies) 6-12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean physical functioning (sf36 physical functioning sub-scale) ranged across control groups was 60.2	The mean physical functioning (sf36 physical functioning sub-scale) in the intervention groups was 6.25 higher (2.58 to 9.92 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
Physical functioning (SF36 physical functioning sub-scale) - group-based CBT Scale from: 0 to 100.	204 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning sub-scale in the control groups was 63.3	The mean physical functioning (sf36 physical functioning sub-scale) in the intervention groups was 11.1 higher (4.87 to 17.33 higher)
Physical functioning (SF-36 physical functioning sub-scale) - individual face-to-face CBT Scale from: 0 to 100.	234 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf-36 physical functioning sub-scale) in the control groups was 57.4	The mean physical functioning (sf-36 physical functioning sub-scale) in the intervention groups was 2.8 higher (3.2 lower to 8.8 higher)
Cognitive function (total words recalled) - group-based CBT Pooled 6 and 12 months data	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean cognitive function (total words recalled) in the control groups was 12.43	The mean cognitive function (total words recalled) in the intervention groups was 0.69 higher (0.47 lower to 1.85 higher)
Cognitive function (correct words) - group-based CBT Pooled 6 and 12 months data	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (correct words) in the control groups was 11.76	The mean cognitive function (correct words) in the intervention groups was 0.8 higher (0.3 lower to 1.9 higher)
Cognitive function (reaction time) - group-based CBT Pooled 6 and 12 months data	103 (1 study) 6- 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean cognitive function (reaction time) in the control groups was 386.8	The mean cognitive function (reaction time) in the intervention groups was 0.93 higher (0.86 to 1 higher)
Psychological status (Symptom Checklist 90 - psychological distress) - web/written	240 (1 study)	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of		The mean psychological status (symptom checklist 90 - psychological distress) in the	The mean psychological status (symptom checklist 90 - psychological distress) in the

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
CBT Scale from: 90 to 450.	6 months	bias, indirectness, imprecision		control groups was 154.8	intervention groups was 17.1 lower (29.31 to 4.89 lower)
Psychological status (Symptom Checklist 90 - psychological distress) - group-based CBT Scale from: 90 to 450.	204 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (symptom checklist 90 - psychological distress) in the control groups was 153	The mean psychological status (symptom checklist 90 - psychological distress) in the intervention groups was 18 lower (28.61 to 7.39 lower)
Psychological status (Brief Symptom Inventory - psychological distress) - change scores - web/written CBT	104 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,5 due to risk of bias, indirectness		The mean psychological status (brief symptom inventory - psychological distress) - change scores in the control groups was 0.86	The mean psychological status (brief symptom inventory - psychological distress) - change scores in the intervention groups was 0.1 lower (0.2 lower to 0 higher)
Psychological status (HADS anxiety) - group-based CBT Pooled 6 and 12 months data. Scale from: 0 to 21.	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hads anxiety) in the control groups was 9.83	The mean psychological status (hads anxiety) in the intervention groups was 1.27 lower (2.52 to 0.02 lower)
Psychological status (HADS anxiety) - individual face-to-face CBT Scale from: 0 to 21.	352 (2 studies) 12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		-	The mean psychological status (hads anxiety) in the intervention groups was 1.25 lower (1.95 to 0.55 lower)
Psychological status (HADS depression) - group-based CBT Pooled 6 and 12 months. Scale from: 0 to 21.	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of		The mean psychological status (hads depression) in the control groups was 7.92	The mean psychological status (hads depression) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
		bias, indirectness			0.56 lower (1.69 lower to 0.57 higher)
Psychological status (HADS depression) - individual face-to-face CBT Scale from: 0 to 21.	352 (2 studies) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		-	The mean psychological status (hads depression) in the intervention groups was 1.47 lower (2.17 to 0.76 lower)
Psychological status (General health questionnaire) - group-based CBT Pooled 6 and 12 months. Scale from: 0 to 36.	103 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (general health questionnaire) in the control groups was 16.82	The mean psychological status (general health questionnaire) in the intervention groups was 2.21 lower (4.52 lower to 0.1 higher)
Pain (joint pain numeric rating scale) - individual face-to-face CBT Scale from: 0 to 4.	294 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (joint pain numeric rating scale) in the control groups was 2.11	The mean pain (joint pain numeric rating scale) in the intervention groups was 0.25 lower (0.58 lower to 0.08 higher)
Pain (muscle pain numeric rating scale) - individual face-to-face CBT Scale from: 0 to 4.	294 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (muscle pain numeric rating scale) in the control groups was 1.54	The mean pain (muscle pain numeric rating scale) in the intervention groups was 0.38 lower (0.69 to 0.07 lower)
Sleep quality (Jenkins sleep scale) - individual face-to-face CBT Scale from: 0 to 20.	294 (1 study) 52 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean sleep quality (jenkins sleep scale) in the control groups was 11	The mean sleep quality (jenkins sleep scale) in the intervention groups was 1.1 lower (2.04 to 0.16 lower)
			RR	Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
Adverse events - web/written CBT Fatigue, pain, distress, other	123 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	0.55 (0.26 to 1.14)	261 per 1000	117 fewer per 1000 (from 193 fewer to 37 more)
Adverse events (non-serious) - individual face-to-face CBT	321 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2,6 due to risk of bias, indirectness	RR 0.95 (0.89 to 1.02)	Moderate	
				931 per 1000	47 fewer per 1000 (from 102 fewer to 19 more)
Adverse events (serious) - individual face-to-face CBT	321 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2,3,6 due to risk of bias, indirectness, imprecision	RR 0.99 (0.36 to 2.77)	Moderate	
				44 per 1000	0 fewer per 1000 (from 28 fewer to 78 more)
Adverse events (adverse reactions) - individual face-to-face CBT	321 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.49 (0.25 to 8.8)	Moderate	
				13 per 1000	6 more per 1000 (from 10 fewer to 101 more)
Activity levels (Actigraphy mean score) - web/written CBT	187 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean activity levels (actigraphy mean score) in the control groups was 66.4	The mean activity levels (actigraphy mean score) in the intervention groups was 9.8 higher (3.21 to 16.39 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
Activity levels (Number of days in bed per week) - change scores - individual face-to-face CBT	60 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean activity levels (number of days in bed per week) - change scores in the control groups was 0.5	The mean activity levels (number of days in bed per week) - change scores in the intervention groups was 2.8 lower (4 to 1.6 lower)
Activity levels (Percentage interference with activities) - change scores - individual face-to-face CBT Scale from: 0 to 100.	60 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean activity levels (percentage interference with activities) - change scores in the control groups was -14	The mean activity levels (percentage interference with activities) - change scores in the intervention groups was 14 lower (25 to 3 lower)
Return to school or work (Work and Social Adjustment Scale) - web/written CBT Scale from: 0 to 40.	148 (1 study) 6 months	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school or work (work and social adjustment scale) in the control groups was 20.8	The mean return to school or work (work and social adjustment scale) in the intervention groups was 5 lower (7.62 to 2.38 lower)
Return to school or work (Work and social adjustment scale) - individual face-to-face CBT Scale from: 0 to 40.	234 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school or work (work and social adjustment scale) in the control groups was 21.1	The mean return to school or work (work and social adjustment scale) in the intervention groups was 1.1 lower (3.6 lower to 1.4 higher)
Exercise performance measure (Normal walking speed) - group-based CBT Pooled 6 and 12 months data	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (normal walking speed) in the control groups was 8.76	The mean exercise performance measure (normal walking speed) in the intervention groups was 2.83 higher (1.12 to 4.54 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus no treatment/wait list control/usual care (95% CI)
Exercise performance measure (Shuttles walked) - group-based CBT Pooled 6 and 12 months data	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (shuttles walked) in the control groups was 18.3	The mean exercise performance measure (shuttles walked) in the intervention groups was 1.2 higher (0.99 to 1.41 higher)
Exercise performance measure (6 min walk test) - individual face-to-face CBT	301 (2 studies) 12 months	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, inconsistency, indirectness		The mean exercise performance measure (6 min walk test) ranged across control groups from 354 to 437 m	The mean exercise performance measure (6 min walk test) in the intervention groups was 8.87 higher (7.41 lower to 25.15 higher)
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT Pooled 6 and 12 months data. Scale from: 0 to 10.	103 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness			The mean exercise performance measure (Perceived fatigue - modified Borg scale) in the intervention groups was 0.98 higher (0.87 to 1.09 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC or Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear (Sharpe 1996, O'Dowd 2006, Wiborg 2015, Knoop 2008, Tummers 2012) or <95% (PACE trial, Janse 2018) [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
4 Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.
5 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments): 1. 1994 CDC or Oxford criteria used; PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]; 2. Not all patients turned out to have ME/CFS (Tummers 2012).
6 Downgraded by 1 increment because the majority of the evidence included an indirect outcome (adverse events not necessarily treatment-related).

*Studies contributing to comparison: Individual face-to-face: PACE trial, Sharpe 1996; Group-based: O'Dowd 2006, Wiborg 2015; Web/written: Janse 2018, Knoop 2008, Tummers 2012

Table 9: Clinical evidence summary: Group-based cognitive behavioural stress management versus psychoeducation: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95 % CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBSM versus control (psycho-education) (95% CI)
Quality of life: QOLI Quality of Life Inventory (QOLI) raw score	58 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life: qoli in the control groups was 1.37	The mean quality of life: qoli in the intervention groups was 0.35 higher (0.49 lower to 1.19 higher)
General symptom scales CDC Symptom Inventory. Scale from: 0 to 8.	58 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean general symptom scales in the control groups was 2.08	The mean general symptom scales in the intervention groups was 0.07 lower (0.27 lower to 0.13 higher)
Psychological status (Profile of Mood States - total mood disturbance) Scale from: not reported	58 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (profile of mood states - total mood disturbance) in the control groups was 27.35	The mean psychological status (profile of mood states - total mood disturbance) in the intervention groups was 6.68 higher (7.8 lower to 21.16 higher)
Psychological status (Perceived Stress Scale) Scale from: 0 to 40.	58 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of		The mean psychological status (perceived stress scale) in the control groups was 23.46	The mean psychological status (perceived stress scale) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBSM versus control (psycho-education) (95% CI)
		bias, indirectness, imprecision			3.65 higher (0.7 lower to 8 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear – inadequate description of 'unusual fatigue after exertion' to confirm if patients had PEM [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

*Studies contributing to comparison: Lopez 2011

Table 10: Clinical evidence summary: CBT (group-based) versus education and support group: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus education and support group (95% CI)
Quality of life (SF36 mental) Pooled 6 and 12 month data. Scale from: 0 to 100.	102 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 mental) in the control groups was 40.26	The mean quality of life (sf36 mental) in the intervention groups was 3.16 higher (0.05 lower to 6.37 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus education and support group (95% CI)
Quality of life (SF36 physical) Pooled 6 and 12 month data. Scale from: 0 to 100.	102 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean quality of life (sf36 physical) in the control groups was 33.46	The mean quality of life (sf36 physical) in the intervention groups was 0.4 lower (2.86 lower to 2.06 higher)
Quality of life (Health status (HUI3)) Pooled 6 and 12 month data. Scale from: -0.36 to 1.	102 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean quality of life (health status (hui3)) in the control groups was 0.39	The mean quality of life (health status (hui3)) in the intervention groups was 0.02 higher (0.01 lower to 0.05 higher)
Fatigue (Chalder fatigue score) Pooled 6 and 12 month data. Scale from: 0 to 33.	102 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue score) in the control groups was 21.19	The mean fatigue (chalder fatigue score) in the intervention groups was 3.16 lower (5.59 to 0.73 lower)
Cognitive function (total words recalled) Pooled 6 and 12 month data.	102 (1 study) 6-12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (total words recalled) in the control groups was 12.36	The mean cognitive function (total words recalled) in the intervention groups was 0.77 higher (0.32 lower to 1.86 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus education and support group (95% CI)
Cognitive function (correct words) Pooled 6 and 12 month data.	102 (1 study) 6 or 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (correct words) in the control groups was 11.72	The mean cognitive function (correct words) in the intervention groups was 0.84 higher (0.26 lower to 1.94 higher)
Cognitive function (reaction time) Pooled 6 and 12 month data.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean cognitive function (reaction time) in the control groups was 356.8	The mean cognitive function (reaction time) in the intervention groups was 0.99 higher (0.9 to 1.08 higher)
Psychological status (HADS anxiety) Pooled 6 and 12 month data. Scale from: 0 to 21.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads anxiety) in the control groups was 9.06	The mean psychological status (hads anxiety) in the intervention groups was 0.51 lower (1.7 lower to 0.68 higher)
Psychological status (HADS depression) Pooled 6 and 12 month data. Scale from: 0 to 21.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads depression) in the control groups was 7.49	The mean psychological status (hads depression) in the intervention groups was 0.13 lower (1.13 lower to 0.87 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus education and support group (95% CI)
Psychological status (General health Questionnaire) Pooled 6 and 12 month data. Scale from: 0 to 36.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (general health questionnaire) in the control groups was 16.4	The mean psychological status (general health questionnaire) in the intervention groups was 1.8 lower (4.17 lower to 0.57 higher)
Exercise performance measure (Normal walking speed) Pooled 6 and 12 month data.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (normal walking speed) in the control groups was 9.82	The mean exercise performance measure (normal walking speed) in the intervention groups was 1.77 higher (0.03 to 3.51 higher)
Exercise performance measure (Shuttles walked) Pooled 6 and 12 month data.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (shuttles walked) in the control groups was 19	The mean exercise performance measure (shuttles walked) in the intervention groups was 1.16 higher (0.94 to 1.38 higher)
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT Pooled 6 and 12 months data. Scale from: 0 to 10.	102 (1 study) 6-12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness			The mean exercise performance measure (Perceived fatigue - modified Borg scale) in the intervention groups was 1 higher (0.86 to 1.14 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus education and support group (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: O'Dowd 2006					

Table 11: Clinical evidence summary: CBT (individual face-to-face) versus multidisciplinary rehabilitation: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus pragmatic rehabilitation (95% CI)
Quality of life: SF-36 mental component summary SF36 mental component summary. Scale from: 0 to 100.	122 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life: sf-36 mental component summary in the control groups was 51.1	The mean quality of life: sf-36 mental component summary in the intervention groups was 1.59 lower (5.14 lower to 1.96 higher)
Quality of life: SF-36 physical component summary SF36 physical component summary. Scale from: 0 to 100.	122 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life: sf-36 physical component summary in the control groups was 40.19	The mean quality of life: sf-36 physical component summary in the intervention groups was 2.67 lower (6.79 lower to 1.45 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus pragmatic rehabilitation (95% CI)
General symptom scales Sickness Impact Profile 8. Scale from: 0 to 6160.	122 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean general symptom scales in the control groups was 774.68	The mean general symptom scales in the intervention groups was 50.78 lower (288.24 lower to 186.68 higher)
Fatigue (Checklist Individual Strength - fatigue severity) Scale from: 8 to 56.	122 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (checklist individual strength - fatigue severity) in the control groups was 33.84	The mean fatigue (checklist individual strength - fatigue severity) in the intervention groups was 5.69 higher (0.76 to 10.62 higher)
Psychological status (Symptom Checklist) SCL-90. Scale from: 90 to 450.	122 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (symptom checklist) in the control groups was 130.15	The mean psychological status (symptom checklist) in the intervention groups was 7.83 higher (4.19 to 11.47 higher)
Activity levels (Accelerometer)	122 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean activity levels (accelerometer) in the control groups was 218214.41	The mean activity levels (accelerometer) in the intervention groups was 2009.58 higher (19140.04 lower to 23159.2 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

*Studies contributing to comparison: FatiGo trial

Table 12: Clinical evidence summary: CBT (individual face-to-face) versus relaxation: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus relaxation techniques (i.e. Alexander technique) (95% CI)
General symptom scales (self-rating of much/very much better)	53 (1 study) 5 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.9 (1.08 to 3.35)	Moderate	
				357 per 1000	321 more per 1000 (from 29 more to 839 more)
Fatigue (Chalder Fatigue questionnaire) Scale from: 0 to 11.	53 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (Chalder fatigue questionnaire) in the control groups was 7.2	The mean fatigue (Chalder fatigue questionnaire) in the intervention groups was 3.1 lower (5.25 to 0.95 lower)
Fatigue (Fatigue problem rating) Scale from: 0 to 8.	53 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean fatigue (fatigue problem rating) in the control groups was 5.5	The mean fatigue (fatigue problem rating) in the intervention groups was 2.1 lower (3.21 to 0.99 lower)
Physical functioning (short form general health survey physical functioning scale Scale from: 0 to 100.	53 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean physical functioning (short form general health survey physical functioning scale in the control groups was 38.4	The mean physical functioning (short form general health survey physical functioning scale in the intervention groups was 33.2 higher (18.42 to 47.98 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus relaxation techniques (i.e. Alexander technique) (95% CI)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	53 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) in the control groups was 12.3	The mean psychological status (beck depression inventory) in the intervention groups was 2.2 lower (6.38 lower to 1.98 higher)
Psychological status (General health questionnaire) Scale from: 0 to 12.	53 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (general health questionnaire) in the control groups was 4.3	The mean psychological status (general health questionnaire) in the intervention groups was 0.9 lower (2.95 lower to 1.15 higher)
Return to school or work (Full or part time employment)	53 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.43 (0.8 to 2.54)	Moderate	
				393 per 1000	169 more per 1000 (from 79 fewer to 605 more)
Return to school or work (Work and social adjustment scale) Scale from: 0 to 8.	53 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean return to school or work (work and social adjustment scale) in the control groups was 5.4	The mean return to school or work (work and social adjustment scale) in the intervention groups was 2.1 lower (3.18 to 1.02 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus relaxation techniques (i.e. Alexander technique) (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. 2 The majority of the evidence included an indirect population (downgraded by one increment).: 1991 CDC (Schluederberg 1992)/1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.					
*Studies contributing to comparison: Deale 1997/Deale 2001					

Table 13: Clinical evidence summary: CBT (individual face-to-face) versus adaptive pacing therapy: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus adaptive pacing therapy (95% CI)
Quality of life (EQ5D) Scale from: -0.594 to 1.	291 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (eq5d) in the control groups was 0.54	The mean quality of life (eq5d) in the intervention groups was 0.09 higher (0.02 to 0.16 higher)
General symptoms scales: Clinical Global Impression scale Clinical Global Impression scale change: very much better or much better	237 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectnes	OR 1.2 (0.7 to 2.06)	Moderate	
				381 per 1000	44 more per 1000 (from 80 fewer to 178 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus adaptive pacing therapy (95% CI)
		s, imprecision			
Fatigue (Chalder fatigue questionnaire) Scale from: 0 to 33.	239 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue questionnaire) in the control groups was 20.5	The mean fatigue (chalder fatigue questionnaire) in the intervention groups was 1.6 lower (3.6 lower to 0.4 higher)
Physical functioning (SF-36 physical function subscale) Scale from: 0 to 100.	237 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf-36 physical function subscale) in the control groups was 52.8	The mean physical functioning (sf-36 physical function subscale) in the intervention groups was 6.4 higher (0.4 to 12.4 higher)
Psychological status (HADS anxiety scale) Scale from: 0 to 21.	292 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads anxiety scale) in the control groups was 7.5	The mean psychological status (hads anxiety scale) in the intervention groups was 0.7 lower (1.45 lower to 0.05 higher)
Psychological status (HADS depression scale) Scale from: 0 to 21.	292 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads depression scale) in the control groups was 7.2	The mean psychological status (hads depression scale) in the intervention groups was 0.8 lower (1.56 to 0.04 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus adaptive pacing therapy (95% CI)
Pain (muscle pain numeric rating scale) Scale from: 0 to 4.	296 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (muscle pain numeric rating scale) in the control groups was 2.07	The mean pain (muscle pain numeric rating scale) in the intervention groups was 0.34 lower (0.65 to 0.03 lower)
Pain (joint pain numeric rating scale) Scale from: 0 to 4.	292 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (joint pain numeric rating scale) in the control groups was 1.64	The mean pain (joint pain numeric rating scale) in the intervention groups was 0.35 lower (0.68 to 0.02 lower)
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	293 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean sleep quality (jenkins sleep scale) in the control groups was 10.6	The mean sleep quality (jenkins sleep scale) in the intervention groups was 0.9 lower (1.79 to 0.01 lower)
Adverse events (non-serious AEs)	320 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness	RR 0.93 (0.87 to 0.99)	Moderate	
				956 per 1000	67 fewer per 1000 (from 10 fewer to 124 fewer)
Adverse events (serious AEs)	320 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3,	RR 0.46	Moderate	
				94 per 1000	51 fewer per 1000 (from 76 fewer to 9 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus adaptive pacing therapy (95% CI)
		4 due to risk of bias, indirectness, imprecision	(0.19 to 1.1)		
Adverse events (adverse reactions)	320 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.48 (0.25 to 8.75)	Moderate	
				13 per 1000	6 more per 1000 (from 10 fewer to 101 more)
Return to school/work (Work and Social Adjustment Scale) Scale from: 0 to 40.	293 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school/work (work and social adjustment scale) in the control groups was 24.5	The mean return to school/work (work and social adjustment scale) in the intervention groups was 2.4 lower (4.8 lower to 0 higher)
Exercise performance measure (6 min walk test)	234 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (6 min walk test) in the control groups was 334	The mean exercise performance measure (6 min walk test) in the intervention groups was 4.2 higher (13.99 lower to 22.39 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus adaptive pacing therapy (95% CI)
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is <95% [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs. 4 Downgraded by 1 increment if the majority of the evidence had an indirect outcome (AEs not necessarily treatment-related. *Studies contributing to comparison: PACE trial					

Table 14: Clinical evidence summary: CBT (individual face-to-face) versus GET: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with GET	Risk difference with CBT (95% CI)
Quality of life (EQ5D) Scale from: -0.594 to 1.	286 (1 study) 52 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean quality of life (eq5d) in the control groups was 0.59	The mean quality of life (eq5d) in the intervention groups was 0.04 higher (0.03 lower to 0.11 higher)
General symptom scales (Clinical global impression scale - positive change (very much or much better))	246 (1 study) 134 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.87 (0.66 to 1.16)	Moderate	
				480 per 1000	62 fewer per 1000 (from 163 fewer to 77 more)
Fatigue/fatigability (Chalder fatigue questionnaire) Scale from: 0 to 33.	246 (1 study) 134 weeks	⨁⨀⨀⨀ VERY LOW1,2,3		The mean fatigue/fatigability (chalder fatigue questionnaire)	The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with GET	Risk difference with CBT (95% CI)
		due to risk of bias, indirectness, imprecision		in the control groups was 19.1	0.7 lower (2.75 lower to 1.35 higher)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	246 (1 study) 134 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 59.8	The mean physical functioning (sf36 physical function) in the intervention groups was 2.4 higher (4.45 lower to 9.25 higher)
Psychological status (HADS anxiety) Scale from: 0 to 21.	287 (1 study) 52 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads anxiety) in the control groups was 7.1	The mean psychological status (hads anxiety) in the intervention groups was 0.3 lower (1.25 lower to 0.65 higher)
Psychological status (HADS depression) Scale from: 0 to 21.	287 (1 study) 52 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads depression) in the control groups was 6.1	The mean psychological status (hads depression) in the intervention groups was 0.1 higher (0.75 lower to 0.95 higher)
Pain (numeric rating scale) - muscle pain Scale from: 0 to 4.	289 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (numeric rating scale) - muscle pain in the control groups was 1.69	The mean pain (numeric rating scale) - muscle pain in the intervention groups was 0.04 higher (0.27 lower to 0.35 higher)
Pain (numeric rating scale) - joint pain Scale from: 0 to 4.	287 (1 study) 52 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (numeric rating scale) - joint pain in the control groups was 1.28	The mean pain (numeric rating scale) - joint pain in the intervention groups was 0.01 higher (0.3 lower to 0.32 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with GET	Risk difference with CBT (95% CI)
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	287 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean sleep quality (jenkins sleep scale) in the control groups was 9	The mean sleep quality (jenkins sleep scale) in the intervention groups was 0.9 higher (0.21 lower to 2.01 higher)
Adverse events (non-serious)	321 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness	RR 0.95 (0.89 to 1.02)	Moderate	
				931 per 1000	47 fewer per 1000 (from 102 fewer to 19 more)
Adverse events (serious)	321 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 0.54 (0.22 to 1.31)	Moderate	
				81 per 1000	37 fewer per 1000 (from 63 fewer to 25 more)
Adverse events (adverse reactions)	321 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.49 (0.25 to 8.8)	Moderate	
				13 per 1000	6 more per 1000 (from 10 fewer to 101 more)
Return to school/work (Work and social adjustment scale) Scale from: 0 to 40.	245 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean return to school/work (work and social adjustment scale) in the control groups was 19.4	The mean return to school/work (work and social adjustment scale) in the intervention groups was 0.3 higher (2.33 lower to 2.93 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with GET	Risk difference with CBT (95% CI)
Exercise performance measure (6 minute walk test)	233 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk test) in the control groups was 379 meters	The mean exercise performance measure (6 minute walk test) in the intervention groups was 25 lower (47.54 to 2.46 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
4 Downgraded by 1 increment because the majority of the evidence had indirect outcomes (AEs not necessarily treatment-related)

*Studies contributing to comparison: PACE trial

Table 15: Clinical evidence summary: CBT (group-based) + GET versus usual care/exercise counselling: age and severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT + GET versus usual care (95% CI)
Quality of life (SF36 emotional role) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 emotional role) in the control groups was 46.43	The mean quality of life (sf36 emotional role) in the intervention groups was 10.76 lower (27.42 lower to 5.9 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT + GET versus usual care (95% CI)
Quality of life (SF36 general health) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean quality of life (sf36 general health) in the control groups was 29.76	The mean quality of life (sf36 general health) in the intervention groups was 0.43 higher (5.45 lower to 6.31 higher)
Quality of life (SF36 physical role) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 physical role) in the control groups was 9.82	The mean quality of life (sf36 physical role) in the intervention groups was 5.43 lower (13.4 lower to 2.54 higher)
Quality of life (SF36 social function) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 social function) in the control groups was 37.72	The mean quality of life (sf36 social function) in the intervention groups was 6.8 lower (16.16 lower to 2.56 higher)
Quality of life (SF36 vitality) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 vitality) in the control groups was 18.66	The mean quality of life (sf36 vitality) in the intervention groups was 3.66 lower (9.36 lower to 2.04 higher)
Quality of life (SF36 physical functioning) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias,		The mean quality of life (sf36 physical functioning) in the control groups was 38.28	The mean quality of life (sf36 physical functioning) in the intervention groups was 5.65 lower (13.92 lower to 2.62 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT + GET versus usual care (95% CI)
		indirectness, imprecision			
Quality of life (SF36 mental health) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 mental health) in the control groups was 50.86	The mean quality of life (sf36 mental health) in the intervention groups was 4.61 lower (12.31 lower to 3.09 higher)
Quality of life (SF36 bodily pain) Scale from: 0 to 100.	115 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 bodily pain) in the control groups was 29.34	The mean quality of life (sf36 bodily pain) in the intervention groups was 7.53 lower (15.39 lower to 0.33 higher)
General symptom scales Stanford Health Assessment Questionnaire - global health status. Scale from: 0 to 10.	115 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean general symptom scales in the control groups was 6.83	The mean general symptom scales in the intervention groups was 0.44 higher (0.29 lower to 1.17 higher)
Physical functioning (Stanford Health Assessment Questionnaire) Scale from: 0 to 3.	115 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (stanford health assessment questionnaire) in the control groups was 1.14	The mean physical functioning (stanford health assessment questionnaire) in the intervention groups was 0.13 higher (0.12 lower to 0.38 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT + GET versus usual care (95% CI)
Pain (Stanford Health Assessment Questionnaire - pain intensity) Scale from: 0 to 10.	115 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (stanford health assessment questionnaire - pain intensity) in the control groups was 6.28	The mean pain (stanford health assessment questionnaire - pain intensity) in the intervention groups was 0.63 higher (0.23 lower to 1.49 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.					
*Studies contributing to comparison: Nunez 2011					

Table 16: Clinical evidence summary: CBT (individual face-to-face) versus counselling: age and severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Counselling	Risk difference with CBT (individual face-to-face) (95% CI)
Fatigue (Chalder fatigue scale) Scale from: 0 to 33.	37 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue scale) in the control groups was 18.6	The mean fatigue (chalder fatigue scale) in the intervention groups was 2.2 higher (3.7 lower to 8.1 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Counselling	Risk difference with CBT (individual face-to-face) (95% CI)
Psychological status (Hospital anxiety and depression scale - anxiety) Scale from: 0 to 21.	37 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups was 9.6	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention groups was 1.8 higher (1.04 lower to 4.64 higher)
Psychological status (Hospital anxiety and depression scale - depression) Scale from: 0 to 21.	37 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale - depression) in the control groups was 7.6	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was 2.5 higher (0.22 lower to 5.22 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Studies contributing to comparison: Ridsdale 2001 (note study includes 16-17 years olds but likely mostly adults based on mean age)

Table 17: Clinical evidence summary: CBT (individual face-to-face) versus GET: age and severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with GET	Risk difference with CBT (individual face-to-face) (95% CI)
Fatigue (Chalder fatigue scale) Scale from: 0 to 33.	36 (1 study) 3-8 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue scale) in the control groups was 20.02	The mean fatigue (chalder fatigue scale) in the intervention groups was 2.46 lower (7.28 lower to 2.36 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Ridsdale 2004 (note study includes 16-17 years olds but likely mostly adults based on mean age)					

Table 18: Clinical evidence summary: CBT (individual face-to-face) versus relaxation: adults, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with CBT (95% CI)
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (quality of life scale) in the control groups was 72	The mean quality of life (quality of life scale) in the intervention groups was 2.9 lower (12.95 lower to 7.15 higher)
General symptom scales (self-rated global impression of change improved/much improved/very much improved)	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk	RR 1.92 (1.27	Moderate	
				464 per 1000	427 more per 1000 (from 125 more to 891 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with CBT (95% CI)
		of bias, indirectness	to 2.92)		
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 5.62	The mean fatigue (fatigue severity scale) in the intervention groups was 0.25 lower (0.83 lower to 0.33 higher)
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 61.2	The mean physical functioning (sf36 physical functioning) in the intervention groups was 2.56 lower (17.66 lower to 12.54 higher)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) in the control groups was 13.5	The mean psychological status (beck depression inventory) in the intervention groups was 0.45 higher (5.57 lower to 6.47 higher)
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness		The mean psychological status (beck anxiety inventory) in the control groups was 11.41	The mean psychological status (beck anxiety inventory) in the intervention groups was 0.04 higher (5.23 lower to 5.31 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with CBT (95% CI)
		, imprecision			
Return to school/work (number in employment)	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision	RR 1.8 (1.01 to 3.2)	Moderate	
				345 per 1000	276 more per 1000 (from 3 more to 759 more)
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean pain (brief pain inventory - severity) in the control groups was 3.63	The mean pain (brief pain inventory - severity) in the intervention groups was 0.07 lower (1.43 lower to 1.29 higher)
Pain (Brief Pain Inventory - interference) Scale from: 0 to 10.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean pain (brief pain inventory - interference) in the control groups was 4.44	The mean pain (brief pain inventory - interference) in the intervention groups was 0.34 lower (1.94 lower to 1.26 higher)
Pain (Muscle pain numeric rating scale) Scale from: 0 to 100.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness		The mean pain (muscle pain numeric rating scale) in the control groups was 41.36	The mean pain (muscle pain numeric rating scale) in the intervention groups was 16.14 higher (1.06 lower to 33.34 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with CBT (95% CI)
		, imprecision			
Pain (Joint pain numeric rating scale) Scale from: 0 to 100.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean pain (joint pain numeric rating scale) in the control groups was 41.91	The mean pain (joint pain numeric rating scale) in the intervention groups was 3.62 higher (16.53 lower to 23.77 higher)
Exercise performance measure (6 minute walk)	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean exercise performance measure (6 minute walk) in the control groups was 1378.4 meters	The mean exercise performance measure (6 minute walk) in the intervention groups was 164.2 higher (78.79 lower to 407.19 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Jason 2007

Table 19: Clinical evidence summary: CBT (individual face-to-face) versus cognitive therapy: adults, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with CBT (95% CI)
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (quality of life scale) in the control groups was 72.52	The mean quality of life (quality of life scale) in the intervention groups was 3.42 lower (11.41 lower to 4.57 higher)
General symptom scales (self-rated global impression of change improved/much improved/very much improved)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.34 (0.98 to 1.83)	Moderate	
				643 per 1000	219 more per 1000 (from 13 fewer to 534 more)
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 5.87	The mean fatigue (fatigue severity scale) in the intervention groups was 0.5 lower (1.07 lower to 0.07 higher)
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness		The mean physical functioning (sf36 physical functioning) in the control groups was 61.09	The mean physical functioning (sf36 physical functioning) in the intervention groups was 2.45 lower (16.59 lower to 11.69 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with CBT (95% CI)
		, imprecision			
Psychological status (Beck depression inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean psychological status (beck depression inventory) in the control groups was 11.86	The mean psychological status (beck depression inventory) in the intervention groups was 2.09 higher (3.4 lower to 7.58 higher)
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean psychological status (beck anxiety inventory) in the control groups was 8.96	The mean psychological status (beck anxiety inventory) in the intervention groups was 2.49 higher (2.02 lower to 7 higher)
Return to school/work (number in employment)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision	RR 1.09 (0.71 to 1.67)	Moderate	
				571 per 1000	51 more per 1000 (from 166 fewer to 383 more)
Exercise performance measure (6 minute walk)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness		The mean exercise performance measure (6 minute walk) in the control groups was 1513.5	The mean exercise performance measure (6 minute walk) in the intervention groups was 29.1 higher

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with CBT (95% CI)
		, imprecision			(222.56 lower to 280.76 higher)
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean pain (brief pain inventory - severity) in the control groups was 3.12	The mean pain (brief pain inventory - severity) in the intervention groups was 0.44 higher (0.74 lower to 1.62 higher)
Pain (Brief Pain Inventory - interference) Scale from: 0 to 10.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean pain (brief pain inventory - interference) in the control groups was 3.36	The mean pain (brief pain inventory - interference) in the intervention groups was 0.74 higher (0.85 lower to 2.33 higher)
Pain (Muscle pain numeric rating scale) Scale from: 0 to 100.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness , imprecision		The mean pain (muscle pain numeric rating scale) in the control groups was 40.83	The mean pain (muscle pain numeric rating scale) in the intervention groups was 16.67 higher (1 to 32.34 higher)
Pain (Joint pain numeric rating scale) Scale from: 0 to 100.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness		The mean pain (joint pain numeric rating scale) in the control groups was 31.52	The mean pain (joint pain numeric rating scale) in the intervention groups was 14.01 higher (5.15 lower to 33.17 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with CBT (95% CI)
		, imprecision			
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Jason 2007					

Table 20: Clinical evidence summary: CBT (individual face-to-face) versus anaerobic activity therapy: adults, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anaerobic activity therapy	Risk difference with CBT (95% CI)
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (quality of life scale) in the control groups was 63	The mean quality of life (quality of life scale) in the intervention groups was 6.1 higher (2.46 lower to 14.66 higher)
General symptom scales (self-rated global impression of change improved/much improved/very much improved)	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness	RR 2.08 (1.32 to 3.29)	Moderate	
				414 per 1000	447 more per 1000 (from 132 more to 948 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anaerobic activity therapy	Risk difference with CBT (95% CI)
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 5.77	The mean fatigue (fatigue severity scale) in the intervention groups was 0.4 lower (1.08 lower to 0.28 higher)
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 39.72	The mean physical functioning (sf36 physical functioning) in the intervention groups was 18.92 higher (3.96 to 33.88 higher)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) in the control groups was 16.94	The mean psychological status (beck depression inventory) in the intervention groups was 2.99 lower (9.41 lower to 3.43 higher)
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck anxiety inventory) in the control groups was 12.11	The mean psychological status (beck anxiety inventory) in the intervention groups was 0.66 lower (5.88 lower to 4.56 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anaerobic activity therapy	Risk difference with CBT (95% CI)
Return to school/work (number in employment)	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.8 (1.01 to 3.2)	Moderate 345 per 1000	276 more per 1000 (from 3 more to 759 more)
Exercise performance measure (6 minute walk)	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk) in the control groups was 1378.4 meters	The mean exercise performance measure (6 minute walk) in the intervention groups was 164.2 higher (78.79 lower to 407.19 higher)
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - severity) in the control groups was 3.63	The mean pain (brief pain inventory - severity) in the intervention groups was 0.07 lower (1.43 lower to 1.29 higher)
Pain (Brief Pain Inventory - interference) Scale from: 0 to 10.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - interference) in the control groups was 3.75	The mean pain (brief pain inventory - interference) in the intervention groups was 0.35 higher (1.32 lower to 2.02 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anaerobic activity therapy	Risk difference with CBT (95% CI)
Pain (Muscle pain numeric rating scale) Scale from: 0 to 100.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (muscle pain numeric rating scale) in the control groups was 54.11	The mean pain (muscle pain numeric rating scale) in the intervention groups was 3.39 higher (14.09 lower to 20.87 higher
Pain (Joint pain numeric rating scale) Scale from: 0 to 100.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (joint pain numeric rating scale) in the control groups was 39.74	The mean pain (joint pain numeric rating scale) in the intervention groups was 5.79 higher (15.78 lower to 27.36 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Jason 2007

Table 21: Clinical evidence summary: CBT (individual face-to-face) versus psychoeducation/pacing: children and young people, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus psycho-education/pacing (95% CI)
				Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus psycho-education/pacing (95% CI)
General symptom scales Self-reported global improvement - much better or very much better	44 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.88 (0.68 to 1.13)	900 per 1000	108 fewer per 1000 (from 288 fewer to 117 more)
General symptom scales Strengths and Difficulties Questionnaire. Scale from: 0 to 40.	44 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean general symptom scales in the control groups was 13.61	The mean general symptom scales in the intervention groups was 3.98 lower (6.51 to 1.45 lower)
Fatigue/fatigability (Chalder Fatigue Scale) Scale from: 0 to 33.	44 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (Chalder fatigue scale) in the control groups was 12.15	The mean fatigue/fatigability (Chalder fatigue scale) in the intervention groups was 1.75 lower (4.85 lower to 1.35 higher)
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	44 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 71.2	The mean physical functioning (sf36 physical functioning) in the intervention groups was 5.59 higher (11.52 lower to 22.7 higher)
Adverse events (Serious adverse events)	63 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3	Peto OR 7.16	Moderate	
				0 per 1000	30 more per 1000 (from 50 fewer to 110 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with CBT versus psycho-education/pacing (95% CI)
		due to risk of bias, indirectness, imprecision	(0.14 to 361.11)		
Return to school or work (% school attendance over 2 weeks) Scale from: 0 to 100.	59 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school or work (% school attendance over 2 weeks) in the control groups was 64.9	The mean return to school or work (% school attendance over 2 weeks) in the intervention groups was 8.5 higher (12.35 lower to 29.35 higher)
Return to school or work (Work and Social Adjustment Scale) Scale from: 0 to 40.	56 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school or work (work and social adjustment scale) in the control groups was 3.3	The mean return to school or work (work and social adjustment scale) in the intervention groups was 0.8 lower (1.88 lower to 0.28 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford/1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

*Studies contributing to comparison: Chalder 2010/Lloyd 2012

Table 22: Clinical evidence summary: CBT (individual face-to-face) versus waiting list: children and young people, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waiting list	Risk difference with CBT (95% CI)
General symptom scales (self-rated improvement recovered or much better)	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.62 (1.05 to 2.5)	Moderate 441 per 1000	273 more per 1000 (from 22 more to 661 more)
Fatigue (Checklist Individual Strength - fatigue severity sub scale) Scale from: 8 to 56.	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean fatigue (checklist individual strength - fatigue severity sub scale) in the control groups was 44	The mean fatigue (checklist individual strength - fatigue severity sub scale) in the intervention groups was 13.8 lower (20.96 to 6.94 lower)
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 55.3	The mean physical functioning (sf36 physical functioning) in the intervention groups was 14.1 higher (2.42 to 25.78 higher)
Return to school or work (School attendance (hours attended/total hours))	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school or work (school attendance (hours attended/total hours)) in the control groups was 66.7 hours	The mean return to school or work (school attendance (hours attended/total hours)) in the intervention groups was 8 higher (9.41 lower to 25.41 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waiting list	Risk difference with CBT (95% CI)
Cognitive function (Checklist individual strength – concentration sub scale)	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (Checklist individual strength – concentration sub scale) in the control groups was 13.4	The mean cognitive function (Checklist individual strength – concentration sub scale) in the intervention groups was 13.8 lower (20.96 to 6.64 lower)
Cognitive function (Reaction time tests – simple & choice) (change scores) – simple	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (Reaction time tests – simple & choice) (change scores) – simple in the control groups was -18 ms	The mean cognitive function (Reaction time tests – simple & choice) (change scores) – simple in the intervention groups was 12 lower (42.67 lower to 18.67 higher)
Cognitive function (Reaction time tests – simple & choice) (change scores) – choice	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (Reaction time tests – simple & choice) (change scores) – choice in the control groups was -10 ms	The mean cognitive function (Reaction time tests – simple & choice) (change scores) – choice in the intervention groups was 2.0 lower (26.2 lower to 22.2 higher)
Pain (Daily pain – 0-4 scale) (change scores)	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (Daily pain – 0-4 scale) (change scores) in the control groups was -0.36	The mean pain (Daily pain – 0-4 scale) (change scores) in the intervention groups was 1.85 lower (3.32 to 0.38 lower)
Pain (Muscle pain & joint pain – 1-4 scale) – muscle pain	69 (1 study) 5 months	⊕⊖⊖⊖ VERY LOW1,2,3		The mean pain (Muscle pain & joint pain – 1-4 scale) – muscle pain in the control groups was	The mean pain (Muscle pain & joint pain – 1-4 scale) – muscle pain in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waiting list	Risk difference with CBT (95% CI)
		due to risk of bias, indirectness, imprecision		2.7	0.3 lower (0.73 lower to 0.13 higher)
Pain (Muscle pain & joint pain – 1-4 scale) – joint pain	69 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (Muscle pain & joint pain – 1-4 scale) – joint pain in the control groups was 2.3	The mean pain (Muscle pain & joint pain – 1-4 scale) – joint pain in the intervention groups was 0.3 lower (0.8 lower to 0.2 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Stulemeijer 2005//Knoop 2007/Knoop 2007)

Table 23: Clinical evidence summary: CBT (web/written) versus usual care: children and young people, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Young people and severity mixed or unclear. CBT versus no treatment/wait list control/usual care (95% CI)
General symptom scales Self rated improvement completely recovered or much better	131 (1 study) 6 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness	RR 2.92 (1.91 to 4.48)	Moderate 266 per 1000	511 more per 1000 (from 242 more to 926 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Young people and severity mixed or unclear. CBT versus no treatment/wait list control/usual care (95% CI)
Fatigue/fatigability (Fatigue severity (CIS-20)) Scale from: 8 to 56.	131 (1 study) 6 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean fatigue/fatigability (fatigue severity (cis-20)) in the control groups was 42.3	The mean fatigue/fatigability (fatigue severity (cis-20)) in the intervention groups was 18.3 lower (22.84 to 13.76 lower)
Physical functioning (Child health questionnaire physical functioning) Scale from: 0 to 100.	131 (1 study) 6 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean physical functioning (child health questionnaire physical functioning) in the control groups was 70.1	The mean physical functioning (child health questionnaire physical functioning) in the intervention groups was 18.4 higher (12.97 to 23.83 higher)
Adverse events (serious adverse events)	131 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW 1,2,3 due to risk of bias, indirectness, imprecision	RD 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 more per 1000 (from 30 fewer to 30 more)
Return to school or work (mean school attendance @ 6 months) Scale from: 0 to 100.	131 (1 study) 6 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean return to school or work (mean school attendance @ 6 months) in the control groups was 51.7 percentage points	The mean return to school or work (mean school attendance @ 6 months) in the intervention groups was 32.6 higher (21.66 to 43.54 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Young people and severity mixed or unclear. CBT versus no treatment/wait list control/usual care (95% CI)
3 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70					
Studies contributing to comparison: FITNET trial					

Table 24: Clinical evidence summary: CBT (individual face-to-face) + biofeedback versus usual care: children and young people, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Children; severity mixed or unclear. CBT versus no treatment/wait list control/usual care (95% CI)
Fatigue (Fatigue Assessment Scale %) Scale from: 0 to 100.	92 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean fatigue (fatigue assessment scale %) in the control groups was 46.5 percentage points	The mean fatigue (fatigue assessment scale %) in the intervention groups was 14.3 lower (18.72 to 9.88 lower)
Return to school or work (School attendance hours/month)	92 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean return to school or work (school attendance hours/month) in the control groups was 66.6 hours	The mean return to school or work (school attendance hours/month) in the intervention groups was 26.2 higher (17.62 to 34.78 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]					

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Children; severity mixed or unclear. CBT versus no treatment/wait list control/usual care (95% CI)
*Studies contributing to comparison: Al-Haggar 2005					

1.1.5.2.2 Other psychological interventions

Table 25: Clinical evidence summary: Education and support groups versus usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Education/support group (95% CI)
Quality of life (SF36 physical) Pooled 6 and 12 month data. Scale from: 0 to 100.	101 (1 study) 6-12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean quality of life (sf36 physical) in the control groups was 34.7	The mean quality of life (sf36 physical) in the intervention groups was 1.23 lower (3.52 lower to 1.06 higher)
Quality of life (SF36 mental) Pooled 6 and 12 month data. Scale from: 0 to 100.	101 (1 study) 6-12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean quality of life (sf36 mental) in the control groups was 39.07	The mean quality of life (sf36 mental) in the intervention groups was 1.19 higher (2.26 lower to 4.64 higher)
Quality of life (Health status (HUI3)) Pooled 6 and 12 month data. Scale from: -0.36 to 1.	101 (1 study) 6- 12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean quality of life (health status (hui3)) in the control groups was 0.39	The mean quality of life (health status (hui3)) in the intervention groups was 0.01 higher (0.08 lower to 0.09 higher)
Fatigue (Chalder fatigue score) Pooled 6 and 12 month data. Scale from: 0 to 33.	101 (1 study) 6- 12 months	⊕⊕⊖⊖ LOW1,2,3 due to risk of		The mean fatigue (chalder fatigue score) in the control	The mean fatigue (chalder fatigue score) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Education/support group (95% CI)
		bias, indirectness		groups was 20.64	0.55 higher (1.56 lower to 2.66 higher)
Cognitive function (total words recalled) Pooled 6 and 12 month data.	101 (1 study) 6- 12 months	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness		The mean cognitive function (total words recalled) in the control groups was 12.43	The mean cognitive function (total words recalled) in the intervention groups was 0.08 lower (1.2 lower to 1.05 higher)
Cognitive function (correct words) Pooled 6 and 12 month data.	101 (1 study) 6- 12 months	⨁⨁⨀⨀ LOW1,2,3 due to risk of bias, indirectness		The mean cognitive function (correct words) in the control groups was 11.76	The mean cognitive function (correct words) in the intervention groups was 0.04 lower (1.14 lower to 1.05 higher)
Cognitive function (reaction time) Pooled 6 and 12 month data.	101 (1 study) 6- 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean cognitive function (reaction time) in the control groups was 386.8	The mean cognitive function (reaction time) in the intervention groups was 0.95 higher (0.87 to 1.03 higher)
Psychological status (HADS anxiety) Pooled 6 and 12 month data. Scale from: 0 to 21.	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads anxiety) in the control groups was 9.83	The mean psychological status (hads anxiety) in the intervention groups was 0.95 higher (0.87 to 1.03 higher)
Psychological status (HADS depression) Pooled 6 and 12 month data. Scale from: 0 to 21.	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hads depression) in the control groups was 7.92	The mean psychological status (hads depression) in the intervention groups was 0.43 lower (0.56 to 0.3 lower)
Psychological status (General health Questionnaire) Pooled 6 and 12 month data. Scale from: 0 to 36.	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of		The mean psychological status (general health questionnaire) in the control groups was 16.82	The mean psychological status (general health questionnaire) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Education/support group (95% CI)
		bias, indirectness			0.41 lower (2.8 lower to 1.98 higher)
Exercise performance measure (Normal walking speed) Pooled 6 and 12 month data.	101 (1 study) 6-12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (normal walking speed) in the control groups was 8.76	The mean exercise performance measure (normal walking speed) in the intervention groups was 1.06 higher (0.37 lower to 2.49 higher)
Exercise performance measure (Shuttles walked) Pooled 6 and 12 month data.	101 (1 study) 6-12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (shuttles walked) in the control groups was 18.3	The mean exercise performance measure (shuttles walked) in the intervention groups was 1.04 higher (0.86 lower to 1.22 higher)
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT Pooled 6 and 12 months data. Scale from: 0 to 10.	101 (1 study) 6-12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness			The mean exercise performance measure (Perceived fatigue - modified Borg scale) in the intervention groups was 0.99 higher (0.87 to 1.11 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: O'Dowd 2006

Table 26: Clinical evidence summary: Cognitive therapy versus relaxation: adults, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation	Risk difference with Cognitive therapy (95% CI)
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (quality of life scale) in the control groups was 72	The mean quality of life (quality of life scale) in the intervention groups was 0.52 higher (7.81 lower to 8.85 higher)
General symptom scales (self-rated global impression of change improved/much improved/very much improved)	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.38 (0.85 to 2.25)	Moderate	
				464 per 1000	176 more per 1000 (from 70 fewer to 580 more)
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 5.62	The mean fatigue (fatigue severity scale) in the intervention groups was 0.25 higher (0.29 lower to 0.79 higher)
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 61.2	The mean physical functioning (sf36 physical functioning) in the intervention groups was 0.11 lower (13.62 lower to 13.4 higher)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) in the control groups was 13.5	The mean psychological status (beck depression inventory) in the intervention groups was 1.64 lower (6.23 lower to 2.95 higher)
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	56 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,		The mean psychological status (beck anxiety inventory) in the control groups was 11.41	The mean psychological status (beck anxiety inventory) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation	Risk difference with Cognitive therapy (95% CI)
		indirectness, imprecision			2.45 lower (6.96 lower to 2.06 higher)
Return to school/work (number in employment)	56 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.33 (0.78 to 2.28)	Moderate	
				429 per 1000	142 more per 1000 (from 94 fewer to 549 more)
Exercise performance measure (6 minute walk)	56 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk) in the control groups was 1429.33 meters	The mean exercise performance measure (6 minute walk) in the intervention groups was 84.17 higher (61.81 lower to 230.15 higher)
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	56 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - severity) in the control groups was 4.6	The mean pain (brief pain inventory - severity) in the intervention groups was 1.48 lower (2.54 to 0.42 lower)
Pain (Brief Pain Inventory - interference) Scale from: 0 to 10.	56 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - interference) in the control groups was 4.44	The mean pain (brief pain inventory - interference) in the intervention groups was 1.08 lower (2.53 lower to 0.37 higher)
Pain (Muscle pain numeric rating scale) Scale from: 0 to 100.	56 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (muscle pain numeric rating scale) in the control groups was 41.36	The mean pain (muscle pain numeric rating scale) in the intervention groups was 0.53 lower (16.78 lower to 15.72 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation	Risk difference with Cognitive therapy (95% CI)
Pain (Joint pain numeric rating scale) Scale from: 0 to 100.	56 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (joint pain numeric rating scale) in the control groups was 41.91	The mean pain (joint pain numeric rating scale) in the intervention groups was 10.39 lower (27.5 lower to 6.72 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Jason 2007

Table 27: Clinical evidence summary: Buddy/mentor programme versus Wait-list: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Buddy/mentor programme (95% CI)
Quality of life (Quality of Life Index) Scale from: 0-30	47 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (quality of life index) in the control groups was 14.6	The mean quality of life (quality of life index) in the intervention groups was 1.1 higher (1.13 lower to 3.33 higher)
General Symptom Scales (Chronic Fatigue Syndrome	47 (1 study)	⨁⊖⊖⊖ VERY		The mean general symptom scales (chronic fatigue syndrome symptom	The mean general symptom scales (chronic fatigue syndrome symptom

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Buddy/mentor programme (95% CI)
Symptom Rating Form) Scale from: 0 to 100.	12 months	LOW1,2,3 due to risk of bias, indirectness, imprecision		rating form) in the control groups was 14.8	rating form) in the intervention groups was 0.9 lower (2.72 lower to 0.92 higher)
Fatigue (Fatigue Severity Scale) Scale from: 1 to 63.	30 (1 study) 4 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) in the control groups was 59.4	The mean fatigue (fatigue severity scale) in the intervention groups was 6.5 lower (12.13 to 0.87 lower)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	30 (1 study) 4 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 29.7	The mean physical functioning (sf36 physical functioning) in the intervention groups was 6.4 higher (8.08 lower to 20.88 higher)
Psychological Status (Perceived Stress Scale) Scale from: 0 to 16.	30 (1 study) 4 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (perceived stress scale) in the control groups was 12.9	The mean psychological status (perceived stress scale) in the intervention groups was 0.2 lower (1.6 lower to 1.2 higher)
Psychological Status (CORE-E - Overall Resource Gain) Scale from: 0 to 518.	47 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,		The mean psychological status (core-e - overall resource gain) in the control groups was 53.29	The mean psychological status (core-e - overall resource gain) in the intervention groups was 28.53 higher (7.86 lower to 64.92 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Buddy/mentor programme (95% CI)
		indirectness, imprecision			
Psychological Status (CORE-E - Overall Resource Loss) Scale from: 0 to 518.	47 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (core-e - overall resource loss) in the control groups was 124.96	The mean psychological status (core-e - overall resource loss) in the intervention groups was 15.91 lower (69.04 lower to 37.22 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs *Studies contributing to comparison: Jason 2010, Taylor 2004					

Table 28: Clinical evidence summary: Pragmatic rehabilitation versus Supportive listening: adults, severity mixd or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Supportive listening	Risk difference with Pragmatic rehabilitation (95% CI)
Fatigue (Chalder Fatigue Scale 11-item) Scale from: 0 to 11.	171 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (Chalder fatigue scale 11-item) in the control groups was 9.39	The mean fatigue (Chalder fatigue scale 11-item) in the intervention groups was 0.67 lower (1.71 lower to 0.37 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Supportive listening	Risk difference with Pragmatic rehabilitation (95% CI)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	171 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 35.72	The mean physical functioning (sf36 physical functioning) in the intervention groups was 7.55 higher (0.47 lower to 15.57 higher)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	171 (1 study) 70 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the control groups was 9.62	The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the intervention groups was 0.08 lower (1.52 lower to 1.36 higher)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	171 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2.3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the control groups was 8.67	The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the intervention groups was 0.79 lower (2.13 lower to 0.55 higher)
Sleep Quality (Jenkin's Sleep Scale) Scale from: 0 to 20.	171 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean sleep quality (Jenkin's sleep scale) in the control groups was 13.18	The mean sleep quality (Jenkin's sleep scale) in the intervention groups was 0.86 lower (2.56 lower to 0.84 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Supportive listening	Risk difference with Pragmatic rehabilitation (95% CI)
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: FINE trial					

Table 29: Clinical evidence summary: Pragmatic rehabilitation versus Usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Pragmatic rehabilitation (95% CI)
Fatigue (Chalder Fatigue Scale 11-item) Scale from: 0 to 11.	167 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (Chalder fatigue scale 11-item) in the control groups was 9.48	The mean fatigue (Chalder fatigue scale 11-item) in the intervention groups was 0.76 lower (1.74 lower to 0.22 higher)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	167 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 39.83	The mean physical functioning (sf36 physical functioning) in the intervention groups was 3.44 higher (4.93 lower to 11.81 higher)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	166 (1 study) 70 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the control groups was 8.89	The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the intervention groups was 0.65 higher (0.89 lower to 2.19 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Pragmatic rehabilitation (95% CI)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	166 (1 study) 70 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the control groups was 8.06	The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the intervention groups was 0.18 lower (1.58 lower to 1.22 higher)
Sleep Quality (Jenkin's Sleep Scale) Scale from: 0 to 20.	167 (1 study) 70 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean sleep quality (Jenkin's sleep scale) in the control groups was 12.63	The mean sleep quality (Jenkin's sleep scale) in the intervention groups was 0.31 lower (1.97 lower to 1.35 higher)
Exercise Performance Measure (Step-Test) - Number of Steps Completed	71 (1 study) 70 weeks	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (step-test) - number of steps completed in the control groups was 19.31	The mean exercise performance measure (step-test) - number of steps completed in the intervention groups was 0.21 lower (1.56 lower to 1.14 higher)
Exercise Performance Measure (Step-Test) - Time Taken to Complete Steps	71 (1 study) 70 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (step-test) - time taken to complete steps in the control groups was 54.67 sec	The mean exercise performance measure (step-test) - time taken to complete steps in the intervention groups was 4.77 lower (10.99 lower to 1.45 higher)
Exercise Performance Measure (Borg rating of perceived exertion) Scale from: 6 to 20.	71 (1 study) 70 weeks	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness		The mean exercise performance measure (Borg rating of perceived exertion) in the control groups was 11.87	The mean exercise performance measure (Borg rating of perceived exertion) in the intervention groups was 0.14 lower (1.12 lower to 0.84 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Pragmatic rehabilitation (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: FINE trial					

Table 30: Clinical evidence summary: Supportive listening versus Usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Supportive listening (95% CI)
Fatigue (Chalder Fatigue Scale 11-item) Scale from: 0 to 11.	176 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (Chalder fatigue scale 11-item) in the control groups was 9.48	The mean fatigue (Chalder fatigue scale 11-item) in the intervention groups was 0.09 lower (0.97 lower to 0.79 higher)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	176 (1 study) 70 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 39.83	The mean physical functioning (sf36 physical functioning) in the intervention groups was 4.11 lower (12.06 lower to 3.84 higher)
Psychological Status (Hospital Anxiety and Depression Scale sub	175 (1 study)	⨁⨁⊖⊖ LOW1,2		The mean psychological status (hospital anxiety and depression	The mean psychological status (hospital anxiety and depression

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Supportive listening (95% CI)
scales) - Anxiety Scale from: 0 to 21.	70 weeks	due to risk of bias, indirectness		scale sub scales) - anxiety in the control groups was 9.65	scale sub scales) - anxiety in the intervention groups was 0.03 lower (1.5 lower to 1.44 higher)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	175 (1 study) 70 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the control groups was 8.06	The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the intervention groups was 0.61 higher (0.76 lower to 1.98 higher)
Sleep Quality (Jenkin's Sleep Scale) Scale from: 0 to 20.	176 (1 study) 70 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean sleep quality (Jenkin's sleep scale) in the control groups was 12.63	The mean sleep quality (Jenkin's sleep scale) in the intervention groups was 0.55 higher (1.08 lower to 2.18 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: FINE trial					

Table 31: Clinical evidence summary: Mindfulness and medical Qigong versus Usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Mindfulness + Medical Qigong (95% CI)
				Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Mindfulness + Medical Qigong (95% CI)
Quality of Life (SF36 Health Transition Score - Improvement)	60 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.78 (0.48 to 1.28)	594 per 1000	131 fewer per 1000 (from 309 fewer to 166 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Collinge 1998

Table 32: Clinical evidence summary: Mindfulness based cognitive therapy versus Wait-list: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Mindfulness based cognitive therapy (95% CI)
Fatigue (Chalder Fatigue Scale) SMD used as two different scales combined (0-33 and 0-42)	51 (2 studies) 2-4 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		N/A (SMD analysis)	The mean fatigue (Chalder fatigue scale) in the intervention groups was 0.46 standard deviations lower (1.02 lower to 0.1 higher)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	52 (2 studies)	⨁⊖⊖⊖ VERY LOW1,2,3		The mean physical functioning (sf36 physical functioning) was 46.2	The mean physical functioning (sf36 physical functioning) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Mindfulness based cognitive therapy (95% CI)
	2-4 months	due to risk of bias, indirectness, imprecision			7.46 higher (5.81 lower to 20.72 higher)
Psychological Status (Hospital Anxiety and Depression scale sub scales) - Anxiety Scale from: 0 to 21.	52 (2 studies) 2-4 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety was 8.8	The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the intervention groups was 0.84 lower (3.14 lower to 1.47 higher)
Psychological Status (Hospital Anxiety and Depression scale sub scales) - Depression Scale from: 0 to 21.	52 (2 studies) 2-4 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale sub scales) - depression was 8.6	The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the intervention groups was 1.71 lower (3.62 lower to 0.2 higher)
Return to School/Work (Work and Social Adjustment Scale) Scale from: 0 to 40.	35 (1 study) 4 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school/work (work and social adjustment scale) in the control groups was 25.8	The mean return to school/work (work and social adjustment scale) in the intervention groups was 5.8 lower (11.72 lower to 0.12 higher)
Adverse Events ('Substantive' Adverse Events)	37 (1 study) 4 months	⊕⊖⊖⊖ VERY LOW 1,2,4 due to risk of bias, indirectness, imprecision	RD 0.00 (-0.1 to 0.1)	Moderate	
				0 per 1000	0 more per 1000 (from 100 fewer to 100 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Mindfulness based cognitive therapy (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC/Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70					
*Studies contributing to comparison: Rimes 2013, Surawy 2005					

Table 33: Clinical evidence summary: Focused group therapy versus Wait-list: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Focused group therapy (95% CI)
Quality of Life (Gothenburg Quality of Life Scale) Scale from: 18 to 126.	13 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (Gothenburg quality of life scale) in the control groups was 64.6	The mean quality of life (Gothenburg quality of life scale) in the intervention groups was 1.7 lower (17.59 lower to 14.19 higher)
Quality of life (Visual analogue scale) Scale from: 0 to 10	13 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (VAS) in the control groups was 3.1	The mean quality of life (VAS) in the intervention groups was 1.3 higher (1.1 lower to 3.7 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Wait-list	Risk difference with Focused group therapy (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Soderberg 2001					

Table 34: Clinical evidence summary: The Lightning Process and specialist medical care versus specialist medical care: children and young people, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with SMC	Risk difference with The Lightning Process + Specialist medical care (SMC) (95% CI)
Fatigue (Chalder Fatigue Scale) Scale from: 0 to 33.	80 (1 study) 12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean fatigue (Chalder fatigue scale) in the control groups was 15.7	The mean fatigue (Chalder fatigue scale) in the intervention groups was 4 lower (7.25 to 0.75 lower)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	80 (1 study) 12 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean physical functioning (sf36 physical functioning) in the control groups was 73.1	The mean physical functioning (sf36 physical functioning) in the intervention groups was 18.6 higher (6.85 to 30.35 higher)
Psychological Status (Spence Children's Anxiety Scale) Scale from: 0 to 114.	58 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk		The mean psychological status (Spence children's anxiety scale) in the control groups was 36.3	The mean psychological status (Spence children's anxiety scale) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with SMC	Risk difference with The Lightning Process + Specialist medical care (SMC) (95% CI)
		of bias, imprecision			14.5 lower (22.35 to 6.65 lower)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	60 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the control groups was 8.3	The mean psychological status (hospital anxiety and depression scale sub scales) - anxiety in the intervention groups was 2.6 lower (4.75 to 0.45 lower)
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	60 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the control groups was 4.6	The mean psychological status (hospital anxiety and depression scale sub scales) - depression in the intervention groups was 1.8 lower (3.45 to 0.15 lower)
Pain (Visual Analogue Scale) Scale from: 0 to 100.	59 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (visual analogue scale) in the control groups was 32	The mean pain (visual analogue scale) in the intervention groups was 6.5 lower (19.45 lower to 6.45 higher)
Return to School/Work (School/college attendance in the previous week)	70 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean return to school/work (school/college attendance in the previous week) in the control groups was 3.1	The mean return to school/work (school/college attendance in the previous week) in the intervention groups was 1 higher (0.2 to 1.8 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with SMC	Risk difference with The Lightning Process + Specialist medical care (SMC) (95% CI)
Adverse events (Serious adverse events attributable to study interventions)	85 (1 study) 12 months	⨁⨁⊖⊖ LOW1,3 due to risk of bias, imprecision		Moderate	
				0 per 1000	0 more per 1000 (from 50 fewer to 50 more)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Zero events in both study arms – serious imprecision if sample size 70-350; very serious imprecision if sample size <70					
*Studies contributing to comparison: SMILE trial					

1.1.5.3 Exercise interventions

1.1.5.3.1 Graded exercise therapy

Table 35: Clinical evidence summary: Graded exercise therapy versus standard care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
Quality of life (EQ5D) Scale from: -0.594 to 1.	294 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean quality of life (eq5d) in the control groups was 0.53	The mean quality of life (eq5d) in the intervention groups was 0.06 higher (0.01 lower to 0.13 higher)
				Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
General symptom scales (patient reported global impression of change in CFS positive/much/very much better)	231 (2 studies) 12-42 weeks	⊕⊖⊖⊖ VERY LOW1,4 due to risk of bias, imprecision	RR 2.2 (1.16 to 4.16)	93 per 1000	112 more per 1000 (from 15 more to 294 more)
	<u>PEM re-analysis (subgroup analysis)</u>**				
	PEM subgroup: 198 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,4 due to risk of bias, imprecision	RR 2.43 (0.97 to 6.07)	Moderate 59 per 1000	85 more per 1000 (from 2 fewer to 301 more)
	Unclear PEM subgroup: 33 (1 study) 42 weeks	⊕⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, indirectness, imprecision	RR 1.91 (0.81 to 4.49)	Moderate 29 per 1000	268 more per 1000 (from 56 fewer to 1000 more)
General symptom scales (patient reported global impression of change in overall health positive vs. negative/minimal change)	198 (1 study) 12 weeks	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 3.54 (1.36 to 9.22)	Moderate 50 per 1000	126 more per 1000 (from 18 more to 407 more)
General symptom scales (clinical global impression of change in overall health positive vs. negative/minimal change)	242 (1 study) 134 weeks	⊕⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	OR 1.1 (0.6 to 2.02)	Moderate 93 per 1000	23 more per 1000 (from 117 fewer to 174 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
Fatigue/fatigability (Chalder fatigue questionnaire) SMD used as two different scales combined (0-33 and 0-42)	242 (2 studies) 12 weeks	⨁⊖⊖⊖ VERY LOW1,4 due to risk of bias, imprecision		N/A (SMD analysis)	The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was 0.66 standard deviations lower (0.92 to 0.4 lower)
	<u>PEM re-analysis (subgroup analysis)</u>**				
	PEM subgroup: 199 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,4 due to risk of bias, imprecision		The mean fatigue/fatigability (chalder fatigue questionnaire) in the control groups was 22.9	The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was 0.6 standard deviations lower (0.88 to 0.31 lower)
					The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was 4.3 (6.3 to 2.3 lower)
	Unclear PEM subgroup: 43 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (chalder fatigue questionnaire) in the control groups was 24.4	The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was 1.0 standard deviations lower (1.64 to 0.36 lower)
					The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was 4.3 lower (16.7 to 4.4 lower)
Fatigue/fatigability (Chalder fatigue questionnaire) Scale from: 0 to 33.	242 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias,		The mean fatigue/fatigability (chalder fatigue questionnaire) in the control groups was 20.2	The mean fatigue/fatigability (chalder fatigue questionnaire) in the intervention groups was 0.8 lower (2.8 lower to 1.2 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
		indirectness, imprecision			
Physical functioning (SF36 physical function) Scale from: 0 to 100.	242 (2 studies) 12 weeks	⨁⊖⊖⊖ VERY LOW1,4 due to risk of bias, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 52.9	The mean physical functioning (sf36 physical function) in the intervention groups was 7.68 higher (3.24 to 12.12 higher)
	<u>PEM re-analysis (subgroup analysis)</u>**				
	PEM subgroup: 199 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,4 due to risk of bias, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 50.8	The mean physical functioning (sf36 physical function) in the intervention groups was 6.9 higher (2.2 to 11.6 higher)
	Unclear PEM subgroup: 43 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 55.0	The mean physical functioning (sf36 physical function) in the intervention groups was 14.1 higher (0.62 to 27.5 higher)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	242 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 57.4	The mean physical functioning (sf36 physical function) in the intervention groups was 2 higher (4 lower to 8 higher)
Psychological status (Hospital Anxiety and Depression Scale -	493 (2 studies) 12-52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of		The mean psychological status (hospital anxiety and depression scale - depression) in the control	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
depression) Scale from: 0 to 21.		bias, indirectness		groups was 7.35	1.15 lower (1.66 to 0.64 lower)
	PEM re-analysis (subgroup analysis)**				
	PEM subgroup: 198 (1 study) 12 weeks	⨁⨁⨀⨀ LOW1 due to risk of bias		The mean psychological status (hospital anxiety and depression scale - depression) in the control groups was	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was
	<95% PEM subgroup: 299 (1 study) 52 weeks	⨁⨁⨀⨀ LOW1,3 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale - depression) in the control groups was	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was
Psychological status (Hospital Anxiety and Depression Scale - anxiety) Scale from: 0 to 21.	493 (2 studies) 12-52 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups was 7.9	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention groups was 1.04 lower (1.64 to 0.45 lower)
	PEM re-analysis (subgroup analysis)**				
	PEM subgroup: 198 (1 study) 12 weeks PEM subgroup: 198 (1 study) 12 weeks	⨁⨁⨀⨀ LOW1 due to risk of bias		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups was 8.6	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention groups was 1.1 lower (2.0 to 0.2 lower)
	<95% PEM subgroup:	⨁⨁⨀⨀ LOW1,3		The mean psychological status (hospital anxiety and depression	The mean psychological status (hospital anxiety and depression

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
	299 (1 study) 52 weeks	due to risk of bias, indirectness		scale - anxiety) in the control groups was 8.0	scale - anxiety) in the intervention groups was 1.0 lower (1.8 to 0.2 lower)
Pain (numeric rating scale 0-4) - muscle pain Scale from: 0 to 4.	293 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean pain (numeric rating scale 0-4) - muscle pain in the control groups was 2.11	The mean pain (numeric rating scale 0-4) - muscle pain in the intervention groups was 0.42 lower (0.73 to 0.11 lower)
Pain (numeric rating scale 0-4) - joint pain Scale from: 0 to 4.	295 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (numeric rating scale 0-4) - joint pain in the control groups was 1.54	The mean pain (numeric rating scale 0-4) - joint pain in the intervention groups was 0.26 lower (0.58 lower to 0.06 higher)
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	295 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean sleep quality (sleep problem questionnaire) in the control groups was 11	The mean sleep quality (sleep problem questionnaire) in the intervention groups was 1.4 lower (2.3 to 0.5 lower)
Adverse events (non-serious)	518 (2 studies) 12-52 weeks	⨁⊖⊖⊖ VERY LOW1,2,5 due to risk of bias, indirectness	RR 1.03 (0.94 to 1.12)	Moderate	
				659 per 1000	20 more per 1000 (from 40 fewer to 79 more)
	PEM re-analysis (subgroup analysis)**				
				Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
	PEM subgroup: 198 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,4,5 due to risk of bias, indirectness, imprecision	RR 1.22 (0.76 to 1.98)	230 per 1000	50 more per 1000 (from 55 fewer to 223 more)
	<95% PEM subgroup: 320 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,3,5 due to risk of bias, indirectness	RR 1.0 (0.94 to 1.06)	Moderate	
				931 per 1000	0 more per 1000 (from 56 fewer to 56 more)
Adverse events (serious)	518 (2 studies) 12-52 weeks	⨁⊖⊖⊖ VERY LOW1,2,4,5 due to risk of bias, indirectness, imprecision	RR 1.56 (0.69 to 3.54)	Moderate	
				20 per 1000	11 more per 1000 (from 6 fewer to 51 more)
	PEM re-analysis (subgroup analysis)**				
	PEM subgroup: 198 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,4,5 due to risk of bias, indirectness, imprecision	RR 0.52 (0.05 to 5.65)	Moderate	
				20 per 1000	10 fewer per 1000 (from 19 fewer to 92 more)
	<95% PEM subgroup:	⨁⊖⊖⊖ VERY LOW1,3,4,5	RR 1.86 (0.76	Moderate	
				44 per 1000	38 more per 1000 (from 10 fewer to 154 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
	320 (1 study) 52 weeks	due to risk of bias, indirectness, imprecision	to 4.53)		
Adverse events (adverse reactions)	518 (2 studies) 12-52 weeks	⨁⊖⊖⊖ VERY LOW 1,2,6 due to risk of bias, indirectness, imprecision	RD 0.00 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 more per 1000 (from 20 fewer to 20 more)
	PEM re-analysis (subgroup analysis)**				
	PEM subgroup: 198 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,8 due to risk of bias, imprecision	RD 0 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 more per 1000 (from 20 fewer to 20 more)
	<95% PEM subgroup: 320 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, indirectness, imprecision	RR 1.0 (0.14 to 7.01)	Moderate	
				13 per 1000	0 fewer per 1000 (from 11 fewer to 75 more)
Activity levels (International Physical Activity Questionnaire high vs. low/moderate level of activity prev week)	196 (1 study) 12 weeks	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 3.2 (1.8 to 5.69)	Moderate	
				202 per 1000	246 more per 1000 (from 11 more to 388 more)
Return to school/work (Work and Social Adjustment Scale) Scale from: 0 to 40.	199 (1 study) 12 weeks	⨁⨁⊖⊖ LOW1,4 due to risk of		The mean return to school/work (work and social adjustment	The mean return to school/work (work and social adjustment scale) in the intervention groups

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
		bias, imprecision		scale) in the control groups was 25.4	was 1.9 lower (3.7 to 0.1 lower)
Return to school/work (Work and social adjustment scale) Scale from: 0 to 40.	241 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean return to school/work (work and social adjustment scale) in the control groups was 21.1	The mean return to school/work (work and social adjustment scale) in the intervention groups was 0.8 lower (3.2 lower to 1.6 higher)
Exercise performance measure (6 minute walk)	228 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk) in the control groups was 348 meters	The mean exercise performance measure (6 minute walk) in the intervention groups was 35.3 higher (16.84 to 53.76 higher)
Exercise performance measure (VO2 peak/aerobic capacity)	84 (3 studies) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vo2 peak/aerobic capacity) in the control groups was 21.07 ml/kg/min	The mean exercise performance measure (vo2 peak/aerobic capacity) in the intervention groups was 2.02 higher (0.33 lower to 4.36 higher)
Exercise performance measure (Peak power)	58 (2 studies) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (peak power) was 90 W	The mean exercise performance measure (peak power) in the intervention groups was 7.54 higher (9.48 lower to 24.56 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
Exercise performance measure (Elapsed exercise test time - cycle ergometer)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (elapsed exercise test time - cycle ergometer) in the control groups was 11.3 min	The mean exercise performance measure (elapsed exercise test time - cycle ergometer) in the intervention groups was 0.6 higher (2.5 lower to 3.7 higher)
Exercise performance measure (VEpeak)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vepeak) in the control groups was 44.7 L/min	The mean exercise performance measure (vepeak) in the intervention groups was 8 higher (5.72 lower to 21.72 higher)
Exercise performance measure (perceived exertion – Borg scale)	58 (2 studies) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,4,7 due to risk of bias, inconsistency, indirectness, imprecision		The mean exercise performance measure (perceived exertion – Borg scale) in the control groups was 12.9	The mean exercise performance measure (perceived exertion – Borg scale) in the intervention groups was 0.64 higher (1.18 to 0.1 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford or CDC 1994 criteria used; PEM is not a compulsory feature (majority of evidence came from PACE trial) [original analysis]
3 The majority of the evidence included an indirect population (downgraded by one increment): Unclear if participants had PEM (Moss-Morris 2005) or the percentage of participants with PEM was <95% (PACE trial) [PEM re-analysis]
4 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
5 Downgraded by 1 increment because the majority of the evidence was based on indirect outcomes (AEs not necessarily treatment-related)
6 Downgraded by 1 increment because 1 study reported zero events in either arm and optimal information size power calculation <80%

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
7 Downgraded by 1 or 2 increments because heterogeneity, I^2=96%, p=<0.00001; random effects model used. 8 Zero events – serious imprecision if sample size 70-350; very serious imprecision if sample size <70					
*Studies contributing to comparison: Broadbent 2016, GETSET trial, Guillamo 2016, Moss-Morris 2005, PACE trial **See Appendix G for additional details on the rationale, methods, and results of the PEM re-analysis.					

Table 36: Clinical evidence summary: Graded exercise therapy versus flexibility/relaxation treatment: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Flexibility/relaxation treatment (95% CI)
General symptom scales (Clinical global impression of change - much or very much better)	59 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 2.07 (1.05 to 4.08)	Moderate 267 per 1000	285 more per 1000 (from 13 more to 821 more)
Fatigue/fatigability (Chalder fatigue scale total) Scale from: 0 to 42.	59 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (chalder fatigue scale total) in the control groups was 27.4	The mean fatigue/fatigability (chalder fatigue scale total) in the intervention groups was 6.9 lower (11.08 to 2.72 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Flexibility/relaxation treatment (95% CI)
Physical function (SF36 physical function) Scale from: 0 to 100.	59 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical function (sf36 physical function) in the control groups was 55	The mean physical function (sf36 physical function) in the intervention groups was 14 higher (3.7 to 24.3 higher)
Exercise performance measure (Treadmill walking test duration)	59 (1 study) 12 weeks	⨁⨁⊖⊖ LOW2,3 due to indirectness, imprecision		The mean exercise performance measure (treadmill walking test duration) in the control groups was min	The mean exercise performance measure (treadmill walking test duration) in the intervention groups was 1.4 higher (0.34 lower to 3.14 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford or CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Fulcher 1997

Table 37: Clinical evidence summary: Graded exercise therapy versus flexibility/relaxation treatment: age and severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Flexibility/relaxation treatment (95% CI)
General symptom scales (Clinical global impression of change - much or very much better)	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.43 (0.85 to 2.41)	414 per 1000	178 more per 1000 (from 62 fewer to 583 more)
Fatigue/fatigability (Chalder fatigue scale sub scales) - Mental Scale from: 0 to 21.	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (chalder fatigue scale sub scales) - mental in the control groups was 4.8	The mean fatigue/fatigability (chalder fatigue scale sub scales) - mental in the intervention groups was 0.3 lower (1.29 lower to 0.69 higher)
Fatigue/fatigability (Chalder fatigue scale sub scales) - Physical Scale from: 0 to 21.	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (chalder fatigue scale sub scales) - physical in the control groups was 9.6	The mean fatigue/fatigability (chalder fatigue scale sub scales) - physical in the intervention groups was 1.5 lower (3.34 lower to 0.34 higher)
Cognitive function (Stroop test) - 82 questions	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (stroop test) - 82 questions in the control groups was 71.1	The mean cognitive function (stroop test) - 82 questions in the intervention groups was 8.3 higher (0.38 to 16.22 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Flexibility/relaxation treatment (95% CI)
Cognitive function (Stroop test) - 95 questions	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (stroop test) - 95 questions in the control groups was 73.1	The mean cognitive function (stroop test) - 95 questions in the intervention groups was 14.4 higher (0.22 to 28.58 higher)
Psychological status (Hospital Anxiety and Depression Scale - depression) Scale from: 0 to 21.	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale - depression) in the control groups was 6.5	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was 1.7 lower (3.25 to 0.15 lower)
Psychological status (Hospital Anxiety and Depression Scale - anxiety) Scale from: 0 to 21.	61 (1 study) 16 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups was 7.8	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention groups was 2.1 lower (4.08 to 0.12 lower)
Exercise performance measure (VO2peak)	61 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vo2peak) in the control groups was 14.4 ml/kg/min	The mean exercise performance measure (vo2peak) in the intervention groups was 2.7 higher (0.2 lower to 5.6 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Flexibility/relaxation treatment (95% CI)
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford or CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]					
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Wallman 2004					

Table 38: Clinical evidence summary: Graded exercise therapy versus heart rate variability biofeedback therapy: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Heart rate variability biofeedback therapy (95% CI)
Quality of life (SF36 physical component) Scale from: 0 to 100.	28 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 physical component) in the control groups was 47.1	The mean quality of life (sf36 physical component) in the intervention groups was 0.5 lower (8.04 lower to 7.04 higher)
Quality of life (SF36 mental component) Scale from: 0 to 100.	24 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,indirectness, imprecision		The mean quality of life (sf36 mental component) in the control groups was 51	The mean quality of life (sf36 mental component) in the intervention groups was 12.7 lower (22.95 to 2.45 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Heart rate variability biofeedback therapy (95% CI)
Fatigue/fatigability (Multidimensional Fatigue Inventory) Scale from: 20 to 100.	24 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (multidimensional fatigue inventory) in the control groups was 43.6	The mean fatigue/fatigability (multidimensional fatigue inventory) in the intervention groups was 12 higher (3.27 lower to 27.27 higher)
Psychological status (Patient Health Questionnaire-9)	24 (1 study) 5 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (patient health questionnaire-9) in the control group was 4.2	The mean psychological status (patient health questionnaire-9) in the intervention groups was 4.6 higher (0.67 to 8.53 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Windthorst 2017

Table 39: Clinical evidence summary: Graded exercise therapy versus adaptive pacing therapy: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Adaptive pacing therapy (95% CI)
Quality of life (EQ5D) Scale from: -0.594 to 1.	291 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean quality of life (eq5d) in the control groups was 0.54	The mean quality of life (eq5d) in the intervention groups was 0.05 higher (0.02 lower to 0.12 higher)
General symptom scales (Clinical global impression of change positive vs. negative/minimal change)	245 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	OR 1.4 (0.8 to 2.45)	Moderate	
				381 per 1000	82 more per 1000 (from 51 fewer to 220 more)
Fatigue/fatigability (Chalder fatigue scale) Scale from: 0 to 33.	245 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (chalder fatigue scale) in the control groups was 20.5	The mean fatigue/fatigability (chalder fatigue scale) in the intervention groups was 1.1 lower (3 lower to 0.8 higher)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	318 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 52.8	The mean physical functioning (sf36 physical function) in the intervention groups was 5.6 higher (0.3 lower to 11.5 higher)
Psychological status (Hospital anxiety and depression scale - depression) Scale from: 0 to 21.	293 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of		The mean psychological status (hospital anxiety and depression scale - depression) in the control	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Adaptive pacing therapy (95% CI)
		bias, indirectness		groups was 7.2	0.5 lower (1.23 lower to 0.23 higher)
Psychological status (Hospital anxiety and depression scale - anxiety) Scale from: 0 to 21.	293 (1 study) 52 weeks	⨁⨁◯◯ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups was 7.5	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention groups was 0.3 lower (1.17 lower to 0.57 higher)
Pain (NRS 0-4) - muscle pain Scale from: 0 to 4.	295 (1 study) 52 weeks	⨁◯◯◯ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (nrs 0-4) - muscle pain in the control groups was 2.07	The mean pain (nrs 0-4) - muscle pain in the intervention groups was 0.38 lower (0.7 to 0.06 lower)
Pain (NRS 0-4) - joint pain Scale from: 0 to 4.	293 (1 study) 52 weeks	⨁◯◯◯ VERY LOW1,2 due to risk of bias, indirectness		The mean pain (nrs 0-4) - joint pain in the control groups was 1.64	The mean pain (nrs 0-4) - joint pain in the intervention groups was 0.36 lower (0.68 to 0.04 lower)
Sleep quality (Jenkins sleep scale)	294 (1 study) 52 weeks	⨁⨁◯◯ LOW1,2 due to risk of bias, indirectness		The mean sleep quality (jenkins sleep scale) in the control groups was 10.6	The mean sleep quality (jenkins sleep scale) in the intervention groups was 1.3 lower (2.22 to 0.38 lower)
Adverse events (non-serious)	319 (1 study) 52 weeks	⨁◯◯◯ VERY LOW1,2,4 due to risk of bias, indirectness	RR 0.97 (0.92 to 1.03)	Moderate	
				956 per 1000	29 fewer per 1000 (from 76 fewer to 29 more)
Adverse events (serious)				Moderate	

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Adaptive pacing therapy (95% CI)
	319 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to risk of bias, indirectness, imprecision	RR 0.86 (0.42 to 1.75)	94 per 1000	13 fewer per 1000 (from 55 fewer to 71 more)
Adverse events (adverse reactions)	319 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.99 (0.14 to 6.97)	Moderate	
				13 per 1000	0 fewer per 1000 (from 11 fewer to 78 more)
Return to school/work (Work and social adjustment scale)	246 (1 study) 134 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean return to school/work (work and social adjustment scale) in the control groups was 22.9	The mean return to school/work (work and social adjustment scale) in the intervention groups was 2.1 lower (4.5 lower to 0.3 higher)
Exercise performance measure (6 minute walk test)	221 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk test) in the control groups was 314 meters	The mean exercise performance measure (6 minute walk test) in the intervention groups was 41 higher (20.53 to 61.47 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Adaptive pacing therapy (95% CI)
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford or criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is < 95% [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 4 Downgraded by 1 increment because the majority of the evidence was based on an indirect outcome (AEs not necessarily treatment-related)					
*Studies contributing to comparison: PACE trial					

Table 40: Clinical evidence summary: Graded exercise therapy versus intermittent exercise: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Intermittent Exercise (IE) (95% CI)
Exercise performance measure (VO2 peak/aerobic capacity)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vo2 peak/aerobic capacity) in the control groups was 24.5 ml/kg/min	The mean exercise performance measure (vo2 peak/aerobic capacity) in the intervention groups was 1.3 lower (6.89 lower to 4.29 higher)
Exercise performance measure (Peak power)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (peak power) in the control groups was 108.8 W	The mean exercise performance measure (peak power) in the intervention groups was 6.8 lower (20.11 lower to 6.51 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Intermittent Exercise (IE) (95% CI)
Exercise performance measure (Elapsed exercise test time - cycle ergometer)	16 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (elapsed exercise test time - cycle ergometer) in the control groups was 12.9 min	The mean exercise performance measure (elapsed exercise test time - cycle ergometer) in the intervention groups was 1 lower (3.5 lower to 1.5 higher)
Exercise performance measure (VEpeak)	16 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vepeak) in the control groups was 58.4 L/min	The mean exercise performance measure (vepeak) in the intervention groups was 5.7 lower (18.04 lower to 6.64 higher) VEpeak)
Exercise performance measure (rated perceived exertion – modified Borg scale) Scale from: 0 to 10.	16 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (rated perceived exertion – modified Borg scale) in the control groups was 7.1	The mean exercise performance measure (rated perceived exertion – modified Borg scale) in the intervention groups was 0.20 lower (1.18 lower to 0.78 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Broadbent 2016

Table 41: Clinical evidence summary: GET versus Activity diaries: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus Activity diaries (exercise control) (95% CI)
Fatigue (Chalder fatigue scale - change scores)	68 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue scale - change scores) in the control groups was -2.7	The mean fatigue (chalder fatigue scale - change scores) in the intervention groups was 3 lower (7.67 lower to 1.67 higher)
Psychological status (Hospital anxiety and depression scale - depression - change scores) Scale from: 0 to 21.	68 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale - depression - change scores) in the control groups was -1.3	The mean psychological status (hospital anxiety and depression scale - depression - change scores) in the intervention groups was 0.1 higher (1.54 lower to 1.74 higher)
Exercise performance measure (VO2 peak - change scores)	68 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vo2 peak - change scores) in the control groups was -0.1	The mean exercise performance measure (vo2 peak - change scores) in the intervention groups was 2.9 higher (0.27 to 5.53 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Wearden 1998

Table 42: Clinical evidence summary: GET versus Standard care: age and severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
Fatigue/fatigability (Chalder fatigue questionnaire 0-11 scale) Scale from: 0 to 11.	148 (1 study) 12 months	⨁⨁⨀⨀ LOW1 due to risk of bias, indirectness		The mean fatigue/fatigability (chalder fatigue questionnaire 0-11 scale) in the control groups was 10.1	The mean fatigue/fatigability (chalder fatigue questionnaire 0-11 scale) in the intervention groups was 6.83 lower (7.87 to 5.79 lower)
Physical functioning (SF36 physical function 10-30 scale) Scale from: 10 to 30.	148 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean physical functioning (sf36 physical function 10-30 scale) in the control groups was 16.9	The mean physical functioning (sf36 physical function 10-30 scale) in the intervention groups was 7.86 higher (6.13 to 9.59 higher)
Psychological status (Hospital Anxiety and Depression Scale - depression) Scale from: 0 to 21.	148 (1 study) 12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale - depression) in the control groups was 10.1	The mean psychological status (hospital anxiety and depression scale - depression) in the intervention groups was 5.76 lower (7.56 to 3.97 lower)
Psychological status (Hospital Anxiety and Depression Scale - anxiety) Scale from: 0 to 21.	148 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale - anxiety) in the control groups was 10.1	The mean psychological status (hospital anxiety and depression scale - anxiety) in the intervention groups was 3.01 lower (4.83 to 1.18 lower)
Sleep quality (Sleep problem questionnaire) Scale from: 0 to 20.	148 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW1,2,3		The mean sleep quality (sleep problem questionnaire) in the	The mean sleep quality (sleep problem questionnaire) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with GET versus standard care (95% CI)
		due to risk of bias, indirectness, imprecision		control groups was 11.5	4.02 lower (5.99 to 2.04 lower)
1 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Powell 2001					

1.1.5.3.2 Other exercise interventions

Table 43: Clinical evidence summary: Intermittent exercise versus standard care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Intermittent Exercise (IE) versus standard care (95% CI)
Exercise performance measure (VO2 peak/aerobic capacity)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vo2 peak/aerobic capacity) in the control groups was 19.7 ml/kg/min	The mean exercise performance measure (vo2 peak/aerobic capacity) in the intervention groups was 4.8 higher (2.57 lower to 12.17 higher)
Exercise performance measure (Peak power)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3		The mean exercise performance measure (peak power) in the control	The mean exercise performance measure (peak power) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Intermittent Exercise (IE) versus standard care (95% CI)
		due to risk of bias, indirectness, imprecision		groups was 94.2 W	14.6 higher (13.68 lower to 42.88 higher)
Exercise performance measure (Elapsed exercise test time - cycle ergometer)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (elapsed exercise test time - cycle ergometer) in the control groups was 11.3 min	The mean exercise performance measure (elapsed exercise test time - cycle ergometer) in the intervention groups was 1.6 higher (1.86 lower to 5.06 higher)
Exercise performance measure (VEpeak)	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (vepeak) in the control groups was 44.7 L/min	The mean exercise performance measure (vepeak) in the intervention groups was 13.7 higher (1.36 to 26.04 higher)
Exercise performance measure (rated perceived exertion – modified Borg scale) Scale from: 0 to 10.	16 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (rated perceived exertion – modified Borg scale) in the control groups was 6.6	The mean exercise performance measure (rated perceived exertion – modified Borg scale) in the intervention groups was 0.5 higher (0.48 lower to 1.48 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Broadbent 2016

Table 44: Clinical evidence summary: Orthostatic training versus sham: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Orthostatic training versus sham (95% CI)
Fatigue/fatigability (Fatigue Impact Scale)	36 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (fatigue impact scale) in the control group was 92.5	The mean fatigue/fatigability (fatigue impact scale) in the intervention groups was 0.4 higher (20.02 lower to 20.82 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Sutcliffe 2010					

Table 45: Clinical evidence summary: Qigong versus no treatment: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Qigong versus no treatment (95% CI)
Quality of life (SF36 sub scales) - change scores - Mental health Scale from: 0 to 100.	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,		The mean quality of life (sf36 sub scales) - change scores - mental health in the control groups was -5	The mean quality of life (sf36 sub scales) - change scores - mental health in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Qigong versus no treatment (95% CI)
		indirectness, imprecision			12.2 higher (0.77 lower to 25.17 higher)
Quality of life (SF36 sub scales) - change scores - Vitality Scale from: 0 to 100.	28 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - vitality in the control groups was 6.6	The mean quality of life (sf36 sub scales) - change scores - vitality in the intervention groups was 1.9 lower (14.49 lower to 10.69 higher)
Quality of life (SF36 sub scales) - change scores - Bodily pain Scale from: 0 to 100.	28 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - bodily pain in the control groups was 0.4	The mean quality of life (sf36 sub scales) - change scores - bodily pain in the intervention groups was 12.9 higher (3.24 lower to 29.04 higher)
Quality of life (SF36 sub scales) - change scores - General health Scale from: 0 to 100.	28 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - general health in the control groups was 4.5	The mean quality of life (sf36 sub scales) - change scores - general health in the intervention groups was 7 lower (20.22 lower to 6.22 higher)
Quality of life (SF36 sub scales) - change scores - Social functioning Scale from: 0 to 100.	28 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - social functioning in the control groups was 5.5	The mean quality of life (sf36 sub scales) - change scores - social functioning in the intervention groups was 0.5 lower (22.19 lower to 21.19 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Qigong versus no treatment (95% CI)
Quality of life (SF36 sub scales) - change scores - Role emotional Scale from: 0 to 100.	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - role emotional in the control groups was -4.2	The mean quality of life (sf36 sub scales) - change scores - role emotional in the intervention groups was 15.3 higher (23.8 lower to 54.4 higher)
Quality of life (SF36 sub scales) - change scores - Physical functioning Scale from: 0 to 100.	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - physical functioning in the control groups was 4.7	The mean quality of life (sf36 sub scales) - change scores - physical functioning in the intervention groups was 3.4 lower (14.2 lower to 7.4 higher)
Quality of life (SF36 sub scales) - change scores - Role physical Scale from: 0 to 100.	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - change scores - role physical in the control groups was 1.6	The mean quality of life (sf36 sub scales) - change scores - role physical in the intervention groups was 1.7 higher (17.48 lower to 20.88 higher)
Fatigue (Fatigue severity scale) Scale from: 9 to 63.	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue severity scale) - change scores in the control groups was 0.0	The mean fatigue (fatigue severity scale) in the intervention groups was 0.5 lower (0.98 to 0.02 lower)
Exercise performance measure (VO2 max)	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2		The mean exercise performance measure (vo2 max) - change scores	The mean exercise performance measure (vo2 max) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Qigong versus no treatment (95% CI)
		due to risk of bias, indirectness, imprecision		in the control groups was -1.3	3.8 higher (0.95 to 6.65 higher)
Exercise performance measure (Max workload)	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (max workload) - change scores in the control groups was 7.3 W	The mean exercise performance measure (max workload) in the intervention groups was 3.6 higher (12 lower to 19.2 higher)
Exercise performance measure (Borg scale – rated perceived exertion) Scale from: 6 to 20.	28 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (Borg scale – rated perceived exertion) - change scores in the control groups was 0.1	The mean exercise performance measure (Borg scale – rated perceived exertion) in the intervention groups was 2.7 lower (6.2 lower to 0.8 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Dybwad 2007

Table 46: Clinical evidence summary: Isometric yoga versus Usual care: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care/wait-list	Risk difference with Isometric yoga (95% CI)
Fatigue (Chalder fatigue scale) Scale from: 0 to 42.	30 (1 study) 9.2 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (Chalder fatigue scale) in the control groups was 25.8	The mean fatigue (Chalder fatigue scale) in the intervention groups was 6.6 lower (11.43 to 1.77 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Oka 2014

Table 47: Clinical evidence summary: Anaerobic activity therapy versus cognitive therapy: adults, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with Anaerobic activity therapy (95% CI)
Quality of life (Quality of life scale) Scale from: 16 to 112.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (quality of life scale) in the control groups was 72.52	The mean quality of life (quality of life scale) in the intervention groups was 9.52 lower (15.97 to 3.07 lower)
General symptom scales (participant global impression of change - improved/much/very much improved)	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3	RR 0.64 (0.39	Moderate	
				643 per 1000	231 fewer per 1000 (from 392 fewer to 51 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with Anaerobic activity therapy (95% CI)
		due to risk of bias, indirectness, imprecision	to 1.08)		
Fatigue/fatigability (Fatigue severity scale) Scale from: 1 to 7.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (fatigue severity scale) in the control groups was 5.87	The mean fatigue/fatigability (fatigue severity scale) in the intervention groups was 0.1 lower (0.74 lower to 0.54 higher)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 61.09	The mean physical functioning (sf36 physical function) in the intervention groups was 21.37 lower (34.73 to 8.01 lower)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) in the control groups was 11.86	The mean psychological status (beck depression inventory) in the intervention groups was 5.08 higher (0.01 lower to 10.17 higher)
Psychological status (Beck anxiety inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck anxiety inventory) in the control groups was 8.96	The mean psychological status (beck anxiety inventory) in the intervention groups was 3.15 higher (1.31 lower to 7.61 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with Anaerobic activity therapy (95% CI)
Return to school/work (number in employment)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.6 (0.33 to 1.09)	Moderate	
				571 per 1000	228 fewer per 1000 (from 383 fewer to 51 more)
Exercise performance measure (6 minute walk test)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk test) in the control groups was 1513.5 meters	The mean exercise performance measure (6 minute walk test) in the intervention groups was 135.1 lower (261.01 to 9.19 lower)
Pain (Brief pain inventory - severity) Scale from: 0 to 10.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - severity) in the control groups was 3.12	The mean pain (brief pain inventory - severity) in the intervention groups was 0.51 higher (0.72 lower to 1.74 higher)
Pain (Brief Pain Inventory - interference) Scale from: 0 to 10.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - interference) in the control groups was 3.36	The mean pain (brief pain inventory - interference) in the intervention groups was 0.39 higher (1.14 lower to 1.92 higher)
Pain (Muscle pain numeric rating scale) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3		The mean pain (muscle pain numeric rating scale) in	The mean pain (muscle pain numeric rating scale) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Cognitive therapy	Risk difference with Anaerobic activity therapy (95% CI)
		due to risk of bias, indirectness, imprecision		the control groups was 40.83	13.28 higher (3.27 lower to 29.83 higher)
Pain (Joint pain numeric rating scale) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (joint pain numeric rating scale) in the control groups was 31.52	The mean pain (joint pain numeric rating scale) in the intervention groups was 8.22 higher (10.54 lower to 26.98 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Jason 2007					

Table 48: Clinical evidence summary: Anaerobic activity therapy versus relaxation techniques: adults, moderate severity

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with Anaerobic activity therapy (95% CI)
Quality of life (Quality of life scale) Scale from: 16 to 112.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of		The mean quality of life (quality of life scale) in the control groups was 72	The mean quality of life (quality of life scale) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with Anaerobic activity therapy (95% CI)
		bias, indirectness, imprecision			9 lower (17.87 to 0.13 lower)
General symptom scales (participant global impression of change - improved/much/very much improved)	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.89 (0.49 to 1.6)	Moderate	
				464 per 1000	51 fewer per 1000 (from 237 fewer to 278 more)
Physical functioning (SF36 physical function) Scale from: 0 to 100.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean physical functioning (sf36 physical function) in the control groups was 61.2	The mean physical functioning (sf36 physical function) in the intervention groups was 21.48 lower (35.85 to 7.11 lower)
Fatigue/fatigability (Fatigue severity scale) Scale from: 1 to 7.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue/fatigability (fatigue severity scale) in the control groups was 5.62	The mean fatigue/fatigability (fatigue severity scale) in the intervention groups was 0.15 higher (0.5 lower to 0.8 higher)
Psychological status (Beck depression inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck depression inventory) (copy) in the control groups was 13.5	The mean psychological status (beck depression inventory) (copy) in the intervention groups was 3.44 higher (2.23 lower to 9.11 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with Anaerobic activity therapy (95% CI)
Psychological status (Beck anxiety inventory) Scale from: 0 to 63.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (beck anxiety inventory) (copy) in the control groups was 11.41	The mean psychological status (beck anxiety inventory) (copy) in the intervention groups was 0.7 higher (4.53 lower to 5.93 higher)
Return to school/work (number in employment)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.8 (0.42 to 1.56)	Moderate	
				429 per 1000	86 fewer per 1000 (from 249 fewer to 240 more)
Exercise performance measure (6 minute walk test)	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (6 minute walk test) (copy) in the control groups was 1429.33 meters	The mean exercise performance measure (6 minute walk test) (copy) in the intervention groups was 50.93 lower (181.39 lower to 79.53 higher)
Pain (Brief pain inventory - severity) Scale from: 0 to 10.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (brief pain inventory - severity) (copy) in the control groups was 4.6	The mean pain (brief pain inventory - severity) (copy) in the intervention groups was 0.97 lower (2.23 lower to 0.29 higher)
Pain (Brief Pain Inventory - interference) Scale from: 0 to 10.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3		The mean pain (brief pain inventory - interference) in	The mean pain (brief pain inventory - interference) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Relaxation techniques	Risk difference with Anaerobic activity therapy (95% CI)
		due to risk of bias, indirectness, imprecision		the control groups was 4.44	0.69 lower (2.23 lower to 0.85 higher)
Pain (Muscle pain numeric rating scale) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (muscle pain numeric rating scale) in the control groups was 41.36	The mean pain (muscle pain numeric rating scale) in the intervention groups was 12.75 higher (5.25 lower to 30.75 higher)
Pain (Joint pain numeric rating scale) Scale from: 0 to 100.	57 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (joint pain numeric rating scale) in the control groups was 41.91	The mean pain (joint pain numeric rating scale) in the intervention groups was 2.17 lower (21.92 lower to 17.58 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Jason 2007

1.1.5.4 Complementary and alternative therapies

Table 49: Clinical evidence summary: Music therapy and Traditional Chinese Medicine versus Traditional Chinese Medicine: age and severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TCM	Risk difference with Music therapy + TCM (95% CI)
Fatigue (Fatigue Scale based on Chalder Fatigue Scale)	90 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue scale based on Chalder fatigue scale) in the control groups was 20.2	The mean fatigue (fatigue scale based on Chalder fatigue scale) in the intervention groups was 2.66 lower (5.01 to 0.31 lower)
Psychological status (Hamilton depression scale) Scale from: 0 to 52.	90 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (Hamilton depression scale) in the control groups was 11.5	The mean psychological status (Hamilton depression scale) in the intervention groups was 1.1 lower (2.87 lower to 0.67 higher)
Psychological status (Hamilton anxiety scale) Scale from: 0 to 56.	90 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (Hamilton anxiety scale) in the control groups was 10.5	The mean psychological status (Hamilton anxiety scale) in the intervention groups was 1.1 lower (2.16 to 0.04 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by 1 increment) or a very indirect population (downgraded by 2 increments): 1. Study included only a subset of CFS population who also met TCM definition for liver stagnation and spleen deficiency syndrome; 2. 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

*Studies contributing to comparison: Zhang 2015

Table 50: Clinical evidence summary: Homeopathy versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Homeopathy (95% CI)
Quality of life (Functional limitations profile subscales) - Physical dimension	86 (1 study) 7 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean quality of life (functional limitations profile subscales) - physical dimension in the control groups was -2.72 (change score)	The mean quality of life (functional limitations profile subscales) - physical dimension in the intervention groups was 2.39 lower (6.03 lower to 1.25 higher)
Quality of life (Functional limitations profile subscales) - Psychosocial dimension	86 (1 study) 7 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (functional limitations profile subscales) - psychosocial dimension in the control groups was -6.76 (change score)	The mean quality of life (functional limitations profile subscales) - psychosocial dimension in the intervention groups was 3.05 lower (8.36 lower to 2.26 higher)
Fatigue (Fatigue impact scale subscales) - Cognitive dimension Scale from: 0 to 40.	86 (1 study) 7 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean fatigue (fatigue impact scale subscales) - cognitive dimension in the control groups was -4.21 (change score)	The mean fatigue (fatigue impact scale subscales) - cognitive dimension in the intervention groups was 0.67 lower (4.18 lower to 2.84 higher)
Fatigue (Fatigue impact scale subscales) - Physical dimension Scale from: 0 to 40.	86 (1 study) 7 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue impact scale subscales) - physical dimension in the control groups was -5.3 (change score)	The mean fatigue (fatigue impact scale subscales) - physical dimension in the intervention groups was 0.32 higher (2.91 lower to 3.55 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Homeopathy (95% CI)
Fatigue (Fatigue impact scale subscales) - Social dimension Scale from: 0 to 40.	86 (1 study) 7 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean fatigue (fatigue impact scale subscales) - social dimension in the control groups was -8.2 (change score)	The mean fatigue (fatigue impact scale subscales) - social dimension in the intervention groups was 0.28 higher (6.55 lower to 7.11 higher)
Fatigue (Multidimensional fatigue inventory subscales) - General fatigue Scale from: 4 to 20.	86 (1 study) 7 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (multidimensional fatigue inventory subscales) - general fatigue in the control groups was -1.35 (change score)	The mean fatigue (multidimensional fatigue inventory subscales) - general fatigue in the intervention groups was 1.35 lower (2.77 lower to 0.07 higher)
Fatigue (Multidimensional fatigue inventory subscales) - Physical fatigue Scale from: 4 to 20.	86 (1 study) 7 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (multidimensional fatigue inventory subscales) - physical fatigue in the control groups was -1.28 (change score)	The mean fatigue (multidimensional fatigue inventory subscales) - physical fatigue in the intervention groups was 0.85 lower (2.3 lower to 0.6 higher)
Fatigue (Multidimensional fatigue inventory subscales) - Mental fatigue Scale from: 4 to 20.	86 (1 study) 7 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (multidimensional fatigue inventory subscales) - mental fatigue in the control groups was -2.05 (change score)	The mean fatigue (multidimensional fatigue inventory subscales) - mental fatigue in the intervention groups was 0.65 lower (2.12 lower to 0.82 higher)
Fatigue (Multidimensional fatigue inventory subscales) - Reduced activity Scale from: 4 to 20.	86 (1 study) 7 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,		The mean fatigue (multidimensional fatigue inventory subscales) - reduced activity in the control groups was -1.81 (change score)	The mean fatigue (multidimensional fatigue inventory subscales) - reduced activity in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Homeopathy (95% CI)
		indirectness, imprecision			0.91 lower (2.49 lower to 0.67 higher)
Fatigue (Multidimensional fatigue inventory subscales) - Reduced motivation Scale from: 4 to 20.	86 (1 study) 7 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean fatigue (multidimensional fatigue inventory subscales) - reduced motivation in the control groups was -1.65 (change score)	The mean fatigue (multidimensional fatigue inventory subscales) - reduced motivation in the intervention groups was 0.3 higher (1.23 lower to 1.83 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
*Studies contributing to comparison: Weatherly-Jones 2004					

Table 51: Clinical evidence summary: Acupuncture versus Sham acupuncture: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Acupuncture versus Sham acupuncture (95% CI)
Quality of life (SF12 subscales) - Physical Scale from: 0 to 100.	99 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf12 subscales) - physical in the control groups was 38.72	The mean quality of life (sf12 subscales) - physical in the intervention groups was 2.64 higher (0.99 lower to 6.27 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Acupuncture versus Sham acupuncture (95% CI)
Quality of life (SF12 subscales) - Mental Scale from: 0 to 100.	99 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean quality of life (sf12 subscales) - mental in the control groups was 47.76	The mean quality of life (sf12 subscales) - mental in the intervention groups was 0.2 higher (3.77 lower to 4.17 higher)
Fatigue (Chalder fatigue scale subscales - 14-item) - Physical fatigue	99 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue scale subscales - 14-item) - physical fatigue in the control groups was 23.7	The mean fatigue (chalder fatigue scale subscales - 14-item) - physical fatigue in the intervention groups was 1.41 lower (3.96 lower to 1.14 higher)
Fatigue (Chalder fatigue scale subscales - 14-item) - Mental fatigue	99 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (chalder fatigue scale subscales - 14-item) - mental fatigue in the control groups was 14.82	The mean fatigue (chalder fatigue scale subscales - 14-item) - mental fatigue in the intervention groups was 1.17 lower (3.08 lower to 0.74 higher)
Psychological status (GHQ12) Scale from: 0 to 12.	99 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean psychological status (ghq12) in the control groups was 1.06	The mean psychological status (ghq12) in the intervention groups was 0.37 higher (0.74 lower to 1.48 higher)
Adverse events	127 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2,4 due to risk of bias,	RD 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	0 more per 1000 (from 30 fewer to 30 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Acupuncture versus Sham acupuncture (95% CI)
		indirectness, imprecision			

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

*Studies contributing to comparison: Ng 2013

Table 52: Clinical evidence summary: Abdominal tuina versus Acupuncture: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Acupuncture	Risk difference with Abdominal tuina (95% CI)
Fatigue (fatigue scale 14) Scale from: 0 to 14.	72 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue scale 14) in the control groups was 8.2	The mean fatigue (fatigue scale 14) in the intervention groups was 1.1 lower (1.96 to 0.24 lower)
Psychological status (self-rating anxiety scale) Scale from: 20 to 80.	72 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (self-rating anxiety scale) in the control groups was 51.3	The mean psychological status (self-rating anxiety scale) in the intervention groups was 3.6 lower (5.64 to 1.56 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Acupuncture	Risk difference with Abdominal tuina (95% CI)
Psychological status (Hamilton rating scale for depression)	72 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hamilton rating scale for depression) in the control groups was 7	The mean psychological status (hamilton rating scale for depression) in the intervention groups was 0.7 lower (1.33 to 0.07 lower)
Adverse events	77 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.49 (0.05 to 5.15)	53 per 1000	27 fewer per 1000 (from 50 fewer to 218 more)
Serious adverse events	77 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	RD 0.00 (-0.05 to 0.05)	0 per 1000	0 more per 1000 (from 50 fewer to 50 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

*Studies contributing to comparison: Huanan 2017

Table 53: Clinical evidence summary: Myelophil versus placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Myelophil (95% CI)
Fatigue (numeric rating scale) Scale from: 0 to 99.	97 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	-	The mean fatigue (numeric rating scale) in the control groups was 40.53	The mean fatigue (numeric rating scale) in the intervention groups was 5.73 lower (12.79 lower to 1.33 higher)
Fatigue (visual analogue scale change score) Scale from: 0 to 10.	97 (1 study) 12 weeks	⊕⊕⊖⊖ LOW2,3 due to indirectness, imprecision	-	The mean fatigue (visual analogue scale change score) in the control groups was 2.5	The mean fatigue (visual analogue scale change score) in the intervention groups was 0.5 higher (0.44 lower to 1.44 higher)
Fatigue (fatigue severity scale change score) Scale from: 9 to 63.	97 (1 study) 12 weeks	⊕⊕⊖⊖ LOW2,3 due to indirectness, imprecision	-	The mean fatigue (fatigue severity scale change score) in the control groups was 11.1	The mean fatigue (fatigue severity scale change score) in the intervention groups was 4.2 higher (0.99 lower to 9.39 higher)
Adverse events	97 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW2,3 due to indirectness, imprecision	RR 0.79 (0.32 to 1.96)	184 per 1000	39 fewer per 1000 (from 125 fewer to 176 more)
Adverse events (serious)	97 (1 study) 12 weeks	⊕⊕⊖⊖ LOW2,4 due to indirectness, imprecision	RD 0.00 (-0.04 to 0.04)	0 per 1000	0 more per 1000 (from 40 fewer to 40 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Myelophil (95% CI)
*Studies contributing to comparison: Joung 2019					

1.1.5.5 Dietary Strategies

Table 54: Clinical evidence summary: Low sugar, low yeast diet versus Healthy eating (advice): adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Healthy eating (advice)	Risk difference with Low sugar, low yeast diet (95% CI)
Quality of life (SF36 subscales) - General health Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 subscales) - general health in the control groups was 40.6	The mean quality of life (sf36 subscales) - general health in the intervention groups was 6.1 lower (18.57 lower to 6.37 higher)
Quality of life (SF36 subscales) - Physical function Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 subscales) - physical function in the control groups was 52.2	The mean quality of life (sf36 subscales) - physical function in the intervention groups was 9.9 lower (26.75 lower to 6.95 higher)
Quality of life (SF36 subscales) - Role function Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3		The mean quality of life (sf36 subscales) - role function in the	The mean quality of life (sf36 subscales) - role function in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Healthy eating (advice)	Risk difference with Low sugar, low yeast diet (95% CI)
		due to risk of bias, indirectness, imprecision		control groups was 23.8	2.5 higher (19.71 lower to 24.71 higher)
Quality of life (SF36 subscales) - Role emotion Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 subscales) - role emotion in the control groups was 61.7	The mean quality of life (sf36 subscales) - role emotion in the intervention groups was 1.6 higher (26.9 lower to 30.1 higher)
Quality of life (SF36 subscales) - Social function Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 subscales) - social function in the control groups was 50.6	The mean quality of life (sf36 subscales) - social function in the intervention groups was 8.6 lower (27.03 lower to 9.83 higher)
Quality of life (SF36 subscales) - Body pain Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 subscales) - body pain in the control groups was 54.7	The mean quality of life (sf36 subscales) - body pain in the intervention groups was 15.1 lower (33.94 lower to 3.74 higher)
Quality of life (SF36 subscales) - Vitality Scale from: 0 to 100.	39 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW1,2,3		The mean quality of life (sf36 subscales) - vitality in the control	The mean quality of life (sf36 subscales) - vitality in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Healthy eating (advice)	Risk difference with Low sugar, low yeast diet (95% CI)
		due to risk of bias, indirectness, imprecision		groups was 36.2	6.4 lower (21.25 lower to 8.45 higher)
Quality of life (SF36 subscales) - Mental health Scale from: 0 to 100.	39 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 subscales) - mental health in the control groups was 67.8	The mean quality of life (sf36 subscales) - mental health in the intervention groups was 2.9 higher (9.71 lower to 15.51 higher)
Fatigue: Chalder fatigue scale (14-item) Scale from: 0 to 42.	39 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue: Chalder fatigue scale (14-item) in the control groups was 17.7	The mean fatigue: Chalder fatigue scale (14-item) in the intervention groups was 1.7 lower (7.43 lower to 4.03 higher)
Psychological status (Hospital anxiety and depression scale subscales) - Anxiety Scale from: 0 to 21.	39 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale subscales) - anxiety in the control groups was 7.3	The mean psychological status (hospital anxiety and depression scale subscales) - anxiety in the intervention groups was 1.2 higher (1.75 lower to 4.15 higher)
Psychological status (Hospital anxiety and depression scale	39 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW1,2,3		The mean psychological status (hospital anxiety and depression scale subscales) - depression in the	The mean psychological status (hospital anxiety and depression scale subscales) - depression in the

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Healthy eating (advice)	Risk difference with Low sugar, low yeast diet (95% CI)
subscales) - Depression Scale from: 0 to 21.		due to risk of bias, indirectness, imprecision		control groups was 5.4	intervention groups was 1.1 higher (1.19 lower to 3.39 higher)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					
Studies contributing to comparison: Hobday 2008					

1.1.5.6 Dietary Supplementation

Table 55: Clinical evidence summary: Acclydine and amino acids versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Acclydine + amino acids (95% CI)
General symptom scales (Sickness impact profile-8) Scale from: 0 to 5799.	57 (1 study) 14 weeks	⨁⊖⊖⊖ VERY LOW 1,2 due to indirectness, imprecision		The mean general symptom scales (sickness impact profile-8) in the control groups was 1120.2	The mean general symptom scales (sickness impact profile-8) in the intervention groups was 107.9 higher (193.97 lower to 409.77 higher)
Fatigue (Checklist individual strength - fatigue severity	57 (1 study) 14 weeks	⨁⊖⊖⊖ VERY LOW 1,2		The mean fatigue (checklist individual strength - fatigue severity	The mean fatigue (checklist individual strength - fatigue severity subscale) in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Acclydine + amino acids (95% CI)
subscale) Scale from: 8 to 56.		due to indirectness, imprecision		subscale) in the control groups was 43	0.6 lower (6.91 lower to 5.71 higher)
Activity levels (Actometer)	57 (1 study) 14 weeks	⨁⊖⊖⊖ VERY LOW 1,2 due to indirectness, imprecision		The mean activity levels (actometer) in the control groups was 64.9	The mean activity levels (actometer) in the intervention groups was 0 higher (12.19 lower to 12.19 higher)
Adverse events (Important side effects)	57 (1 study) 14 weeks	⨁⊖⊖⊖ VERY LOW 1,3,4 due to risk of bias, indirectness, imprecision	RD 0 (-0.07 to 0.07)	Moderate	
				0 per 1000	0 more per 1000 (from 70 fewer to 70 more)

1 The majority of the evidence included an indirect population (downgraded by 1 increment) or a very indirect population (downgraded by 2 increments): 1. Study included only a subset of CFS population who had a IGFBP3/IGF1 ratio >2.5; 2. 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

*Studies contributing to comparison: The 2007

Table 56: Clinical evidence summary: Polynutrient supplement versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Polynutrient supplement (95% CI)
General symptom scales (Sickness impact profile-8) Scale from: 0 to 5799.	53 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW 1,2,3 due to risk of bias, indirectness, imprecision		The mean general symptom scales (sickness impact profile-8) in the control groups was 1710	The mean general symptom scales (sickness impact profile-8) in the intervention groups was 60 lower (381.29 lower to 261.29 higher)
Fatigue (Checklist individual strength - fatigue subscale) Scale from: 8 to 56.	53 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW 1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (checklist individual strength - fatigue subscale) in the control groups was 48.2	The mean fatigue (checklist individual strength - fatigue subscale) in the intervention groups was 0.4 higher (3.64 lower to 4.44 higher)
Activity levels (Actometer) Scale from: 0 to 300.	53 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW 1,2,3 due to risk of bias, indirectness, imprecision		The mean activity levels (actometer) in the control groups was 65.6 accelerations	The mean activity levels (actometer) in the intervention groups was 8.4 lower (18.62 lower to 1.82 higher)
Adverse events (nausea)	53 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	Peto OR 7.7 (0.77 to 77.47)	Moderate	
				0 per 1000	110 more per 1000 (from 20 fewer to 240 more)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Polynutrient supplement (95% CI)
Quality of life (Self-reported improvement in severity of complaints) - Completely recovered	53 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW 1,2,4 due to risk of bias indirectness, imprecision	RD 0 (-0.07 to 0.07)	Moderate	
				0 per 1000	0 more per 1000 (from 70 fewer to 70 more)
Quality of life (Self-reported improvement in severity of complaints) - Improved	53 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.2 (0.36 to 3.99)	Moderate	
				154 per 1000	31 more per 1000 (from 99 fewer to 460 more)
Quality of life (Self-reported improvement in severity of complaints) - Similar	53 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.12 (0.81 to 1.56)	Moderate	
				692 per 1000	83 more per 1000 (from 131 fewer to 388 more)
Quality of life (Self-reported improvement in severity of complaints) - Worse	53 (1 study) 12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	Peto OR 7.12 (0.14 to 359.1)	Moderate	
				0 per 1000	40 more per 1000 (from 60 fewer to 130 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Polynutrient supplement (95% CI)
[original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70					
*Studies contributing to comparison: Brouwers 2002					

Table 57: Clinical evidence summary: Aribinoxylane versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aribinoxylane (95% CI)
Quality of life (WHOQOL-BREF subscales) - Physical wellbeing Scale from: 0 to 100.	64 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW 1,2 due to indirectness, imprecision		The mean quality of life (WHOQOL-BREF subscales) - physical wellbeing in the control groups was 5 (change score)	The mean quality of life (WHOQOL-BREF subscales) - physical wellbeing in the intervention groups was 1.9 lower (9.23 lower to 5.43 higher)
Quality of life (WHOQOL-BREF subscales) - Psychological wellbeing Scale from: 0 to 100.	64 (1 study) 8 weeks	⨁⨁⊖⊖ LOW1 due to indirectness		The mean quality of life (WHOQOL-BREF subscales) - psychological wellbeing in the control groups was -1 (change score)	The mean quality of life (WHOQOL-BREF subscales) - psychological wellbeing in the intervention groups was 2.4 higher (3.27 lower to 8.07 higher)
Quality of life (WHOQOL-BREF subscales) - Social wellbeing Scale from: 0 to 100.	64 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to		The mean quality of life (WHOQOL-BREF subscales) - social wellbeing in the control groups was 6.9 (change score)	The mean quality of life (WHOQOL-BREF subscales) - social wellbeing in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aribinoxylane (95% CI)
		indirectness, imprecision			8.2 lower (14.78 to 1.62 lower)
Quality of life (WHOQOL-BREF subscales) - Environmental wellbeing Scale from: 0 to 100.	64 (1 study) 8 weeks	⊕⊕⊖⊖ LOW1 due to indirectness		The mean quality of life (WHOQOL-BREF subscales) - environmental wellbeing in the control groups was 1.6 (change score)	The mean quality of life (WHOQOL-BREF subscales) - environmental wellbeing in the intervention groups was 2.2 lower (7.29 lower to 2.89 higher)
General symptom scales (Patient global impression of change - improvement)	64 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	RR 0.88 (0.24 to 3.22)	Moderate	
				133 per 1000	133 per 1000
General symptom scales (Measure yourself medical outcomes profile 2) Scale from: 0 to 6.	64 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision		The mean general symptom scales (measure yourself medical outcomes profile 2) in the control groups was -0.5 (change score)	The mean general symptom scales (measure yourself medical outcomes profile 2) in the intervention groups was 0.4 higher (0.29 lower to 1.09 higher)
Fatigue (Chalder fatigue scale 11-item) Scale from: 0 to 11.	64 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision		The mean fatigue (Chalder fatigue scale 11-item) in the control groups was -1.4 (change score)	The mean fatigue (Chalder fatigue scale 11-item) in the intervention groups was 0.3 higher (1.71 lower to 2.31 higher)
Psychological status (Hospital anxiety and depression scale) - Anxiety Scale from: 0 to 21.	64 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to		The mean psychological status (hospital anxiety and depression scale) - anxiety in the control groups was -0.1 (change score)	The mean psychological status (hospital anxiety and depression scale) - anxiety in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aribinoxylane (95% CI)
		indirectness, imprecision			0.9 lower (3.03 lower to 1.23 higher)
Psychological status (Hospital anxiety and depression scale) - Depression Scale from: 0 to 21.	64 (1 study) 8 weeks	⊕⊕⊖⊖ LOW1 due to indirectness		The mean psychological status (hospital anxiety and depression scale) - depression in the control groups was -1 (change score)	The mean psychological status (hospital anxiety and depression scale) - depression in the intervention groups was 0.6 higher (0.57 lower to 1.77 higher)
Adverse events (serious)	71 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW1,3, 4 due to risk of bias, indirectness, imprecision	RD 0 (-0.05 to 0.05)	Moderate	
				0 per 1000	0 more per 1000 (from 50 fewer to 50 more)
Adverse events (minor side effects causing withdrawal)	71 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	RR 2.76 (0.3 to 25.25)	Moderate	
				29 per 1000	51 more per 1000 (from 20 fewer to 703 more)

1 The majority of the evidence included an indirect population (downgraded by 1 increment) or a very indirect population (downgraded by 2 increments): 1. Study included only a subset of CFS population with symptoms suggestive of immune activation (≥2 of: tender lymph nodes, sore throat or poor temperature control); 2. 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

*Studies contributing to comparison: McDermott 2006

Table 58: Clinical evidence summary: Vitamin D versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Vitamin D (95% CI)
Adverse events (deaths)	50 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	RD 0 (-0.07 to 0.07)	Moderate 0 per 1000	0 more per 1000 (from 70 fewer to 70 more)
Fatigue (Piper fatigue scale)	45 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (piper fatigue scale) in the control groups was 7	The mean fatigue (piper fatigue scale) in the intervention groups was 0.2 higher (0.8 lower to 1.2 higher)
Psychological status (Hospital anxiety and depression scale) - Anxiety Scale from: 0 to 21.	45 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean psychological status (hospital anxiety and depression scale) - anxiety in the control groups was 5	The mean psychological status (hospital anxiety and depression scale) - anxiety in the intervention groups was 0.4 higher (0.95 lower to 1.75 higher)
Psychological status (Hospital anxiety and depression scale) - Depression Scale from: 0 to 21.	45 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean psychological status (hospital anxiety and depression scale) - depression in the control groups was 7.6	The mean psychological status (hospital anxiety and depression scale) - depression in the intervention groups was 1 lower (2.55 lower to 0.55 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Vitamin D (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): Study included only a subset of CFS population who also had 25OHD (serum vit D) level <75nmol/L 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70					
*Studies contributing to comparison: Witham 2015					

Table 59: Clinical evidence summary: Coenzyme Q10 and NADH versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Coenzyme Q10 + NADH (95% CI)
Fatigue (Fatigue Index Scale) Scale from: 0 to 160.	73 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (fatigue index scale) in the control groups was 132.3	The mean fatigue (fatigue index scale) in the intervention groups was 7.9 lower (18.02 lower to 2.22 higher)
Pain (McGill pain questionnaire subscales) - Affective Scale from: 0 to 12.	73 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (McGill pain questionnaire subscales) - affective in the control groups was 6.8	The mean pain (McGill pain questionnaire subscales) - affective in the intervention groups was 2.1 higher (0.55 to 3.65 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Coenzyme Q10 + NADH (95% CI)
Pain (McGill pain questionnaire subscales) - Sensory Scale from: 0 to 33.	73 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (McGill pain questionnaire subscales) - sensory in the control groups was 17.7	The mean pain (McGill pain questionnaire subscales) - sensory in the intervention groups was 4.1 higher (0.98 to 7.22 higher)
Sleep quality (Global Pittsburgh sleep quality index) Scale from: 0 to 21.	73 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean sleep quality (global Pittsburgh sleep quality index) in the control groups was 14.9	The mean sleep quality (global Pittsburgh sleep quality index) in the intervention groups was 0.9 higher (0.78 lower to 2.58 higher)
Exercise performance measure (VO2 max)	80 (1 study) 8 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (vo2 max) in the control groups was 18.6 ml/kg/min	The mean exercise performance measure (vo2 max) in the intervention groups was 0 higher (0.44 lower to -0.44 higher)
Exercise performance measure (Max workload in km/h)	80 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean exercise performance measure (max workload in km/h) in the control groups was 88.8	The mean exercise performance measure (max workload in km/h) in the intervention groups was 4.4 higher (4.46 lower to 13.41 higher)
Exercise performance measure (Perceived exertion – Borg scale – change scores) Scale from: 6 to 20.	80 (1 study) 8 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness		The mean exercise performance measure (Perceived exertion – Borg scale – change scores) in the control groups was 0.12	The mean exercise performance measure (Perceived exertion – Borg scale – change scores) in the intervention groups was 0.13 higher

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Coenzyme Q10 + NADH (95% CI)
					(0.53 lower to 0.79 higher)
Adverse events (moderate)	80 (1 study) 8 weeks	⊕⊖⊖⊖ VERY LOW 2,3,4 due to indirectness, imprecision	Peto OR 0.13 (0.01 to 1.27)	Moderate	
				75 per 1000	65 fewer per 1000 (from 74 fewer to 18 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 The majority of the evidence included an indirect population (downgraded by one increment): CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 The majority of the evidence included an indirect outcome (downgraded by one increment): Adverse events not necessarily treatment-related

*Studies contributing to comparison: Castro-Marrero 2016

Table 60: Clinical evidence summary: Guanidinoacetic acid (GAA) versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Guanidinoacetic acid (95% CI)
Quality of life (SF36 sub scales) - PCS Scale from: 0 to 100.	28 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectnes		The mean quality of life (sf36 sub scales) - pcs in the control groups was 52.8	The mean quality of life (sf36 sub scales) - pcs in the intervention groups was 2.4 higher (0.24 lower to 5.04 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Guanidinoacetic acid (95% CI)
		s, imprecision			
Quality of life (SF36 sub scales) - MCS Scale from: 0 to 100.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf36 sub scales) - mcs in the control groups was 45.8	The mean quality of life (sf36 sub scales) - mcs in the intervention groups was 5.3 higher (0.84 to 9.76 higher)
Fatigue (Multidimensional fatigue inventory sub scales) - General fatigue Scale from: 4 to 20.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (multidimensional fatigue inventory sub scales) - general fatigue in the control groups was 11.8	The mean fatigue (multidimensional fatigue inventory sub scales) - general fatigue in the intervention groups was 0.2 lower (1.24 lower to 0.84 higher)
Fatigue (Multidimensional fatigue inventory sub scales) - Physical fatigue Scale from: 4 to 20.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (multidimensional fatigue inventory sub scales) - physical fatigue in the control groups was 11.6	The mean fatigue (multidimensional fatigue inventory sub scales) - physical fatigue in the intervention groups was 0.1 higher (0.87 lower to 1.07 higher)
Fatigue (Multidimensional fatigue inventory sub scales) - Mental fatigue Scale from: 4 to 20.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias,		The mean fatigue (multidimensional fatigue inventory sub scales) - mental fatigue in the control groups was 14	The mean fatigue (multidimensional fatigue inventory sub scales) - mental fatigue in the intervention groups was 1.8 lower (2.81 to 0.79 lower)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Guanidinoacetic acid (95% CI)
		indirectness			
Fatigue (Multidimensional fatigue inventory sub scales) - Reduced activity Scale from: 4 to 20.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, indirectness		The mean fatigue (multidimensional fatigue inventory sub scales) - reduced activity in the control groups was 13.9	The mean fatigue (multidimensional fatigue inventory sub scales) - reduced activity in the intervention groups was 2.2 lower (3.33 to 1.07 lower)
Fatigue (Multidimensional fatigue inventory sub scales) - Reduced motivation Scale from: 4 to 20.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean fatigue (multidimensional fatigue inventory sub scales) - reduced motivation in the control groups was 15	The mean fatigue (multidimensional fatigue inventory sub scales) - reduced motivation in the intervention groups was 1.9 lower (3.27 to 0.57 lower)
Pain (Visual analogue scale) - At rest Scale from: 0 to 10.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean pain (visual analogue scale) - at rest in the control groups was 1.4	The mean pain (visual analogue scale) - at rest in the intervention groups was 0.2 lower (1.06 lower to 0.66 higher)
Pain (Visual analogue scale) - During activity Scale from: 0 to 10.	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectnes		The mean pain (visual analogue scale) - during activity in the control groups was 5	The mean pain (visual analogue scale) - during activity in the intervention groups was 0.6 lower (1.83 lower to 0.63 higher)

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Guanidinoacetic acid (95% CI)
		s, imprecision			
Adverse events (Self-reported side effects)	28 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	RD 0 (-0.13 to 0.13)	Moderate	
				0 per 1000	0 more per 1000 (from 130 fewer to 130 more)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis] 3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70					
*Studies contributing to comparison: Ostojic 2016					

Table 61: Clinical evidence summary: Ubiquinol-10 versus Placebo: adults, severity mixed or unclear

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Ubiquinol-10 (95% CI)
Cognitive function (Uchida-Kraepelin psychodiagnostic test) - Number of responses	31 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of		The mean cognitive function (uchida-kraepelin psychodiagnostic test) - number of responses in the	The mean cognitive function (uchida-kraepelin psychodiagnostic test) - number of responses in the intervention groups was

Outcomes	No of Participants (studies*) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Ubiquinol-10 (95% CI)
		bias, indirectness, imprecision		control groups was 217.2	5.7 higher (43.65 lower to 55.05 higher)
Cognitive function (Uchida-Kraepelin psychodiagnostic test) - Number of correct responses	31 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean cognitive function (uchida-kraepelin psychodiagnostic test) - number of correct responses in the control groups was 211.9	The mean cognitive function (uchida-kraepelin psychodiagnostic test) - number of correct responses in the intervention groups was 4.1 higher (46.35 lower to 54.55 higher)
Adverse events (Serious)	34 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision	RD 0 (-0.11 to 0.11)	Moderate	
				0 per 1000	0 more per 1000 (from 110 fewer to 110 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

*Studies contributing to comparison: Fukuda 2016

See appendices (Evidence Review H) for full GRADE tables.

More information on the minimally important differences (MIDs) used and the interpretation can be found in Appendix K of Evidence Review H and the Methods Chapter of this guideline.

1.1.6 Economic evidence

1.1.6.1 Included studies

Five health economic studies with a relevant comparison were included in this review.[24, 53, 64, 77, 96] These are summarised in the health economic evidence profiles below (Table 62 to Table 65) and the health economic evidence tables in the appendices. The studies evaluated the following interventions:

- Self-management
  - Adaptive pacing – 1 study
- Behavioural/psychological support
  - Cognitive behavioural therapy – 3 studies
  - Lightning Process – 1 study
  - Multidisciplinary rehabilitation 1 study
  - Education and support – 1 study
  - Pragmatic rehabilitation – 1 study
- Exercise
  - Graduated exercise – 1 study
- Usual care
  - GP-led care – 2 studies
  - Specialist medical care – 2 studies
  - Supportive listening – 1 study

There were no economic evaluations of:

- Buddy/mentoring programmes
- Mindfulness
- Dietary strategies or supplementation
- Complementary and alternative therapies.

1.1.6.2 Excluded studies

Two published economic evaluations relating to this review question were identified but were excluded due to methodological limitations[81] or lack of applicability.[82] These are listed in the appendices, with reasons for exclusion given.

See also the health economic study selection flow chart in the appendices.

1.1.6.3 Summary of studies included in the economic evidence review

Table 62: Health economic evidence profile: Supported self-management vs usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
McCrone 2012[53] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• RCT (PACE) • Population: Oxford criteria • Comparators: Adaptive pacing therapy (APT) vs Specialist medical care • Time horizon: 12 months	£823	0.0149 QALYs	£55,235 per QALY gained	Probability intervention is the most cost effective (£20K/£30K threshold): SMC: 24%/8% CBT: 48%/63% APT: 3%/3% GET: 25%/27% The cost of APT would have to fall by 35% for the incremental cost effectiveness ratio to fall below £30k per QALY gained.

Abbreviations: APT=adaptive pacing therapy; CBT=cognitive behavioural therapy; GET=graded exercise therapy; QALY= quality-adjusted life year; RCT= randomised controlled trial; SMC=specialist medical care

(a) Population were diagnosed using the Oxford criteria and therefore might not have post exertional malaise.

(b) Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short.

Table 63: Health economic evidence profile: Cognitive behavioural therapy (CBT)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
McCrone 2012[53] UK	Partially applicable[(a)]	Potentially serious limitations[(b)]	• RCT (PACE) • Population: Oxford • Comparators: CBT vs specialist medical care • Time horizon: 12 months	£904	0.0492 QALYs	£18,374 per QALY gained	Probability intervention is the most cost effective (£20K/£30K threshold): SMC: 24%/8% CBT: 48%/63% APT: 3%/3% GET: 25%/27%
O'Dowd 2006[64] UK	Partially applicable [(c)]	Potentially serious limitations[(d)]	• RCT (O'Dowd 2006) • Population: Fukuda • Comparators: CBT vs GP care • Time horizon: 12 months	£248	0.013 QALYs	£19,000 per QALY gained	Not conducted

Abbreviations: APT=adaptive pacing therapy; CBT=cognitive behavioural therapy; GET=graded exercise therapy; GP=general practitioner-led care; QALY= quality-adjusted life year; RCT= randomised controlled trial; SMC=specialist medical care

(a) Population were diagnosed using the Oxford criteria and therefore might not have post exertional malaise

(b) Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short.

(c) Population were diagnosed using the CDC/ Fukuda criteria and therefore might not have post exertional malaise. Used HUI3 rather than EQ-5D

(d) Treatment effects were from a single trial rather than a systematic review. There is a very high risk of bias for the effectiveness outcome due to lack of blinding and incomplete outcome data Time horizon might be too short.

Table 64: Health economic evidence profile: Other psychological/behavioural support

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Crawley 2018[24] (UK)	Directly applicable	Potentially serious limitations[(a)]	• RCT (SMILE) • Population: Young people – NICE(2007) criteria • Comparators: LP+SMC vs SMC • Time horizon: 12 months	£331	0.095 QALYs	£3,484 per QALY gained	Probability LP cost effective (£20/£30K threshold): 78%/80%
O'Dowd 2006[64] UK	Partially applicable [(b)]	Potentially serious limitations[(c)]	• RCT (O'Dowd 2006) • Population: Fukuda • Comparators: ES vs GP care • Time horizon: 12 months	ES vs GP £358 ES vs CBT £110	ES vs GP 0.027 QALYs ES vs CBT 0.014 QALYs	ES vs GP £13,259 per QALY gained ES vs CBT £7,929 per QALY gained	Not conducted
Richardson 2013[77] UK	Partially applicable [(d)]	Potentially serious limitations[(e)]	• RCT (FINE) • Population: Oxford • Comparators: PR vs GP • Time horizon: 70 weeks	£218	-0.012 QALYs	Dominated by GP care	Probability GP care is cost effective (£20/£30K threshold): 65%/63%
Vos-Vromans 2017[96] Netherlands	Partially applicable [(f)]	Potentially serious limitations[(g)]	• RCT (FatiGo) • Population: Fukuda • Comparators: MDR vs CBT • Time horizon: 12 months	£4,835[(h)]	0.05 QALYs	£105,975 per QALY gained	Probability MDR is cost effective (£20/£30K threshold): 0%/0%

Abbreviations: CBT=cognitive behavioural therapy; ES=education& support (sharing, relation techniques and stretching); GP=general practitioner-led care; LP=Lightning Process; MDR=multidisciplinary rehabilitation; QALY= quality-adjusted life year; PR=pragmatic rehabilitation; RCT= randomised controlled trial; SMC=specialist medical care

(a) Limitations: Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short. The authors have reported methods to calculate the costs of the loss of productivity incurred by patients and parents. While in the text, the authors state that they have used an NHS/healthcare perspective, they have not made it explicit that these costs have not been included.

(b) Population were diagnosed using the CDC/Fukuda criteria and therefore might not have post exertional malaise. Used HUI3 rather than EQ-5D

(c) Treatment effects were from a single trial rather than a systematic review. There is a very high risk of bias for the effectiveness outcome due to lack of blinding and incomplete outcome data Time horizon might be too short.

(d) Population were diagnosed using the Oxford criteria and therefore might not have post exertional malaise.

(e) Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short. Outcomes are very imprecise.
(f) Population were diagnosed using the Oxford criteria and therefore might not have post exertional malaise. Cost perspective is the Netherlands health service.
(g) Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short. Patients were required to report resource use on a monthly basis, which resulted in incomplete data. Unclear how QALYs were calculated.
(h) 2012 Euros converted to UK pounds.[66].

Table 65: Health economic evidence profile: Graduated Exercise Therapy

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
McCrone 2012[53] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• RCT (PACE) • Population: Oxford criteria • Comparators: Graduated exercise therapy (GET) vs Specialist medical care • Time horizon: 12 months	£810	0.0343 QALYs	£23,615 per QALY gained	Probability intervention is the most cost effective (£20K/£30K threshold): SMC: 24%/8% CBT: 48%/63% APT: 3%/3% GET: 25%/27% The cost of GET would have to increase by 22% for the incremental cost effectiveness ratio to go above £30k per QALY gained.

Abbreviations: APT=adaptive pacing therapy; CBT=cognitive behavioural therapy; GET=graded exercise therapy; QALY= quality-adjusted life year; RCT= randomised controlled trial; SMC=specialist medical care

(a) Population were diagnosed using the Oxford criteria and therefore might not have post exertional malaise.

(b) Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short.

1.1.6.4 Health economic modelling

The model from the original NICE guideline compared cognitive behavioural therapy with usual care. This was based on a trial of patients, not all of whom had ME/CFS. This trial has now been excluded from this review for that reason and therefore so has the previous guideline's model. However, there are now two included economic evaluations that do evaluate CBT in an ME/CFS population.

1.1.7 Evidence statements

1.1.7.1 Effectiveness

- See GRADE tables above

1.1.7.2 Economic

Self-management strategies

- One cost–utility analysis found that adaptive pacing therapy was not cost effective compared as an adjunct to specialist medical care for adults with ME/CFS (ICER: £55,200 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

Cognitive behavioural therapy

- One cost–utility analysis found that cognitive behavioural therapy was cost effective as an adjunct to specialist medical care for adults with ME/CFS (ICER: £18,400 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that cognitive behavioural therapy was cost effective as an adjunct to usual GP-led care for adults with ME/CFS. (ICER: £19,000 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

Other psychological/behavioural interventions

- One cost–utility analysis found that the Lightning Process was cost effective as an adjunct to specialist medical care for children with ME/CFS. (ICER: £3,500 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.
- One cost–utility analysis found that multidisciplinary rehabilitation was not cost effective compared to cognitive behavioural therapy for adults with ME/CFS (ICER: £106,000 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that education and support by a specialist team was cost effective compared to GP-led care for adults with ME/CFS (ICER: £13,300 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that education and support by a specialist team was cost effective compared with CBT for adults with ME/CFS (ICER: £7,900 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that in adults with ME/CFS GP-led care was dominant (less costly and more effective) compared to pragmatic rehabilitation. This analysis was assessed as partially applicable with potentially serious limitations.

Graded Exercise Therapy

- One cost–utility analysis found that graduated exercise therapy was cost effective as an adjunct to specialist medical care for adults with ME/CFS at a threshold of £30,000 per QALY gained for but was not cost-effective at a threshold of £20,000 per QALY gained (ICER: £23,600 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

Other exercise therapies

- No relevant economic evaluations were identified.

Complementary and alternative therapies

- No relevant economic evaluations were identified.

Dietary strategies

- No relevant economic evaluations were identified.

Dietary supplements

- No relevant economic evaluations were identified.

2 Experience of interventions

2.1 Review question

What are the experiences of people who have had interventions for ME/CFS?

2.1.1 Summary of the protocol

For full details see the review protocol in the appendices.

Table 66: Characteristics of review question

Objective	This is a controversial research area and one of the criticisms is that the trials do not capture or reflect the breadth of experiences of people with ME/CFS when interventions are implemented. This review aims to explore the experiences of people who have had interventions for ME/CFS.
Population and setting	People who have had interventions for ME/CFS.
Context	Experiences of people that have had interventions for ME/CFS and the benefits and harms they experienced.
Review strategy	Synthesis of qualitative research, following a thematic analysis approach. Results presented in narrative and in table format with summary statements of main review findings. Quality of the evidence will be assessed by a GRADE CerQual approach for each review finding.

2.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

2.1.3 Effectiveness evidence

2.1.3.1 Included studies

We searched for qualitative studies exploring the experiences of people who have had interventions for ME/CFS. Thirteen studies were identified.[4, 6, 7, 11, 19, 28, 36, 49, 71, 73, 76, 90, 101]

Call for evidence

Submissions were received from 42 separate organisations or individuals, consisting of 508 reports or references to publications. Of submissions that were considered to be relevant to this review question, 13 were included.[3, 5, 9, 10, 25, 34, 50, 56, 59, 68-70, 85]

Twenty-five qualitative studies (26 papers) were included in the review in total. These are summarised in Table 67 and 3 below. Key findings from these studies are summarised in Section 1.5.4 below. See also the study selection flow chart in, study evidence tables in and excluded studies lists in the appendices.

Eighteen studies were in adults and 7 were in children/young people. Evidence was identified on the experiences of cognitive behavioural therapy, counselling, the Lightning Process, graded exercise therapy, other exercise interventions, education programmes/information

resources, pharmacological interventions and complementary and alternative therapies. A variety of qualitative methodologies were used to inform the research (see Table 67 and Table 68). Only findings that were relevant to the review question were included; therefore findings related to ME/CFS services and not specific interventions were not extracted.

2.1.3.2 Excluded studies

See the excluded studies list in appendices.

2.1.4 Summary of qualitative studies included in the evidence review

Table 67: Summary of studies included in the review (identified through database searching)

Study	Design	Intervention	Population	Research aim	Comments
Bayliss 2016[4]	Semi structured interviews with thematic analysis	Resources for practitioners and patients to support the diagnosis and management of 'CFS/ME' in primary care.	Individuals with an existing diagnosis of 'CFS/ME', recruited from participating GP practices. Patients with other conditions, or other factors that may account for their fatigue were excluded. N=11; male/female 2/9; age range 27-74 years.	Following the development of an online training module for GPs, and an information pack and DVD for patients, this study explored the extent to which these resources can be implemented in routine primary care.	UK study Only 53 % of patients who took part in this study reported receiving a copy of the information resource and for those who did receive it, it was often incomplete. All participants were provided with a copy prior to interview. PEM reanalysis: moderate concerns over applicability due to participants being selected by GPs after excluding other conditions but it being unclear if selection was also based on PEM.
Beasant 2014[6]	Semi structured interviews with thematic analysis	Specialist medical care + Lightning Process	Adolescents taking part in the Specialist Medical Intervention and Lightning Evaluation (SMILE) study and their mothers. Inclusion criteria: diagnosed with 'CFS/ME', aged between 12 and 18 years, mildly or moderately affected by the condition; (not house bound). Purposive sampling to ensure that interviews included a range of participants in terms of age, sex, socioeconomic circumstance and ethnicity	To understand the experiences of adolescents and families in accessing and using a specialist service and to explore whether or not adolescents and their mothers value referral to a specialist service for young people with 'CFS/ME'.	UK study Moderate concerns regarding applicability due to study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and

Study	Design	Intervention	Population	Research aim	Comments
			as well as families from both intervention arms. N=12 adolescents; male/female 3/9; age mean (SD) 13.9 (1.6) years; illness duration median (IQR) 13 (9 to 18) months; 5 were interviewed post randomisation but before receiving the intervention, and 7 after the intervention. N=13 mothers; 5 mothers were interviewed at all three time points, 8 took part in one-off interviews: 4 post randomisation and 4 after their child received an intervention.		unclear which intervention arm the findings relate to.
Beaulieu 2000[7]	Mixture of structured and semi structured questions, analysed using thematic analysis	Complementary and alternative therapies	N=15 Health professionals People who were English-speaking and who had a diagnosis of CFS from a medical doctor, recruited from physicians practices, support groups and identified by leaders of associations. N=43; male/female 16/27; 26% were in school or working full or part time; mean age at onset was 34.2 years (range 15 to 58 years); people had been ill for an average of seven years. Significant others including friends, parents, spouses, adult children and a sibling, recruited following identification by people with CFS participating in the study. N=23; male/female not reported; 69% were working	To examine multiple perspectives on stigmatization and legitimation of CFS	Canadian study Only relevant data reported by people with ME/CFS were extracted PEM reanalysis: serious concerns over applicability due to limited details on the interventions received and it being unclear if participants experienced PEM.
Broadbent 2020[11]	Semi structured interviews with	Aquatic exercise intervention	People with a diagnosis of ME/CFS (International Canadian Consensus criteria	To explore the experiences of	Australian study

Study	Design	Intervention	Population	Research aim	Comments
	thematic analysis		or the 1994 Fukuda criteria) who had participated in an aquatic exercise intervention. N=11; all females; mean age 54.8 (12.4) years; duration of ME/CFS symptoms 17.0 (7.6) years; time since medical diagnosis 13.4 (6.2) years; other common co-conditions included fibromyalgia (n = 6), depression/anxiety (n = 5), sleep disorders (n = 5), asthma/breathing difficulties (n = 7) and osteoarthritis (n = 6).	participants in a short aquatic exercise programme for individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, and to gain insight into the perceived psychosocial benefits.	Moderate concerns regarding applicability due to all participants being female PEM reanalysis: serious concerns over applicability due to existing reasons and it being unclear if participants had PEM as it is not a compulsory feature in the 1994 Fukuda criteria and the number of those diagnosed using the International Canadian Consensus criteria cannot be determined.
Cheshire 2020[19]	Semi structured interviews with thematic analysis	Guided graded Exercise Self-help	People who had participated in the GES arm of the GETSET trial and had rated themselves as improved or deteriorated after the intervention (using clinical global impression of change scale); severely affected patients were not included in the trial. N=19 (n=9 reported feeling 'much better', n=10 reported feeling 'a little worse' – initial aim to recruit 10 reporting 'much better' or 'very much better' and 10 reporting 'much worse' or 'very much worse', but none reported feeling 'much worse' or 'very much worse', so inclusion criteria were expanded to include 'a little worse'); majority Caucasian (17/19); male/female 2/17; mean age (IQR) for 'much better' group 39 (21-54)	To explore patient experiences of Guided graded Exercise Self-help (GES) delivered as part of a randomised controlled trial (GETSET) for people with ME/CFS to answer the research question: 'What are the differences and similarities in treatment perceptions and experiences of GES among 'CFS/ME' participants reporting an improvement compared with those reporting a	UK study

Study	Design	Intervention	Population	Research aim	Comments
			years, for the 'a little worse group 43 (28-66) years; median (IQR) length of time since symptom onset for the 'much better' group 4 (3-5) years, for the 'a little worse' group 13 (8-21) years.	deterioration in their condition?'	
Dennison 2010[28]	Semi structured interviews with thematic analysis	Family focused CBT Psychoeducation	Young people and their parents who had participated in a randomised controlled trial comparing family focused CBT with psychoeducation. N=16 young people; all white British; male/female 6/10; mean age (range) 19.9 (16-24; 13-18 at the time of starting therapy) years; n=7 received CBT, n=9 received psychoeducation. N=16 parents; all white British; male/female 2/14; n=9 were involved in CBT, n=7 were involved in psychoeducation	To explore in detail adolescent patients' and their parents' experience of both family-focused CBT and psychoeducation for CFS. The study aimed to elicit participants' experiences in their own terms in order to better understand participants' expectations, therapy experiences and views regarding the effectiveness of their treatment.	UK study Moderate concerns about applicability due to findings for both interventions being combined. PEM reanalysis: serious concerns due to existing reasons and it being unclear if participants had PEM.
Harris 2017[36]	Semi structured interviews with thematic analysis	General	Adolescents with a primary diagnosis of ME/CFS, aged between 12-18 years who experienced at least one of the following: difficulty with eating, frequent nausea, lack of appetite, weight loss, abdominal pain, bloating, diarrhoea or constipation. The sample was drawn from a 'CFS/ME' specialist hospital service providing regional support for assessment and treatment of over 300 children a year in the Gloucester, Bristol, Wiltshire and Somerset areas, covering a population of 400,000 children aged 5-19 years (Office of national statistics, 2011).	To explore what adolescents felt had caused their problems with eating, whether there were triggers and maintaining factors and what interventions they felt would be helpful.	UK study Moderate concerns over applicability due to the population being limited to adolescents with ME/CFS who experienced eating difficulties; findings may not be equally relevant to the wider population of ME/CFS who did not experience such difficulties. PEM reanalysis: serious concerns over applicability

Study	Design	Intervention	Population	Research aim	Comments
					due to existing reasons and it being unclear if participants had PEM.
Larun 2011[49]	Focus groups with thematic analysis	Six week comprehensive treatment program for CFS patients including physical activities e.g. walking, hydrotherapy, relaxation and breathing exercises in addition to physiotherapy, theme discussions and individual counselling.	Adults >18 years attending a treatment program for CFS. Participants joined the program for variety of reasons, not because they were particularly convinced of the benefits of physical activity. Purposive sample representing variations on gender, illness duration, and social background. N=10; male/female 2/8; mean age (range) 50 (40-64) years; mean illness duration (range) 3.4 (1-7.5) years; all scored close to maximum on the Chalder fatigue scale; none in employment.	To explore contexts of experiences of physical activity perceived as beneficial or harmful for CFS patients.	Norwegian study Moderate concerns about applicability due to setting (several references to farming suggests rural area) and aim of the study to elicit responses regarding physical activity beyond the clinic's specific program. PEM reanalysis: serious concerns over applicability due to existing reasons and it being unclear if participants had PEM.
Picariello 2017[71]	Semi-structured interviews with thematic analysis	Face-to-face CBT	Patients who had finished CBT or were in the follow up stage, recruited consecutively. Participants were excluded if they did not have a diagnosis of CFS. N=13; male/female 2/11; age range 18-24 (n=1), 25-34 (n=7), 35-44 (n=2), 45-54 (n=2), 55-64 (n=1).	To explore the experiences of patients with CFS who undertook CBT at a specialist service for CFS.	UK study PEM reanalysis: moderate concerns over applicability due to participants meeting criteria where PEM was not compulsory.
Pinxsterhuis 2015[73]	Focus group semi-structured interviews with thematic analysis	Patient education programme	Participants in the CFS patient education programme. Participants were excluded if their diagnosis did not comply with the Canadian diagnostic criteria (Carruthers 2003) and/or CDC 1994 criteria.	To elicit participants' experiences with a multidisciplinary patient education programme and their views regarding the usefulness	Norwegian study PEM reanalysis: moderate concerns over applicability with PEM being a

Study	Design	Intervention	Population	Research aim	Comments
			N=10; male/female 2/8; mean age (range) 43.7 (32-57) years; illness duration mean (range) 6.6 (2.5-13.5) years; one participant was working.	of the programme immediately and nine months following participation in the programme.	compulsory feature in only one set of criteria used to exclude participants (Canadian) and not the other (CDC 1994).
Reme 2013[76]	Semi-structured interviews with thematic analysis	The Lightning Process	Young people who were English speaking, aged 11-25 years and who had undergone the Lightning Process, recruited through an advertisement on the Association of Young People with ME website. Three young people were 18 years of age or under and thus supplementary interviews were conducted with their mothers. N=9; male/female 1/8; age (range) 14-26 years; illness duration (range) 2-12 years; 8/9 met Sharpe 1991 criteria for CFS prior to undergoing the Lightning Process, 7 of these no longer met the criteria at the time of the study.	To explore the experiences of young people with 'CFS/ME' after they had undergone the Lightning Process. Specifically, to increase understanding of beneficial and possible adverse effects of the Lightning Process, as well as the participants' attributions of the particular aspects of the programme that caused the effects.	UK study PEM reanalysis: moderate concerns about applicability due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on any additional criteria met.
Taylor 2017[90]	Semi-structured interviews with thematic analysis	General	Young people aged between 12 and 18 years with a primary diagnosis of 'CFS/ME' and co-morbid low mood (defined as a depression subscale score of >9 on the Hospital Anxiety and Depression Scale), recruited from a specialist paediatric 'CFS/ME' service provided by a multidisciplinary team of doctors, occupational therapists, physiotherapists and psychologists. Those who were housebound (unable to attend outpatient appointments) were excluded. N=9; male/female 1/8; age median (IQR) 14 (14-15) years; illness duration median (IQR)	To explore the experiences of young people with 'CFS/ME' and depression in order to understand their views on why low mood developed, the impact of having low mood and what they had found to be helpful and unhelpful in treatment.	UK study Moderate concerns about applicability due to study population (ME/CFS with comorbid depression). PEM reanalysis: serious concerns about applicability due to existing reasons and it being unclear if participants had PEM.

Study	Design	Intervention	Population	Research aim	Comments
			12 (8.5 to 37.5) months; 78% (7/9) had <40% school attendance, i.e. 2 days or fewer per week.		
Ward 2008[101]	Unstructured interviews with thematic analysis	Any type of counselling intervention delivered by a counsellor, therapist, or clinical psychologist	People who had received a formal diagnosis of ME from a medical practitioner and who had experienced any type of counselling intervention recruited through advertisements in the newsletters of the ME Association and the Action for ME user group. N=25; male/female 4/21; age mean (SD, range) 44 (11, 23-65) years; illness duration (range) 2-19 years.	To explore users' views and perceptions of their experiences of counselling, in particular what they found useful and what they found unhelpful or negative.	UK study Minor concerns regarding applicability due to unclear interventions PEM reanalysis: serious concerns about applicability due to existing reasons and it being unclear if participants had PEM.

Table 68: Summary of studies included in the review (identified through the call for evidence)

Study	Design	Intervention	Population	Research aim	Comments
Anderson [3]	Semi structured interviews with thematic analysis	Online CBT (FITNET-NHS)	Young people aged 11-17 with a diagnosis of 'CFS/ME' (with no access to local specialist paediatric 'CFS/ME' treatment) together with their parents/carers, recruited to a pilot trial (FITNET). Participants were purposively selected for maximum variation (intervention, age and gender). N=20 families (12 families in the FITNET-NHS-NHS arm and 8 in the Activity Management arm). This included 18 children, (male/female 6/12; age range 12-17 years) and 22 parents (19 mothers, 3 fathers, 2 interviews included both parents).	To assess the feasibility of recruiting families to a trial of a UK-adapted version of the Dutch CBT program: Fatigue In Teenagers on the interNET in the NHS (FITNET-NHS), compared to a version of usual care – Activity Management (delivered via Skype), and to assess the acceptability of the two interventions.	UK study PEM reanalysis: moderate concerns over applicability due to participants in the original pilot trial (FITNET) for which they had been recruited meeting criteria where PEM was not a compulsory feature for diagnosis (CDC Fukuda 1994 criteria as specified in the quantitative evidence)

Study	Design	Intervention	Population	Research aim	Comments
Brigden[9] (Beasant[5])	Semi-structured interviews with thematic analysis	Graded exercise therapy Activity management	Children and young people (age 8-17 years) with a diagnosis of mild to moderate 'CFS/ME' participating in an RCT (MAGENTA) and their parents. Participants recruited from three Specialist Paediatric 'CFS/ME' services. Those who were severely affected (unable to do activity for themselves, only able to carry out minimal daily tasks, or had severe cognitive difficulties and depend on wheelchair for mobility), referred to CBT at their first assessment or unable to attend clinic sessions were excluded. Maximum variation sampling used to ensure a variation in characteristics and recruitment from both intervention groups. N=27 families from one centre (n=12 randomised to GET; male/female 5/7; mean age (range) 14.7 (10-17) years)	To ascertain the feasibility and acceptability of conducting an RCT to investigate the effectiveness and cost effectiveness of GET compared to activity management for paediatric 'CFS/ME'.	UK study
Bristol CFS/ME service[10]	Qualitative service evaluation form and thematic analysis	'CFS/ME' seminars	People with newly diagnosed 'CFS/ME' attending 'CFS/ME' seminars Number of participants and characteristics not reported.	Not explicitly stated.	UK study Moderate concerns regarding applicability due to lack of information on participant characteristics including whether participants experienced PEM.
Bristol CFS/ME service[59]	Survey including closed and open ended questions and thematic analysis.	General	Patients of the Bristol 'CFS/ME' Service and parents of young people attending the Paediatric 'CFS/ME' Service at Bath.	To gather feedback from patients who were either current or recent patients of NHS 'CFS/ME' Services.	UK study Survey asked about experiences of NHS 'CFS/ME' services; findings

Study	Design	Intervention	Population	Research aim	Comments
					related to specific interventions were extracted. Moderate concerns regarding applicability due to lack of information on participant characteristics (including PEM); lack of information on which interventions were received.
De Carvalho Leite 2011[25]	Semi-structured interviews and thematic analysis	General	Adults (18 years and older) with 'CFS/ME' in England. Researchers contacted relevant support groups, community organisations and centres, practitioners, and media to publicise the 'CFS/ME' Observatory and the study across England. Six of the 35 participants were purposively selected (to include a diverse range of illness severity, duration and social variation) for both an initial focus group discussion as well as later one-to-one interviews with a researcher. The other 29 were invited to take part in one-to one interviews only. N=35; male/female 8/27; age 18-25 years (n=4), 26-40 years (n=8), 41-55 years (n=15), 56+ years (n=8)	To produce and to facilitate epidemiological and social research, in response to the needs of people with 'CFS/ME' in England so as to fill a major gap in the evidence of the occurrence and the impact of this disease.	UK study Moderate concerns regarding applicability due to different research aim and limited detail on interventions received. PEM reanalysis: serious concerns regarding applicability due to existing reasons and it being unclear if participants had PEM.
Forward ME survey 2019[68]	Survey including closed ended and open-ended questions	CBT GET CBT + GET combined	Inclusion criteria for participation in the survey was: 1. To have been offered or received CBT and/or GET since 2007 – even if the course was not completed AND	To describe the experiences of adults and children with ME/CFS who have participated in CBT and	UK study Open ended questions were analysed through

Study	Design	Intervention	Population	Research aim	Comments
			2. To have a diagnosis of ME, ME/CFS, CFS or PVFS confirmed by a clinician AND 3. To have received treatment within the UK N=2274; male/female 384/1829; age range 12 years and under (n=17) to 71+ years (n=25); 87% responses were self-reported, 8.1% of responses were completed on behalf of a child and 4% were completed by a carer on behalf of an individual with ME; 62.4% rated their condition as moderate before treatment; 98.5% experienced post exertional malaise (self-reported).	GET interventions. Describe the experiences within subgroups of modifiable and non-modifiable variables.	NVivo 12 Plus qualitative data analysis Software (QSR International Pty Ltd. Version 12). The software automatically coded themes by sentence, indexed words using a word frequency count and coded responses into sentiment, highlighting negative or positive responses. PEM reanalysis: moderate concerns regarding applicability as the experience of PEM was self-reported and diagnosis was confirmed by a clinician, but it was not specified if or which diagnostic criteria were used.
Gladwell 2014[34]	Thematic analysis of qualitative data submitted as "free text" in an online survey	Graded exercise therapy (GET), the functionally oriented Graded Activity Therapy (GAT), or Exercise on	Respondents to 2010 survey of rehabilitation therapies carried out by Action for ME who started rehabilitation during or after 2008 and had tried one of three rehabilitation therapies: GET, the functionally oriented Graded Activity Therapy (GAT), or Exercise on Prescription (EOP).	To explore the experiences of people with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis ('CFS/ME') of rehabilitation therapies so as to build an understanding of reasons for the	UK study PEM reanalysis: moderate concerns regarding applicability due to participants being a self-selected sample for which PEM was unclear.

Study	Design	Intervention	Population	Research aim	Comments
		Prescription (EOP)	N=76; male/female 14/62; age group <30 years n=19, 30<40 years n=20, 40<50 years n=23, 50+ years n=13; decade of onset 1980s n=7, 1990s n=14, 2000+ n=55	discrepancy between the notably mixed experiences regarding effectiveness reported in patient surveys and the RCT evidence about the efficacy of Graded Exercise Therapy (GET). To review patient experiences of two related rehabilitation approaches, Exercise on Prescription (EoP) and Graded Activity Therapy (GAT).	
McManimen 2019[56]	Online survey including closed and open-ended questions and thematic analysis.	General	Individuals at least 18 years of age and able to read and write in English self-reporting a diagnosis of ME or CFS, recruited through a variety of methods including postings on social media websites, patient advocacy newsletters, and internet forums, as part of a larger study. N=464	To analyse the ME and CFS patient perspective and further elucidate this underserved population and any issues in the doctor-patient relationship that may be leading patients to perceive HCPs as dismissive.	USA study Moderate concerns regarding applicability due to different research aim (analysis based only on those who had experienced a dismissive attitude from a health care professional) and limited detail on interventions received. PEM reanalysis: serious concerns regarding applicability due to existing reasons and it being unclear if participants had PEM.

Study	Design	Intervention	Population	Research aim	Comments
ME Action 2019[50]	Survey including closed and open-ended questions with thematic analysis	General	N=1,886 who completed valid questionnaires and had a diagnosis of 'CFS/ME', ME/CFS, ME or CFS; 99.3% responded that they experienced post-exertional malaise (self-reported)	To supply NICE with up to date patient data.	UK study Survey asked about experience of 68 ME services; findings related to specific interventions were extracted. Moderate concerns regarding applicability due to lack of information on participant characteristics and PEM being self-reported).
Physios for ME[70]	Survey with open ended question	Physiotherapy	N=441 people with ME (53% had experienced physiotherapy)	Not reported	UK study Moderate concerns regarding applicability due to lack of information on participant characteristics or interventions. PEM reanalysis: serious concerns regarding applicability due to existing reasons (lack of information on participant characteristics, including PEM, and lack of

Study	Design	Intervention	Population	Research aim	Comments
					information on the interventions received).
Snounou 2019[85]	Mixed methods, focus group interviews and feedback questionnaires with thematic analysis	Eight-week group condition management programme	People who had taken part in the eight-week programme. To be eligible for the group programme, patients must have an established diagnosis of ME/CFS and be 18 years or older. The programme was only available to those with mild to moderate symptom severity. One participant had been unable to attend the group programme but received one-on-one sessions on the group content following the programme. N=16; male/female 3/13; age range 25-70 years; illness duration 4 participants with a diagnosis for 6 months - 1 year, 5 participants with a diagnosis for 1-5 years, 7 participants with a diagnosis for 5 years or more; 2 participants were working part time.	To evaluate, through focus groups and feedback questionnaires, the experience of patients who participated in an eight-week group condition management programme for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (ME/CFS)	Northern Ireland study PEM reanalysis: moderate concerns regarding applicability due to it being unclear if participants had PEM.
Yorkshire Fatigue Clinic[69]	Routinely administered online patient surveys including closed and open-ended questions with thematic analysis	Tailored rehabilitation programme	N=252	To learn from the experiences of patients as part of improving quality of care in an area of healthcare that remains controversial and unpopular with many suffers.	UK study Moderate concerns regarding applicability due to lack of information on participant characteristics including whether they had PEM (after PEM reanalysis).

See appendices for full evidence tables.

2.1.5 Qualitative evidence synthesis

2.1.5.1 Adults (severity mixed or unclear)

Table 69: Review findings: Cognitive behavioural therapy

Main findings	Statement of finding
Hopes and expectations[71]	Feelings of confusion and apprehension at the beginning of therapy were replaced by feeling at ease. Some felt that the treatment exceeded expectations.
Validation[71]	Treatment was perceived as a source of validation. CBT helped people to feel understood and to reaffirm that their suffering is real and recognised.
CBT as support[71]	The simple act of talking to someone was of benefit and people were comforted by the knowledge that the therapist was available if they needed help as a form of safeguard.
Relationship with the therapist[71]	People valued building a relationship with the therapist and reported a preference for face-to-face consultations, which were found by some to be more personal and enabling.
Personalised care[71]	People felt that treatment was shaped by both the client and the therapist, which made them feel in control and able to contribute.
Motivation and engagement[71]	People recognised that they must be ready to invest effort and motivation must come from within. However, this might depend on illness severity and personal circumstances at the time.
Self-monitoring/ management support[59, 71]	Improvement was closely linked to a mastery of self-monitoring. People valued the support to learn skills and strategies to self-manage, specifically through CBT and mindfulness meditation approaches.
Behavioural aspects[71]	Behavioural tasks such as activity or sleep monitoring were found to be helpful in facilitating the development of self-awareness.
Cognitive aspects[71]	Feedback on the cognitive aspects was mixed, with some perceiving it as crucial and others finding it less useful, especially for physical symptoms.
Negative perceptions[101]	Some perceived CBT as controlling, patronising and a form of brainwashing.
Effect on symptoms[50, 68, 71]	Response was mixed, with some reporting a gradual improvement which did not reach a pre-morbid level of functioning, some reporting no change and some reporting a worsening of symptoms. There were criticisms of the therapy being used as a 'treatment' for ME.
Ongoing support[71]	Many felt they would have liked the support of additional sessions; many feared a relapse and did not know how they would cope without CBT.

Table 70: Review findings: Other psychological therapies (counselling)

Main findings	Statement of finding
Activity related counselling interventions[101]	Pacing was the most valued aspect, although in the early stages, people often got this wrong, resulting in periods of crushing fatigue and pain. There was often a delay before the full impact of activity was

Main findings	Statement of finding
	felt and for these people, exercise regimes and sometimes activity programmes were viewed negatively. People often felt pushed to overdo it, leading to significant relapse.
Stress-management counselling interventions[101]	Relaxation and meditation techniques were viewed positively, with people talking of reduced stress levels in terms of the impact of their condition and their life activities.
Thought management counselling interventions[101]	Responses to thought management strategies were mixed. Some found suggestions of negative thoughts being counterproductive to be patronising and negative; some found such notions simplistic; some found the interventions useful, for example in helping them to counter unrealistic or catastrophizing reactions.
Examining the influence of the past counselling interventions[101]	Very few people experienced this approach. Those who had felt very negatively about it because they thought the suggestion was that the cause of their ME might be rooted in the past and they firmly rejected any psychological cause for their condition.
Relationship with the therapist[101]	Positive reflections involved counsellor listening, understanding and offering appropriate challenge, whereas negative reactions to counsellors involved poor communication and non-empathic responding.
Physical impact[101]	Several people mentioned the physical impact of counselling on someone with severe ME, describing the difficulty of making their way to and from the session each week and the strain of keeping up a session of 50 minutes.

Table 71: Review findings: Graded exercise therapy/exercise interventions

Main findings	Statement of finding
Baseline activity levels and false starts[19, 34]	Most people found stabilising their routine, choosing physical activity and setting their baseline level to be straightforward, but baseline levels were not experienced as sustainable. Some experienced 'false starts' as they commenced the programme.
The indeterminate phase [11, 19]	Most people noticed no immediate difference in symptoms, or an exacerbation during the initial phase which resulted in them not knowing if the programme was helping or hindering their condition and during this 'indeterminate phase', it was found to be difficult to maintain motivation.
Too difficult[11, 19, 34]	Most found following the programme to be 'hard work'. The level of exercise was selected by the therapist and experienced by patients as too difficult.
'Push-crash' and worsening of symptoms[11, 19, 34, 49, 50, 68]	People experienced a lack of control over their bodies after exertion subsequent to non-customised activity. For some, debilitating exacerbations of symptoms were a reason for discontinuation. For others, trying to persist with rehabilitation led to a worsening of their symptoms in the longer term.
Competing commitments[19]	People needed enough 'capacity' in their lives to experience an exacerbation of symptoms and for this not to interfere with essential life activities. Higher functioning participants had more to do in their lives and reported more challenges in fitting the programme in to busier lifestyles.
Comorbid conditions[19]	People who reported their condition to be 'a little worse' following treatment reported more comorbid conditions and greater interferences from these conditions when following the programme.
Therapist approach[11, 19, 34, 70]	Approaches and attitudes taken by physiotherapists that were enthusiastic, gentle, understanding and patient centred generally facilitated a positive experience and engagement with them and the

Main findings	Statement of finding
	programme. Conversely miscommunication and not having their opinions taken into account left people feeling unsupported.
Conflict in beliefs[34]	There were therapist-patient differences in beliefs about the nature of their condition and the role of rehabilitation with consequences for the appropriateness of treatment and expertise of therapists needed to provide this.
Pressure to comply with treatment[34, 56]	People felt unreasonably pressured to comply with the rehabilitation therapy, especially when asked to ignore symptoms and continue trying to do more activity than they felt was sensible. People tried in vain to convey to therapists their sense that GET was not successful.
Feeling blamed[34]	Some experienced difficulties in their relationship with the therapist when they reported finding the therapy unhelpful, and the blame was shifted onto them.
Booklet information resource[19]	Some found the information booklet helpful, whereas others found it patronising, having the feel of marketing material or seemingly designed for participants with a higher level of functioning. The statement suggesting that there should be no ill effects from the programme was not accurate in their experience.
Personalised care[19, 34, 49, 70]	Being allowed to choose activities supported motivation and individually adapted advice was perceived to be helpful. People described experiences of becoming extremely ill after organised exercise, whereas similar exercise undertaken in a non-organised way was helpful, enjoyable and easier to adapt to individual energy level.
Overall approach[19]	Some felt that the remit of graded exercise self-help was too narrow and that it needed a broader approach which included CBT, or took into account mental activity.
Knowledge and understanding[19]	An understanding of the theory behind graded exercise helped understanding and engagement in the programme.
Support for self-management[34, 49]	Reviewing the daily workload with an occupational therapist, baseline setting and pacing was found to be helpful. Mapping exercises helped to prioritise tasks and reviewing activities, putting expectations aside and letting things happen diminished stress.
Routines and goals[34]	Some found treatments that encouraged development of routines and setting of goals to be helpful.
Additional benefits[11]	Social benefits of group exercise were found to be extremely important and encouraged attendance and compliance. Additional benefits were enjoyment, better ability to self-manage, increased fitness or use of muscles, enhanced breathing, regulation of body temperature, the engaging mixture and pacing of exercises and improved cognitive symptoms.
Practical limitations[11]	Aspects of an aquatic exercise intervention that some participants did not like included travelling, the time it took to get undressed and dressed, the energy needed to remove wet swimsuits and heart rate monitors, the discomfort of wearing a heart rate monitor and the possible need for more space in the pool.
Other sources of support[19]	People with who reported their condition to be 'much better' following treatment reported use of other complementary therapies such as counselling, CBT, self-help or peer support.

Table 72: Review findings: Education/information interventions

Main findings	Statement of finding
Validation[4, 10]	The provision of reliable evidence-based information meant that their GP was validating people's 'CFS/ME', which enabled them to self-manage their condition. People appreciated meeting health care professionals with knowledge of CFS.

Main findings	Statement of finding
Knowledge and understanding[4, 10, 73]	Learning about the diagnosis, symptoms, possible causes and prognosis increased understanding and confidence. DVD case studies helped people to understand that others shared their experiences, and the format allowed those who found it difficult to read to access the information. As a result of this information some patients felt that they needed to visit their practice less frequently. It was considered helpful to learn that deterioration may occur even when doing everything 'right'.
Sources of information[4, 73]	An evidence-based source of information was welcomed due to issues with identifying reliable information on the internet. After an education programme, some participants felt more able to assess information about the illness and treatments more critically.
Acceptance[73]	Some people with ME/CFS realised that they had to focus on acceptance and coping with the illness rather than curing it. People experienced increased acceptance, although at times still felt that acceptance was equivalent to giving up hope of getting better.
Coping[10, 73]	People found it especially helpful to learn about pacing and energy conservation, relaxation exercises, how to deal with difficult feelings, economic and public support systems, nutrition and sleep management. They experienced better coping with their illness and increased feeling of control, but did not experience better health.
Activity management and diaries[10]	People valued the use of a diary, which gave people a visual representation of their daily activities, which led to more awareness of triggers for setbacks. Help with understanding and setting baselines was also identified as an important outcome.
Difficulties accessing and engaging in seminars[10]	Practical issues related to location, environment, timing and duration made accessibility and engagement difficult for some. Managing fatigue in order to attend the seminar was also an issue for some and a common difficulty experienced was 'CFS/ME' symptoms during the seminars.
Peer support[10, 73]	People found it helpful to meet others in that they no longer felt alone and were able to exchange coping experiences and beneficial coping strategies. The presence of a peer counsellor increased the feeling of safety and fellowship and was valued as an important role model.
Group participation[10]	Group participation was identified as an important part of the seminar delivery as it contributed to creating a collaborative and accepting atmosphere.
Problems with the group setting[10]	Issues raised included a lack of personal focus, difficulty in "opening up" in front of the group, feeling as if others were not as severely affected, information not being shared with the family, some attendees talking more than others and some negative comments made by other attendees.
Impact on friends, family and colleagues[4]	The resources had an impact on the friends, family and colleagues. In some cases, the provision of evidence-based information improved relationships and strengthened support networks.
Emotional impact[10]	There were challenges inherent in confronting the reality of 'CFS/ME' in the seminars; in particular information about prognosis was experienced as difficult.
Difficulty putting theory into practice[10]	Some thought that applying the strategies into practice would be difficult as it depends on work, lifestyle and the severity of their 'CFS/ME'.
Ongoing support[10, 73]	Several people wanted more guidance or follow-up to maintain the coping strategies after an education programme. Some mentioned that they were unsure about what happened next after the seminars.

Table 73: Review findings: Rehabilitation/condition management programmes

Main findings	Statement of finding
Accessibility[85]	Timing of the sessions in the afternoon and a venue which had a lift and high-backed chairs made the programme accessible.
Accessibility[69]	Travel required to access the clinic and carpark and waiting time were found to be less helpful/beneficial.
Validation[69]	Obtaining a diagnosis and validation of symptoms was a key process.
Lack of attendance pressure[85]	There had been no pressure when people missed a week; they felt welcome and appreciated how encouraged they felt to return to the programme.
Handouts[85]	Having handouts was helpful, especially if they were given out at the beginning of the session as it saved energy used to take notes.
Video conferencing[85]	It was suggested that incorporating video calls for example through Skype, Facetime or webcam would be useful for patients who were housebound at the time of the programme.
Duration[85]	There were mixed opinions on the duration of each session. Some felt that the sessions were too long and that 1.5 hours would be a more manageable duration than 2 hours.
Self-management[69, 85]	It was beneficial to learn about the use of diaries, boom and bust patterns, knowing limits, prioritising, planning ahead, time management and pacing, how to rest properly, diet, learning 'not to be so hard on yourself' and the practicalities and the help available to return to work. Additional topics people would like to be covered included benefits, the impact of sunny weather, pain management and stress recognition and management.
Signposting[69]	Some referred to the signposting process as a beneficial aspect.
Science behind ME/CFS[69, 85]	Some people appreciated learning the science behind ME/CFS, although some requested less medical content.
Relationships[85]	Some emphasised the value of discussing the impact of ME on relationships with people who understand.
Exercise/physical activity[85]	Views on physical activity advice were mixed.
Group setting[69, 85]	People placed great value on meeting other patients and hearing others' stories, which helped create a support network. Those who had one-on-one sessions in addition to the group sessions also deemed this as helpful.
Additional and ongoing support[85]	People appreciated having follow-up at three and six months. Several would have liked one-off crisis-type access for during a deterioration or relapse and suggested that some people would require longer-term support.
Staffing[69]	People found staff support, knowledge and individual approaches to be helpful/beneficial. People wanted nutritionist support and counselling services to be provided.

Table 74: Review findings: Complementary and alternative therapies

Main findings	Statement of finding
Range of complementary and alternative therapies[7, 25]	People desperate for relief of symptoms tried a wide range of different alternative therapies.
Holistic approach[7]	People with ME/CFS were attracted to alternative therapies by a holistic approach.
Positive therapist approach[7]	Therapists' positive approaches gave people hope that it was possible to overcome the illness.

Main findings	Statement of finding
Effectiveness[7, 25]	Evaluations of the effectiveness of alternative therapies were mixed. Some experienced temporary effectiveness which reinforced their beliefs in these therapies.
Follow up[7]	Several people with ME/CFS were impressed that unlike their regular doctors, alternative therapists called periodically to find out how they were managing.

Table 75: Review findings: Pharmacological interventions

Main findings	Statement of finding
Antidepressants[50]	Antidepressants were prescribed for ME symptoms by health care professionals, and people experienced negative side effects.

2.1.5.2 Children/young people (severity mixed or unclear)

Table 76: Review findings: Cognitive behavioural therapy

Main findings	Statement of finding
Relationship with the therapist[28]	The therapist's personality and interpersonal skills were important. Having somebody to talk to who was interested in and understood CFS was a key positive feature of therapy sessions.
Acceptability of FITNET-NHS platform/ e-consultations[3]	People liked that they could complete the platform in their own time and think about their answers. Some found it easier to talk about personal topics over email, whereas others found it difficult to portray things in writing and would have preferred some face to face contact.
Validation[28]	Recognition, validation and emotional support were almost always cited as important and benefits were appreciated regardless of whether other aspects of the therapy were deemed useful.
Behavioural aspects[28]	The behavioural aspects of the therapy were particularly valued and accepted by the young people, although many struggled putting them in to practice. Tasks were often initially very hard to achieve and parents found it challenging to watch their children push themselves.
Personalised care[3, 28]	Some parents felt the agenda during the sessions was too narrow and rigid and therefore unresponsive to families' idiosyncratic issues. Participants valued the individual tailored advice from a specialist 'CFS/ME' therapist.
Inclusion of the family[28]	Sessions functioned as support for parents and young people felt they needed their parent/s at the sessions for emotional support. Despite this, many felt that there were certain situations and issues where the young person should have been seen alone.
Psychological aspects[28]	Several disliked the 'psychological' or 'emotional' aspects, finding them irrelevant or inappropriate. Some felt pigeonholed and subjected to generalisations.
Effectiveness[28]	The therapy was useful to some extent, the family was thankful for the help, but improvements were modest. However, the therapy was a principle factor in regaining normality and viewed as a 'starting block' on a gradual journey to recovery.
Effectiveness[90]	Some young people with ME/CFS and depression found CBT helpful and the combination treatment of CBT and medication was also discussed.

Table 77: Review findings: The Lightning Process

Main findings	Statement of finding
Relationship with the therapist[76]	Therapists and staff were mostly described as positive and encouraging. There were different opinions about the therapists; some had only good experiences, while others found their therapist too controlling and not open for critical questions. Alternative viewpoints brought up by the young people were not well-received and a few experienced pressure to be happy all the time and not express any negative feelings. Those who did not recover felt that they were blamed for the lack of treatment success and consequently struggled with feelings of guilt and anger.
Dishonesty[76]	People criticised the impression that staff gave about the Lightning Process always involving a quick recovery and the dishonesty staff showed when they claimed the treatment had a 100% success rate.
Theory behind the Lightning Process[76]	The educational part of the treatment, including the theory behind the Lightning Process and practical examples of previous success stories, gave people a rationale they could believe in.
Confusing[76]	The educational part of the intervention was considered as complicated and difficult to understand, but necessary and helpful. Some found the teaching incomplete and not well-organised. Advice that participants could do anything they wanted conflicted with previous advice they had been given around activity pacing.
Peer support[76]	The support from others and the group setting that allowed people to learn from each other was highlighted as helpful aspects leading to engagement and treatment commitment.
Goal setting[76]	The focus on specific goals and identifying barriers from reaching them was considered a helpful part of treatment.
Practice and application[76]	The practical assignments were described as important for rapid recovery. People realised that it was their own choice that would really help them recover and the behavioural aspects of the treatment stood out as the most important factor for symptom alleviation and continuing recovery.
Intensity[76]	The length of the sessions was thought to be too long and intense, especially since many participants struggled with focus and concentration.
Follow up[76]	Some described the whole treatment as too short; with too little follow up afterwards.
Effectiveness[76]	Some experienced an instant healing; some experienced a gradual improvement that continued after treatment ended and some did not find the treatment helpful.
Secrecy[76]	The secrecy surrounding the Lightning Process was criticised and thought to result in unnecessary sceptical and prejudiced attitudes from people. Participants were specifically encouraged not to talk to anyone about it and they found this unhelpful and difficult.

Table 78: Review findings: The Lightning Process (mild/moderate severity)

Main findings	Statement of finding
Validation[6]	The service recognised and acknowledged the young person's condition, resulting in a sense of relief and reassurance that symptoms were now being understood and they would receive help.
Personalised care[6]	Families had access to an informative team of experts, for some a formal diagnosis, and for all a tailored, patient centred specialist medical intervention that had not been available earlier. This enabled positive change and steps towards a managed recovery.
Professional support[6]	Some found specialist medical care to be positive, as it enabled them to talk about their illness and gave guidance on how to manage their condition, which brought structure and a sense of normality back into their lives.

Main findings	Statement of finding
Challenges of a new routine[6]	Some people reported that, although specialist medical care resulted in better symptom management, accepting that for a time they must reduce activity levels and adopt a routine was challenging. Mothers also noted that specialist medical care strategies had an impact on the whole family and could be difficult to integrate with their lifestyle.
Dialogue between healthcare professionals and education providers[6]	The service opened channels of dialogue between health-care professionals and education providers.

Table 79: Review findings: Graded exercise therapy

Main findings	Statement of finding
Exercise enjoyable[9]([5])	Despite mixed preconceptions, most participants were positive about GET once they entered treatment and reported positive experience of the exercises.
Routine and structure[9]([5])	Many families explained that the program introduced routine, which they experienced as important.
Relationship with therapist[9]([5])	Many families valued the support they received from their clinician in terms of having someone listen and understand and feeling cared for.
Personalised care[9]([5])	Families praised the way the program was tailored so that the clinician identified the individual needs of the young person and collaboratively developed a tailored treatment plan, recognising the fluctuating nature of 'CFS/ME' and that physical capabilities change. Families also reported that they gained extra advice beyond the central focus on activity, such as sleep or diet, when these came up for participants.
Pacing benefits[9]([5])	Some commented that the treatment set helpful boundaries to avoid a pattern of overexertion and that clinicians were flexible in reducing the activity if the increase had been too rapid/ too much.
Pacing challenges[9]([5])	Some found limiting activity was challenging, with evidence that the young person resisted this advice, wanting to do more physical exercise. Concerns about activity reduction included social effects and difficulties with limiting walking in school.
Setbacks[9]([5])	Families described that the young person had a setback or "crash" during the course of treatment, as a result of exceeding the recommended limits of physical activity. Travel to the hospital site for appointments contributed to setbacks.
FITBITS and physical monitoring[9]([5])	Participants commented positively on the use of wearables to accurately detect physical activity, as this demonstrated when they were doing too much and provided other useful functionality such as sleep or steps monitoring in addition to heart rate monitoring. Some comments indicated that the measurements were not always accurate.
Positive outcomes[9]([5])	There was overall recognition that the young people had benefitted from GET, including reductions in fatigue and tiredness, improved sleep, ability to concentrate, functioning and mood.
Uncertain/lack of difference from treatment[9]([5])	Some families did not notice a difference with treatment, either reporting uncertainty, or lack of impact, often related to school and cognitive activities.

Table 80: Review findings: Complementary and alternative therapies

Main findings	Statement of finding
Alternative therapies[36]	Some families sought treatments such as acupuncture, dietician input, sickness bands and the emotional freedom technique, while others spoke to their 'CFS/ME' clinician for advice. External support varied greatly in perceived accessibility and helpfulness.

Table 81: Pharmacological interventions

Main findings	Statement of finding
Sickness/stomach acid relief medication[36]	Some took prescribed sickness or stomach acid relief medication which they found helpful. However, it was not common to have been offered medication to relieve their symptoms which frustrated some people.
Attitude toward medication[90]	Young people generally did not mind taking medication providing they found it helpful.

2.1.5.3 Narrative summary of review findings for adults (severity mixed or unclear) who have had cognitive behavioural therapy

Review finding: Hopes and expectations

As the process of treatment continued, feelings of confusion and apprehension at the beginning of therapy were replaced by feeling as ease. Most people reported high levels of satisfaction with treatment and in some cases felt that the treatment exceeded expectations.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy. **Review finding: Validation**

Treatment was perceived as a source of validation. CBT helped people to feel understood and to reaffirm that their suffering is real and recognised. CBT provided a non-judgemental environment for people to express themselves.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our

confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: CBT as support

People were comforted by the knowledge that the therapist was available to them if they needed help. The simple act of talking to someone was of benefit. To some, the support of CBT acted as a form of safeguard even when sessions were spread out over time.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Relationship with the therapist

People valued building a relationship with the therapist and reported a preference for face-to-face consultations. Some found face-to-face consultations to be more personal and enabled them to be more forthcoming.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Personalised care

People felt that the treatment was shaped by both the client and the therapist, making them feel in control and able to contribute and guide the content and structure of the sessions. People appreciated the fact that the therapy was adaptable to their needs.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Motivation and engagement

People recognised that in order to benefit from CBT, they must be ready to invest effort in it and motivation must come from within. However, the ability to invest effort might depend on illness severity and personal circumstances at the time of therapy. Some people felt that starting CBT was more suitable at a time when symptoms were less severe. Self-monitoring tasks were found to be useful, but at the same time some tasks were found to be tedious or difficult to fit in to their routine.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Self-monitoring/management support

Improvement was closely linked to a mastery of the self-monitoring process and an awareness of behaviours or cognitions that may be contributing. Learning to plan and manage activity according to energy levels allowed people to sustain improvements following CBT. Skills to manage and plan ahead and not to succumb when symptoms arise helped to counterbalance any apprehension of relapse. Through CBT people found it easier to be compassionate to themselves, avoiding 'boom and bust' patterns of behaviour. Some reported an unwanted consequence of a more consistent behavioural routine was discontinuation of loved hobbies and activities, although they were able to see the benefits.

Those who had attended specialist services valued the support to learn skills and strategies to self-manage the condition and specifically mentioned CBT and Mindfulness meditation as being helpful approaches.

Explanation of quality assessment: moderate methodological limitations in both contributing studies (in one study, only participants who had completed treatment were recruited, there was an unclear relationship between the researcher and participants and unclear consideration of ethical issues; in the other study, there was an unclear relationship between the researcher and participants and unclear methods of data analysis); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; very minor concerns about the relevance of the finding with a lack of information reported regarding participant and intervention characteristics in one study, but no concerns about relevance in the other study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of findings with elaboration and examples). There was a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in both contributing studies (in one study, only participants who had completed treatment were recruited, there was an unclear relationship between the researcher and participants and unclear consideration of ethical issues; in the other study, there was an unclear relationship between the researcher and participants and unclear methods of data analysis); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns over relevance with moderate concerns in one study with participants fulfilling diagnostic criteria where PEM was not compulsory and serious concerns in the other study due to a lack of information on participant characteristics including PEM and a lack of information on which interventions were received; no concerns about adequacy as the evidence is sufficiently deep (clear statement of findings with elaboration and examples). There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and relevance. **Review finding**: **Behavioural aspects**

Participants reported finding behavioural tasks such as activity or sleep monitoring to be helpful in facilitating the development of self-awareness.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very

minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Cognitive aspects

Feedback on the cognitive aspects was mixed, with some participants perceiving it as crucial and others finding it less useful, especially for physical symptoms.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Negative perceptions

The suggestion that their condition might not be physical, that they have control over it, or that its roots lie in the past could be found to be very challenging and certain types of counselling were perceived as controlling, patronising and a form of brainwashing. These perceptions generally related to what participants understood as CBT.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities may mean that participants were more likely to be those who did not recover; unclear interventions and insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns regarding relevance due to unclear interventions (finding relates to interventions which participants perceived to be CBT, but no details); minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with

elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities may mean that participants were more likely to be those who did not recover; unclear interventions and insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns regarding relevance due to unclear interventions (finding relates to interventions which participants perceived to be CBT, but no details) and diagnosis made by a medical practitioner, but with no information on PEM; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy. **Review finding: Effect on symptoms**

Change was gradual and people often reported not being aware of the improvement until they reflected on where they started. For some, the improvement was more apparent to those around them. Those who felt they benefitted from CBT often reported improvements in wellbeing, although not to a pre-morbid level of functioning. A minority felt that their improvement was only slight and another felt they had not improved at all.

When asked about reasons for stopping CBT, people mentioned they were too ill to continue, including worsening of symptoms of post exertional malaise (PEM), stress and anxiety. In addition, many respondents quoted treatment being stopped by the practitioner due to detrimental effects or CBT being unnecessary for the individual. When asked about how symptoms worsened, common themes in responses included fatigue, cognitive issues, pain, and activity levels.

Criticisms of CBT related mainly to the therapy being used as a ‘treatment’ for ME rather than it having a negative impact on health.

Explanation of quality assessment: moderate methodological limitations in the majority of the contributing studies (mainly due to concerns regarding recruitment strategies; methods of data collection and analysis; and lack of consideration of ethical issues); moderate concerns about the coherence of the finding with one study reporting worsening of symptoms and the other two reflecting subtle or minimal differences; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and coherence.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the majority of the contributing studies (mainly due to concerns regarding recruitment strategies; methods of data collection and analysis; and lack of consideration of ethical issues); moderate concerns about the coherence of the finding with one study reporting worsening of symptoms and the other two reflecting subtle or minimal differences; moderate concerns over relevance with moderate concerns across contributing studies due to lack of details on diagnosis and PEM being self-reported in one study, with participants fulfilling diagnostic criteria where PEM was not compulsory in one study and diagnosis made by a clinician but the percentage of participants who had PEM being self-reported in the third contributing study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, coherence and relevance.**Review finding: Ongoing support**

People would have liked the support of additional sessions; many feared a relapse and did not know how they would cope without CBT.

Explanation of quality assessment: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (only participants who had completed treatment were recruited; unclear relationship between the researcher and participants; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance with participants in the contributing study fulfilling diagnostic criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

2.1.5.4 Narrative summary of review findings for adults (severity mixed or unclear) who have had other psychological therapies (counselling)

Review finding: Activity related counselling interventions

Activity management included devising routines, increasing the level of activities, keeping diaries, setting goals and pacing. Of these the most useful was found to be pacing – this was the most valued aspect of all counselling interventions. People described how in the early stages they often got this wrong, resulting in periods of crushing fatigue and pain. Exploring the relationship between activity and energy level was complicated by the fact that there was often a delay of sometimes several days before the full impact was felt. For these people, exercise regimes and sometimes activity programmes were viewed negatively. People reported being pushed to overdo it, leading to significant relapse.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance due to unclear interventions and it being unclear if participants had PEM in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Stress-management counselling interventions

Relaxation and meditation techniques were viewed positively, with people talking of reduced stress levels in terms of the impact of their condition and their life activities.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance due to unclear interventions and it being unclear if participants had PEM in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Thought management counselling interventions

Responses to thought management strategies were mixed, with some finding suggestions of negative thoughts being counterproductive to be patronising and negative. Some felt that their condition was being blamed on their negative outlook. Some participants found such notions too simplistic. Others found such interventions very useful, for example in helping them to counter very unrealistic or catastrophizing reactions.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance due to unclear interventions and it being unclear if participants had PEM in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Examining the influence of the past counselling interventions

Very few people had experienced this approach. Those who had felt very negatively about it because they thought the suggestion was that the cause of their ME might be rooted in the past and they firmly rejected any psychological cause for their condition.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance due to unclear interventions and it being unclear if participants had PEM in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Relationship with the therapist

Negative reactions to counsellors involved poor communication, counsellors not understanding the condition and non-empathic responding. Positive reflections involved counsellor listening, understanding and offering appropriate challenge. Perceived benefits of counselling included a good relationship with someone who understands and who is outside of the immediate situation.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance due to unclear interventions and it being unclear if participants had PEM in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Physical impact

Several people mentioned the physical impact of the counselling on someone with severe ME. They described the difficulty of making their way to and from the session each week and the strain of keeping up a session of 50 minutes.

Explanation of quality assessment: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be

those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate methodological limitations in the contributing study (recruitment through ME charities means participants may have been more likely to be those who did not recover; unclear interventions, based on participant recall; insufficient data presented to support all findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance due to unclear interventions and it being unclear if participants had PEM in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

2.1.5.5 Narrative summary of review findings for adults (severity mixed or unclear) who have had graded exercise therapy or other exercise interventions

Review finding: Baseline activity levels and false starts

Most found attempting to stabilise their routine, choosing their specific physical activity and setting their baseline level activity to be relatively straightforward and some found it helpful in setting realistic and manageable targets for activity. Some conveyed how this worked for developing a process of rehabilitation and others identified the new skills that they gained in identifying aspects of their activity. Several described the sense of specific control of activities that could then be gained.

Some respondents clearly did not experience even the baseline levels they had been set as sustainable. This linked with reports of problems following initial exercise testing. Some participants who's conditions were a little worse following treatment reported 'false starts' as they commenced their GES activity – one due to a physical reaction believed to be due to a pre-existing hip condition and was given medical advice to discontinue and the other due to major life events which left her too preoccupied to engage with GES.

Explanation of quality assessment: minor concerns about methodological limitations due to minor limitations in both in of the contributing studies (unclear consideration of ethical issues in both studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered); minor concerns about the coherence of the finding, with some description related to ease and benefits of setting baselines and some related to unsustainability and 'false starts'; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations and coherence.

Explanation of quality assessment after PEM reanalysis: minor concerns about methodological limitations due to minor limitations in both in of the contributing studies (unclear consideration of ethical issues in both studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered); minor concerns about the coherence of the finding, with some description related to ease and benefits of setting baselines and some related to unsustainability and 'false starts'; minor concerns about relevance with moderate concerns over one study due to participants being a self-selected sample and it was unclear if they experienced PEM and no concerns over the other contributing study; no concerns about

adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations, coherence and relevance being minor.

Review finding: The indeterminate phase

Some reported that they felt better immediately after exercise and this immediate positive feedback encouraged them to continue with the programme. However, during the first phase of the GES programme, most people noticed no immediate difference in symptoms, or an exacerbation. For those who did begin to feel better, improvement was reported as remarkably incremental. When people experienced a setback to their incremental progress, it could be experienced as particularly demoralising. Many had delayed gains and little or no short-term benefit, which resulted in them not knowing if GES was helping or hindering their condition. During this 'indeterminate phase', it was found to be difficult to maintain motivation, particularly when experiencing exacerbation of symptoms or when finding the programme hard work or boring. Those who avoided false starts were generally able to stick to their GES programmes through this phase and beyond.

This indeterminate phase was not experienced by those who participated in an aquatic exercise intervention. The emerging trend for these participants was that approximately three weeks after commencing the programme, the severity of post-exercise symptoms declined. Aquatic exercises were experienced to produce less fatigue than other types of exercise that participants had previously experienced, including Tai Chi, yoga, stretching, cycling and running.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations in the majority of the contributing studies, with nothing to lower our confidence; minor concerns regarding relevance due to one study only including female participants;; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but mainly based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor concerns regarding methodological limitations in the majority of the contributing studies, with nothing to lower our confidence; minor concerns regarding relevance with serious concerns in one study due to unclear PEM and the study only including female participants but no concerns in the other contributing study and the majority of the information supporting the theme coming from the study with no concerns; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but mainly based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding relevance and adequacy being minor.

Review finding: Too difficult

The majority of participants reported that following the GES programme was 'hard work'. A recurring theme across reports was the level of exercise being selected by the therapist and experienced as too difficult. However, a minority of people who participated in an aquatic exercise intervention commented that sessions could be longer or more frequent.

Explanation of quality assessment: minor concerns about methodological limitations due to minor limitations in all in of the contributing studies (unclear consideration of ethical issues in two studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered; unclear relationship between researcher and participants in one study); minor concerns about the coherence of the finding, with it being unclear whether 'hard work' reported in one study has the same meaning as 'too difficult' reported in the other and concerns regarding one study reporting participants wanted longer/more frequent sessions being explained by differences in the type

of exercise intervention; no or very minor concerns about the relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples). There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, coherence and adequacy.

Explanation of quality assessment after PEM reanalysis: minor concerns about methodological limitations due to minor limitations in all in of the contributing studies (unclear consideration of ethical issues in two studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered; unclear relationship between researcher and participants in one study); minor concerns about the coherence of the finding, with it being unclear whether 'hard work' reported in one study has the same meaning as 'too difficult' reported in the other and concerns regarding one study reporting participants wanted longer/more frequent sessions being explained by differences in the type of exercise intervention; moderate concerns about relevance with moderate concerns in one study with participants being a self-selected sample and it being unclear if they had PEM, serious concerns in one study due to it being unclear if participants had PEM and the study only including female participants and no concerns in the other contributing study; minor concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples) but is supported by three studies . There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, coherence and adequacy being minor and concerns about relevance being moderate.

Review finding: 'Push-crash' and worsening of symptoms

People described different ways of experiencing lack of control over their bodies after exertion subsequent to non-customised activity. Some related how they would struggle to get home after exercises and a feeling that something completely wrong had happened to their body. Some described a paralysed feeling subsequent to activity, others experienced extreme exhaustion, muscular jerks or clumsiness, loss of balance, visual impairments and loss of concentration and ability to communicate.

Several people experienced a decrease in physical ability and strength and a feeling of physical and mental paralysis if they were inactive over a period of time. During these setbacks, participants described experiences of dizziness and nausea when bending down and headaches, particularly when feeling tired or pressured.

Some people reported how worsening symptoms after each session put them off continuing with the therapy. In those whose condition was a little worse after treatment and who had had ME/CFS for longer, exacerbations of symptoms were reported as more debilitating and half of them reported discontinuing GES activities for this reason.

When asked about reasons for stopping GET, people mentioned an increase of symptoms, pain, discomfort, deterioration and relapse. When asked about how symptoms worsened, common themes in responses included pain, fatigue, muscular symptoms, cognitive issues, malaise, brain fog, and mental well-being. When asked about new symptoms, common themes in responses included pain, sensitivity, muscular symptoms, joints, and brain. In addition, the word frequency count highlighted ideas related to disease/symptom severity and ability to walk.

For some, these effects of worsening their symptoms meant they were prevented from doing anything for a long time. For others, the worsening of symptoms meant specifically increased pain which made continuing therapy too difficult. Several reported that their trying to persist with rehabilitation led to a worsening of their symptoms in the longer term, perhaps a year or more.

In those who had not attended a specialist ME clinic, key themes were exercise (graded exercise therapy GET, increasing activity levels) being a negative experience, experience of deterioration or a desire that they had not followed this advice from healthcare professionals.

Those who had participated in an aquatic exercise intervention reported that water exercises did not exacerbate symptoms, such as breathing difficulties and joint pain. Many participants reported that their initial anxiety and fear of exercising had dissipated when they realised their symptoms were not exacerbated, although of the few sessions missed, one stated that a fibromyalgia symptom flare had stopped her attendance for one day, while another responded that she had been ill and symptomatic.

Explanation of quality assessment: moderate concerns about methodological limitations due to moderate concerns in the majority of the contributing studies (mainly due to recruitment through ME/CFS charities, with potential implications regarding the likelihood of participants being those who had not improved/recovered; and issues regarding data collection and analysis); no or very minor concerns about the coherence of the finding with the majority of studies reporting similar findings and concerns about different findings from one study being explained by differences in the type of exercise intervention; very minor concerns regarding relevance due one study having a different aim to the review question, a lack of information on participant characteristics reported in one study and one study being based on females only, but the majority of the evidence coming from studies with no concerns about relevance; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations and relevance being moderate and very minor.

Explanation of quality assessment after PEM reanalysis: moderate concerns about methodological limitations due to moderate concerns in the majority of the contributing studies (mainly due to recruitment through ME/CFS charities, with potential implications regarding the likelihood of participants being those who had not improved/recovered; and issues regarding data collection and analysis); no or very minor concerns about the coherence of the finding with the majority of studies reporting similar findings and concerns about different findings from one study being explained by differences in the type of exercise intervention; moderate concerns about relevance with serious concerns in two studies due to one study including only female participants and it being unclear if they had PEM and one study including participants with unclear PEM and conducted in a rural area raising concerns over the applicability of the setting, but moderate concerns in three studies due to participants being a self-selected sample and it being unclear if they had PEM in one study (Gladwell 2014), due to it being unclear if participants had PEM in one study, due to PEM being self-reported in one study and no concerns in one contributing study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to moderate concerns regarding methodological limitations and relevance.

Review finding: Competing commitments

Participants described needing enough ‘capacity’ in their lives to experience an exacerbation of symptoms and for this not to interfere with essential life activities. GES worked best for people who had fewer commitments that interfered with GES, such as work, looking after children, housework, lifestyle changes, etc. If a supportive partner or workplace could relieve them of other commitments, they seemed better placed to benefit from GES. For some who were more physically disabled, having lower levels of functioning could create time and space to do GES as they only needed to find a small amount of time each day and they were sometimes in a situation where they had few other commitments due to lower functioning and so could focus on GES more fully. Higher functioning people had more to do in their lives and reported more challenges in fitting GES in to busier lifestyles.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations in the contributing study, coherence of the finding, or relevance with nothing to lower our confidence. Minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Comorbid conditions

People whose conditions were a little worse following treatment reported more comorbid conditions such as joint hypermobility, fibromyalgia, irritable bowel syndrome, endometriosis, depression, arthritis, sciatica and asthma and greater interferences from these conditions when doing GES. One participant reported memory problems, which impacted her ability to undertake GES.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations in the contributing study, coherence of the finding, or relevance with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Therapist approach

Approaches and attitudes taken by physiotherapists that were enthusiastic, gentle, understanding and patient centred (rather than prescriptive) generally facilitated participants' engagement with them and the GES programme. Many comments on assessment and ongoing therapist support affirmed the importance of good communication and a supportive approach. Seeing a specialist could be an especially positive experience. For people who had a positive experience of physiotherapy, physiotherapist was praised for positive personal attributes. Participants also reported that having an understanding session instructor made them feel comfortable in an aquatic and group environment, contributing to their enjoyment of the exercise and good attendance. The quality of instruction and supervision (support, understanding, motivation), including the assisting students, was also mentioned.

Negative comments on the assessment, or ongoing therapist support, were often indicative of poor communication and feelings of being unsupported. Some emphasised how their opinions were not taken into account. Many described this as not being responded to in context. Some experienced miscommunication. For people who had a negative experience of physiotherapy, the physiotherapist had negative personal attributes, a lack of understanding and was unhelpful.

Explanation of quality assessment: minor concerns regarding methodological limitations due to minor or very minor limitations in three studies (unclear consideration of ethical issues in two studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered; unclear relationship between researcher and participants in one study) and serious limitations in one study which did not contribute a significant amount of data to the finding (no clear statement research aim; recruitment through a ME/CFS charity; unclear relationship between researcher and participants; unclear consideration of ethical issues; no information on method of qualitative data analysis; key themes only with no data presented to support findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor

concerns regarding relevance due a lack of information on participant characteristics and interventions from one study and all participants in one study being female; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to concerns regarding methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations due to minor or very minor limitations in three studies (unclear consideration of ethical issues in two studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered; unclear relationship between researcher and participants in one study) and serious limitations in one study which did not contribute a significant amount of data to the finding (no clear statement research aim; recruitment through a ME/CFS charity; unclear relationship between researcher and participants; unclear consideration of ethical issues; no information on method of qualitative data analysis; key themes only with no data presented to support findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns regarding relevance with serious concerns in two studies due to a lack of information on participant characteristics including PEM but also on the interventions received in one study and in one study due to unclear PEM and the study only including female participants but moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM and no concerns in the fourth contributing study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and relevance.

Review finding: Conflict in beliefs

A particular difficulty reported centred on therapist-patient differences in beliefs about the nature of their condition and the role of rehabilitation. Some of these conflicts were about a diagnosis of ME versus that of CFS or Post-Viral Fatigue Syndrome, with consequences for the appropriateness of treatment and expertise of therapists needed to provide this. Others focused on the likely harmful effects of exercise in ME compared with other fatigue-related illnesses. Some emphasised their view that ME was largely misunderstood by health professionals. One saw this as a lack of therapist interest in gaining the necessary accurate and specific knowledge about ME.

Explanation of quality assessment: minor methodological limitations in the contributing study (recruitment through a single ME/CFS charity meaning participants may be more likely to be those who have not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: minor methodological limitations in the contributing study (recruitment through a single ME/CFS charity meaning participants may be more likely to be those who have not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence; moderate concerns over relevance with participants being a self-selected sample and it being unclear if they had PEM; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Pressure to comply with treatment

Several reported feeling unreasonably pressured to comply with the rehabilitation therapy. Such pressure might include recording people's reluctance to comply as a formal refusal of treatment. A key pressure experienced as problematic was where people were asked to ignore their symptoms and to continue trying to do more activity than they felt was sensible. This was found especially problematic when people experienced setbacks in treatment but were given advice to ‘‘push through". Others felt that where they had built an understanding of how to successfully self-manage their exercise in relation to their condition, they were still pushed. Many of these reported trying in vain to convey to therapists their sense that GET was not successful.

Participant descriptions of their interactions with HCPs suggested that some professionals misinterpreted findings related to pacing and/or suggested harmful physical activity. Some people described how their HCP told them to ignore the symptoms they came to interpret as warning signs and push themselves beyond their comfort level. Others described attempting to tell their HCP that GET made them physically worse or that psychological treatment was not helping, but their concerns and viewpoints were often dismissed.

Explanation of quality assessment: minor concerns regarding methodological limitations due to minor concerns in one study (recruitment through a single ME/CFS charity meaning participants may be more likely to be those who have not improved/recovered; unclear consideration of ethical issues) and no concerns in the other contributing study; no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns about relevance due to one study with a different research aim and limited detail on interventions; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to concerns regarding methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations due to minor concerns in one study (recruitment through a single ME/CFS charity meaning participants may be more likely to be those who have not improved/recovered; unclear consideration of ethical issues) and no concerns in the other contributing study; no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns about relevance with moderate concerns in one study with participants being a self-selected sample and it being unclear if they had PEM and serious concerns in the other study due to limited detail on interventions and concerns over the relevance of the population with the analysis being based only on people who had experienced a dismissive attitude from a health care professional and whose diagnosis and experience of PEM were self-reported rather than confirmed by specific criteria or professional; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to minor concerns regarding methodological limitations and concerns over relevance being serious.

Review finding: Feeling blamed

Some found that difficulties arose or were exacerbated in their relationship with the therapist when they reported finding the therapy unhelpful, and the blame was shifted onto them. One person reported that the therapist could not comply, were their assumed lack of effort. Another respondent described then even feeling guilty for being physically ill.

Explanation of quality assessment: minor methodological limitations in the contributing study (recruitment through a single ME charity meaning participants may have been more likely to be those who had not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was

a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: minor methodological limitations in the contributing study (recruitment through a single ME/CFS charity meaning participants may be more likely to be those who have not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence; moderate concerns over relevance with participants being a self-selected sample and it being unclear if they had PEM; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Booklet information resource

Some participants found the GES booklet helpful, whereas two others found it patronising, having the feel of marketing material or seemingly designed for participants with a higher level of functioning. They noted in particular that the statement suggesting that there should be no ill effects from GES was not accurate in their experience.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations, coherence of the finding, or relevance with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding adequacy.

No change in quality assessment after PEM reanalysis

Review finding: Personalised care

People reported that being allowed to choose their own activities supported motivation. An essential difference was reported between leisure activities, which were perceived as enjoyable, and chores. People described experiences of becoming extremely ill after swimming, cycling, cross-country skiing, walking or doing strength exercises at fitness centres. Similar exercises undertaken outdoors in a non-organised way could be perceived as helpful and enjoyable and it was easier to adapt to the individual's energy level and hence did not make them ill. An individualised approach was highlighted, so that attention could be paid to individual problems such as balance, and so to enable working together to be experienced as having specific meaning for the persons themselves. For people who had a positive experience of physiotherapy, treatment was tailored to the individual.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to serious limitations in one study (no clear statement research aim; recruitment through a ME/CFS charity; unclear relationship between researcher and participants; unclear consideration of ethical issues; no information on method of qualitative data analysis; key themes only with no data presented to support findings), moderate limitations in one study (clinic staff assisted with recruitment and may have selected patients with particular views; unclear relationship between researcher and participants) and minor or very minor limitations in two studies (unclear consideration of ethical issues in both studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns regarding the relevance, with one study having a different aim to the review question and a lack of information on participant characteristics and interventions in another; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations due to serious limitations in one study (no clear statement research aim; recruitment through a ME/CFS charity; unclear relationship between researcher and participants; unclear consideration of ethical issues; no information on method of qualitative data analysis; key themes only with no data presented to support findings), moderate limitations in one study (clinic staff assisted with recruitment and may have selected patients with particular views; unclear relationship between researcher and participants) and minor or very minor limitations in two studies (unclear consideration of ethical issues in both studies; recruitment through a single ME charity in one study, meaning that participants may be more likely to have been those who had not improved/recovered); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns regarding relevance, with serious concerns in two studies due the inclusion of participants with unclear PEM and one study being conducted in a rural area raising concerns over the applicability of the setting and a lack of information on participant characteristics including PEM but also on the interventions received in one study but moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM and no concerns in the fourth contributing study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and relevance.

Review finding: Overall approach

Some felt that the remit of GES was too narrow and that it needed a broader approach which included CBT or took into account mental activity.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations, coherence of the finding or relevance with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding adequacy.

No change in quality assessment after PEM reanalysis

Review finding: Knowledge and understanding

An understanding of the theory behind GES helped participants understand and engage in GES. For many, understanding was established when GES was explained at the beginning of the trial or from previous experience of GET. Those who had previously unsuccessfully tried GET or attempted to increase activity levels without support found it useful to have an explanation for the possible failure of previous attempts and could motivate them to stick to their GES programme and do it ‘correctly’.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations of the contributing study, coherence of the finding, or relevance with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding adequacy.

No change in quality assessment after PEM reanalysis

Review finding: Support for self-management

Some found the baseline setting and pacing involved in rehabilitation to be helpful in setting realistic and manageable targets for activity. Others conveyed how this worked for developing a process of rehabilitation. Some identified the new skills that they gained in identifying aspects of their activity. Several participants described the sense of specific control of activities that could then be gained.

Reviewing the daily workload with an occupational therapist was helpful before people entered the rehabilitation program. Mapping exercises helped them to develop priorities of which tasks were important and which were not. Reviewing activities, putting expectations aside and letting things happen was reported to diminish stress. By keeping a diary of everyday life, people recognised emerging patterns. Concrete and individually adapted advice was perceived to be helpful, especially when it took into account the balance between rest and exercise. Several participants would have liked a personal coach or assistant.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to moderate concerns in one study (clinic staff assisted with recruitment and may have selected patients with particular views; unclear relationship between researcher and participants) and minor concerns in the other study (recruitment through a single ME charity meaning participants may have been more likely to be those who had not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns regarding relevance due to moderate concerns in one study (rural setting and the aim of one study being different to the review aim); no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis : moderate concerns regarding methodological limitations due to moderate concerns in one study (clinic staff assisted with recruitment and may have selected patients with particular views; unclear relationship between researcher and participants) and minor concerns in the other study (recruitment through a single ME charity meaning participants may have been more likely to be those who had not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; serious concerns over relevance due to serious concerns in one study contributing the majority of the information to this theme as it included participants with unclear PEM and was conducted in a rural area raising concerns over the applicability of the setting and moderate concerns in the other contributing study with participants being a self-selected sample and it was unclear if they had PEM ; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of very low confidence in this finding due to moderate methodological limitations and serious concerns over relevance.

Review finding: Routines and goals

Being encouraged to develop a routine was helpful for some. Several related comments suggested the desirability of having a goal to work towards. This was seen by some people as helping define the process as clearly directed at improvement. Other exercise-related benefits were seen as additional to any improvements in health which might include social. Others valued being outdoors in the fresh air and getting away. Being able to move about more was linked to increasing confidence.

Explanation of quality assessment: minor methodological limitations in the contributing study (recruitment through a single ME charity meaning participants may have been more likely to be those who had not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding or relevance, with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: minor methodological limitations in the contributing study (recruitment through a single ME/CFS charity meaning participants may be more likely to be those who have not improved/recovered; unclear consideration of ethical issues); no or very minor concerns about the coherence; moderate concerns over

relevance with participants being a self-selected sample and it being unclear if they had PEM; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Additional benefits

Participants in an aquatic exercise intervention reported that the social benefits of group exercise with people with the same medical condition were extremely important. It was emphasised that other participants had a commonality with their ME/CFS, in that they had similar ME/CFS stories and did not have to explain themselves to others. The social benefits of group exercise also encouraged attendance and compliance. Additional benefits of the intervention were enjoyment of the exercise, better ability to self-manage, increased fitness or use of muscles, enhanced breathing, better regulation of body temperature, the engaging mixture and pacing of exercises and improved cognitive symptoms such as ‘better concentration, a clearer head’.

Explanation of quality assessment: minor methodological limitations in the contributing study (unclear relationship between researchers and participants and lack of detail on method of data analysis); no or very minor concerns regarding coherence of the finding; moderate concerns regarding relevance as the contributing study is based only on female participants; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: minor methodological limitations in the contributing study (unclear relationship between researchers and participants and lack of detail on method of data analysis); no or very minor concerns regarding coherence of the finding; serious concerns regarding relevance due to unclear PEM and the contributing study only including female participants; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Practical limitations

Several participants commented that driving was extremely tiring physically and mentally. Another participant was unable to drive and had to rely on community transport which was expensive and often difficult to arrange. There were other aspects of the intervention that some participants did not like including the time it took to get undressed and dressed, the energy needed to remove wet swimsuits and heart rate monitors, the discomfort of wearing a heart rate monitor (one participant only), and the possible need for a bit more space in the pool.

Explanation of quality assessment: minor methodological limitations in the contributing study (unclear relationship between researchers and participants and lack of detail on method of data analysis); no or very minor concerns regarding coherence of the finding; moderate concerns regarding relevance as the contributing study is based only on female participants; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: minor methodological limitations in the contributing study (unclear relationship between researchers and participants and lack of detail on method of data analysis); no or very minor concerns regarding coherence of the

finding; serious concerns regarding relevance due to unclear PEM and the contributing study only including female participants; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Other sources of support

A number of people whose condition was much better after treatment reported use of GES being supported by other complementary therapies, counselling, CBT, self-help or peer support. Two people had used complementary therapies during the trial, which they felt supported their recovery and gave them more energy, making it easier for them to engage with GES.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations in the contributing study, coherence of the finding, or relevance with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding adequacy.

No change in quality assessment after PEM reanalysis

2.1.5.6 Narrative summary of review findings for adults (severity mixed or unclear) who have had education/information interventions

Review finding: Validation

Patients with varying severity and time since diagnosis described how the provision of reliable evidence-based information meant that their GP was validating their ‘CFS/ME’. This enabled them to self-manage their condition. A number of people commented on the value of seminars in helping them to feel believed. This sense of validation and of “being believed” was reported as an important benefit from the seminars.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to minor limitations in one study (unclear relationship between researcher and participants; no clear statement of findings) and serious concerns in the other study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns regarding relevance due to the lack of information on participant characteristics in one study; no or very minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations due to minor limitations in one study (unclear relationship between researcher and participants; no clear statement of findings) and serious concerns in the other study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns over relevance in both contributing studies due to the lack of information on participant characteristics including PEM in one study and participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM in the other study; no or very minor concerns about adequacy as the evidence is sufficiently deep (clear

statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

Review finding: Knowledge and understanding

The resources had a positive impact on people's understanding of 'CFS/ME'. The DVD case studies were seen as particularly important in helping people and carers to understand that others shared their experiences, and the format allowed those who found it difficult to read to access the information. As a result of this information some felt that they needed to visit their practice less frequently. People stated that the resource pack would be of greatest benefit to newly diagnosed patients, although some people who had the condition for a number of years reported that a comprehensive pack of information allowed them to consolidate their knowledge and sometimes learn something new.

People realised that they were actually ill and some expressed greater confidence regarding their diagnosis and awareness their symptoms were related to 'CFS'. Learning about the diagnosis, symptoms, possible causes and prognosis increased understanding and confidence. It was considered helpful to learn that deterioration may occur even when doing everything 'right'.

Many commented that sessions expanded their knowledge of 'CFS/ME' and offered different ways of managing their symptoms. Whilst for some, the seminars reinforced knowledge that they had already gathered, for others the seminars offered more understanding about the condition and helped with "sorting myths from truth". The detailed exploration of 'CFS/ME' symptoms and their behaviour was reported as beneficial. This included knowing what symptoms are typical for 'CFS/ME'. For some people, this helped them to feel more confident in the diagnosis, and this confirmation was valued.

Explanation of quality assessment: minor concerns regarding methodological limitations due to the majority of the contributing studies having minor limitations (due to an unclear relationship between researcher and participants in both studies; data analysis mainly by a single researcher in one study; no clear statement of findings in one study); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns regarding relevance due to the lack of information on participant characteristics in one study; no or very minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations due to the majority of the contributing studies having minor limitations (due to an unclear relationship between researcher and participants in both studies; data analysis mainly by a single researcher in one study; no clear statement of findings in one study); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to moderate concerns across contributing studies due to the lack of information on participant characteristics including PEM in one study, participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM in one study and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (for Fukuda 1994) criteria where (Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria in the third contributing study; no or very minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding with methodological limitations being minor but concerns about relevance being moderate.

Review finding: Sources of information

An evidence-based source of information was welcomed as there are currently issues with identifying reliable information on the internet. Some participants felt more able to assess information about the illness and treatments more critically.

Explanation of quality assessment: minor concerns regarding methodological limitations due to minor concerns in both contributing studies (unclear relationship between researcher and participants in both studies; data analysis mainly by a single researcher in one study; no clear statement of findings in one study), no or very minor concerns about coherence of the finding, relevance or adequacy with nothing to lower our confidence. There was a judgement of moderate confidence in this finding.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations due to minor concerns in both contributing studies (unclear relationship between researcher and participants in both studies; data analysis mainly by a single researcher in one study; no clear statement of findings in one study), no or very minor concerns about coherence of the finding; moderate concerns over relevance in both contributing studies due to participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria in the other study; no or very minor concerns about adequacy with nothing to lower our confidence. There was a judgement of low confidence in this finding with concerns over methodological limitations being minor but concerns over relevance being moderate.

Review finding: Acceptance

Participants described a change in their understanding of the illness trajectory. Some participants had expected participation in the programme to cure them, but then realised that they had to focus on acceptance and coping with the illness. All participants experienced increased acceptance of the illness, although at times still felt that acceptance was equivalent to giving up hope of getting better.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between researcher and participants; data analysis mainly by one researcher); no or very minor concerns about coherence of the finding, or relevance with nothing to lower our confidence; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to the concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations in the contributing study (unclear relationship between researcher and participants; data analysis mainly by one researcher); no or very minor concerns about coherence of the finding, moderate concerns over relevance with participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria in the contributing study; minor concerns regarding adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to the concerns regarding methodological limitations, relevance and adequacy.

Review finding: Coping

People found it helpful to learn about pacing and energy conservation, relaxation exercises, how to deal with difficult feelings, economic and public support systems and nutrition.

Immediately following the programme, people felt they had gained new insights and understandings and envisioned new way of coping. Nine months later, they had begun to use new coping strategies in daily living, although to varying degrees. They experienced better coping with their illness and increased feeling of control but did not experience better health. Most believed they had gained a better insight into the relationship between activity level and symptom severity and felt better able to cope with symptom exacerbations. Resting more than they were accustomed to was experienced to prevent deterioration. People gained a better insight into the amount of energy required for different activities and felt more able to prioritise their use of energy, which occasionally included saying ‘no’. Some participants had begun using assistive devices such as shower stools, work chairs and wheelchairs. Several participants had made changes to their diets, including spreading meals over the day, drinking more water and consuming foods with low carbohydrate content. Others felt unable to changes their diets because they lacked the appetite or energy. Some participants reported feeling more confident talking about the illness with others and had started using new strategies for dealing with people’s misunderstandings and negative attitudes.

Many attendees commented on the value of the coping strategies that seminars introduced. Sleep advice was also valued by a number of people. The reduction of arousal before bedtime was specifically mentioned as a benefit of this session.

Explanation of quality assessment: minor concerns regarding methodological limitations due to the majority of the evidence coming from one study with minor limitations (unclear relationship between researcher and participants; data analysis mainly by one researcher); no or very minor concerns regarding coherence with nothing to lower our confidence; no or very minor concerns regarding relevance due to the majority of the evidence coming from one study in which there were no concerns regarding relevance; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of moderate confidence in this finding due to methodological limitations.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations due to the majority of the evidence coming from one study with minor limitations (unclear relationship between researcher and participants; data analysis mainly by one researcher); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance with moderate concerns in both contributing studies, due to lack of information on participant characteristics including PEM in one study and participants in the other study having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and the concerns over relevance.

Review finding: Activity management and diaries

People valued the use of a diary to identify high, medium and low demand activities. By utilizing the diary, people were able to have a visual representation of their daily activities, which led to more awareness of triggers for setbacks. This helped with “keeping on an even keel”, and “avoiding boom and bust" as they are able to reflect on their activities and plan/spread their low, medium and high activities evenly throughout the day, and throughout the week. Help with understanding and setting baselines was also identified as an important outcome of the seminars. Linked with the activity analysis, the value of recuperative rest in achieving stability was identified.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers

and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics (including PEM); minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Difficulties accessing and engaging in seminars

Some expressed that the location of the seminars and the distance they had to travel was an issue. Managing fatigue in order to attend the seminar was an issue for some. Finding a parking space was also difficult for some. 10.30am was experienced as too early in the morning for some. Others found it difficult to manage the seminars in addition to their work duties. One individual reported difficulty in remembering the date and time for the seminar. A common difficulty experienced was 'CFS/ME' symptoms during the seminars. These issues included concentrating on the topic being discussed and retaining all the information during the seminar. There were also difficulties reported in sitting upright, and a number of comments were made about the uncomfortable chairs. For some, the lights were too bright, and more than one person reported difficulty staying awake. The room was too warm on occasion, and a "lack of fresh air" was also experienced. One person thought that the sessions were too long, whereas another thought that a two-hour seminar would be better to allow people to talk more.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics (including PEM); minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Peer support

It was an overall positive experience for people to receive understanding and acceptance from fellow participants that were experiencing the same type of symptoms and problems. Mutual understanding made it safe to discuss issues they had not been able to discuss elsewhere. The presence of a peer counsellor increased the feeling of safety and fellowship and was valued as an important role model. People found it helpful to exchange coping experiences and share beneficial coping strategies and for some, this was the most valuable part of the programme. People commented that meeting others was very useful in that they no longer felt alone. In addition, many wrote that it was helpful to hear others' knowledge and experience: comments included "sharing feelings and knowledge" and "talking to others and sharing experiences". A few attendees commented in the suggestions section that they would have liked a way of staying in touch with others with 'CFS/ME', demonstrating the value of being with individuals with the same condition.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to minor limitations in one study (unclear relationship between researcher and participants and data analysis mainly by one researcher) and serious limitations in the other study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding

coherence with nothing to lower our confidence; minor concerns regarding relevance due to moderate concerns in one study (lack of information on participant characteristics) and no concerns in the other study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations due to minor limitations in one study (unclear relationship between researcher and participants and data analysis mainly by one researcher) and serious limitations in the other study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concern about relevance with moderate concerns in both studies, due to lack of information on participant characteristics including PEM in one study and participants in the other study having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

Review finding: Group participation

Group participation was identified as an important part of the delivery as this also contributed to creating a collaborative and accepting atmosphere.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics (including PEM); moderate concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples) and only based on one study. There was a judgement of very low confidence in this finding due to methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Problems with the group setting

There were a number of specific issues raised which related to problems with the group setting. One individual commented on the lack of personal focus as being a difficulty with the seminars. One individual reported difficulty in “opening up” in front of the group. One individual commented that it felt as if others were not as severely affected. Some commented that they would like the information to be shared with their family. There were comments made about some attendees talking more than others and about some negative comments made by others attending the seminars. One person found it difficult that staff were not able to answer individual questions, and that they were guided to speak to their clinician or GP about these issues.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but

only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Impact on friends, family and colleagues

The resources were reported to have had an impact on the friends, family and colleagues of the patients interviewed. In some cases, the provision of evidence-based information improved relationships and strengthened support networks.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between researcher and participants; no clear statement of findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; moderate concerns about adequacy as the evidence is not sufficiently deep (no clear statement of finding with elaboration and examples) and only based on one study. There was a judgement of low confidence in this finding due to methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations in the contributing study (unclear relationship between researcher and participants; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns about relevance due to participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM; moderate concerns about adequacy as the evidence is not sufficiently deep (no clear statement of finding with elaboration and examples) and only based on one study. There was a judgement of low confidence in this finding due to methodological limitations, relevance and adequacy.

Review finding: Emotional impact

A number of comments reflected the challenges inherent in confronting the reality of ‘CFS/ME’ in the seminars. The information about prognosis offered in the seminars was experienced as a difficulty, with one person saying that “improvement in condition not a quick fix”, and another saying “there is no simple answer”. One person suggested that staff should be more positive about the statistics about recovery rates, and another indicated that it was “depressing at times”.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics (including PEM); minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Difficulty putting theory into practice

A few people mentioned that applying the strategies into practice would be difficult as it depends on their work and lifestyle as well as the severity of their ‘CFS/ME’. Others also mentioned that in understanding the condition, they became more aware they will have to make changes in their daily life, including “breaking habits” and “facing the necessary changes in lifestyle”.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics (including PEM); minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Ongoing support

Several people wanted more guidance or follow-up to maintain the coping strategies after the programme. Some mentioned that they were unsure about what happens next after the seminars: “not understanding next steps”, “what next?”, “applying things learnt - not sure how to start”. There was recognition that moving forwards would be a difficult process.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to minor limitations in one study (unclear relationship between researcher and participants and data analysis mainly by one researcher) and serious limitations in the other study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; minor concerns regarding relevance due to moderate concerns about relevance in one study (lack of information on participant characteristics), but no concerns in the other study; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations due to minor limitations in one study (unclear relationship between researcher and participants and data analysis mainly by one researcher) and serious limitations in the other study (no clear statement of research aim, recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participant; unclear consideration of ethical issues); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance with moderate concerns in both contributing studies, due to lack of information on participant characteristics including PEM in one study and participants in the other study having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria; no concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples). There was a judgement of low confidence in this finding due to methodological limitations and relevance.

2.1.5.7 Narrative summary of review findings for adults (severity mixed or unclear) who have had rehabilitation/condition management programmes

Review finding: Accessibility

Timing of programme being between 14:00-16:00 was good and they elaborated saying ‘the timing of the group worked well, not too early’. Having high backed supportive chairs throughout the programme was helpful. The lift was useful for times the room the programme took place in was not on the ground floor.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Accessibility

Participants found the travel required to access the clinic and carpark to be least helpful/beneficial.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (participants sent the survey once the treatment episode is closed on the system, so recruitment potentially favoured those who completed treatment; unclear relationship between researchers and participants; unclear methods of data analysis; no clear statement of findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics including PEM; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Validation

Obtaining a diagnosis and validation of symptoms was a key process with some patients describing this as the most beneficial aspect of the service.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (participants sent the survey once the treatment episode is closed on the system, so recruitment potentially favoured those who completed treatment; unclear relationship between researchers and participants; unclear methods of data analysis; no clear statement of findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics including PEM; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Lack of attendance pressure

There had been no pressure placed on attendees when they missed a week: they felt welcome at the programme and they appreciated how encouraged they felt to return to the programme. Anxiety about the implications of missed attendance came up again in suggestions for improvements with the suggestion to cover initial anxieties at the beginning of the first session e.g. 'What if I am too ill to attend a week?'

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); moderate concerns about the coherence of the finding with description of lack of pressure, but also anxiety about missing sessions; no or very minor concerns regarding relevance with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, coherence and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); moderate concerns about the coherence of the finding with description of lack of pressure, but also anxiety about missing sessions; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, coherence, relevance and adequacy.

Review finding: Handouts

Having handouts was good, especially if they were given out at the beginning of the session as it saved energy used if one had to take notes. One person suggested having handouts available online would be useful.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Videoconferencing

It was suggested that incorporating video calls for example through Skype, Facetime or webcam would be useful for patients who were housebound at the time of the programme (including patients who are housebound long-term and those who may find themselves housebound during a particular week of the course.)

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Duration

There were mixed opinions on the duration of each session: One patient commented that the ‘length of sessions was just right’. However, a couple of others felt that the sessions were too long and that 1.5 hours would be a more manageable duration than 2 hours.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Self-management

The most appreciated topics on one course were pacing and activity management, rest and relaxation, followed by understanding the science behind ME/CFS, diet and relationships. It was beneficial to learn about the use of diaries, boom and bust patterns, knowing one's limits, prioritising, planning ahead, time management and pacing. It was positive to learn how to rest properly, with one person explaining they learnt to appreciate 'the importance of complete rest rather than reading or TV rest.' Some expressed that the information regarding diet was beneficial. Other topics included that the focus group thought to be important were learning 'not to be so hard on yourself' and the practicalities and the help available to return to work. Additional topics patients mentioned they would like to be covered included information on benefits, the impact of sunny weather (including heat and vitamin D), pain management and further information on stress recognition and management. The self-knowledge that participants gained allowed them to develop tools in their recovery.

Explanation of quality assessment: serious concerns regarding methodological limitations due to serious limitations in both contributing studies (only those who completed the treatment/programme were recruited in both studies; unclear relationship between the interviewer and the participants in both studies; unclear consideration of ethical issues in one study; issues regarding data analysis in both studies; no clear statement of findings in both studies); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; very minor concerns regarding relevance due to lack of information on participant characteristics in one study, which contributed less data to the finding; moderate concerns regarding adequacy (no clear statement of finding). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations due to serious limitations in both contributing studies (only those who completed the treatment/programme were recruited in both studies; unclear relationship between the interviewer and the participants in both studies; unclear consideration of ethical issues in one study; issues regarding data analysis in both studies; no clear statement of findings in both studies); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies; moderate concerns regarding adequacy (no clear statement of finding). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Signposting

Some participants referred to the signposting process as a beneficial aspect to the service.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (participants sent the survey once the treatment episode is closed on the system, so recruitment potentially favoured those who completed treatment; unclear relationship between researchers and participants; unclear methods of data analysis; no clear statement of findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics including PEM; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Science behind ME/CFS

The most appreciated topics on one course were pacing and activity management, rest and relaxation, followed by understanding the science behind ME/CFS, diet and relationships.

People requested less medical content, more nutrition and group material making individual references from another course.

Explanation of quality assessment: serious concerns regarding methodological limitations due to serious limitations in both contributing studies (only those who completed the treatment/programme were recruited in both studies; unclear relationship between the interviewer and the participants in both studies; unclear consideration of ethical issues in one study; issues regarding data analysis in both studies; no clear statement of findings in both studies); moderate concerns about the coherence of the finding with one study suggesting that science was beneficial and the other suggesting that people wanted less; minor concerns regarding relevance due to lack of information on participant characteristics in one study; moderate concerns regarding adequacy (no clear statement of findings in both studies). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, coherence, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations due to serious limitations in both contributing studies (only those who completed the treatment/programme were recruited in both studies; unclear relationship between the interviewer and the participants in both studies; unclear consideration of ethical issues in one study; issues regarding data analysis in both studies; no clear statement of findings in both studies); moderate concerns about the coherence of the finding with one study suggesting that science was beneficial and the other suggesting that people wanted less; moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies; moderate concerns regarding adequacy (no clear statement of findings in both studies). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, coherence, relevance and adequacy.

Review finding: Relationships

Some emphasised the value of discussing the impact of ME on relationships within the programme. They felt it was positive to open up about impact on relationships with others, with people who understand i.e. the other patients doing the programme.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Exercise/physical activity

One person valued 'Emphasising the importance of regular [physical activity], and the opportunity to successfully complete [physical activity] without increase in symptoms.' However, another was unsure about the physical activity advice.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Group setting

People placed great value on meeting other patients with the same/similar condition(s). They explained the group aspect of the programme helped create a support network for them. The patients that had one-on-one sessions in addition to the group sessions also deemed this as helpful. People referred to the resources and therapy structure with subthemes such as hearing others' stories and social group gatherings.

Explanation of quality assessment: serious concerns regarding methodological limitations due to serious limitations in both contributing studies (only those who completed the treatment/programme were recruited in both studies; unclear relationship between the interviewer and the participants in both studies; unclear consideration of ethical issues in one study; issues regarding data analysis in both studies; no clear statement of findings in both studies); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; minor concerns regarding relevance due to lack of information on participant characteristics in one study; moderate concerns regarding adequacy (no clear statement of findings in both studies). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations due to serious limitations in both contributing studies (only those who completed the treatment/programme were recruited in both studies; unclear relationship between the interviewer and the participants in both studies; unclear consideration of ethical issues in one study; issues regarding data analysis in both studies; no clear statement of findings in both studies); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies; moderate concerns regarding adequacy (no clear statement of findings in both studies). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Additional and ongoing support

Several people said they would like to be able to have one-off crisis-type access e.g. for during a deterioration or relapse and that some patients would require longer-term support.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence or relevance of the finding with nothing to lower our confidence; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (only those who completed the programme were recruited; unclear relationship between the interviewer and the participants; unclear consideration of ethical issues; data analysis by individual researcher; insufficient data presented to support all findings; no clear statement of some findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Staffing

People found staff support, knowledge and individual approaches helpful/beneficial. Team members were referred to, including additional members of the multi-disciplinary team and having more staff. Participants wanted nutritionist support and counselling services to be provided.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (participants sent the survey once the treatment episode is closed on the system, so recruitment potentially favoured those who completed treatment; unclear relationship between researchers and participants; unclear methods of data analysis; no clear statement of findings); no or very minor concerns about the coherence of the finding with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics including PEM; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

2.1.5.8 Narrative summary of review findings for adults (severity mixed or unclear) who have had complementary and alternative therapies

Review finding: Range of complementary and alternative therapies

Several people, desperate for relief of symptoms, tried a range of healers practicing Eastern and Western complementary therapies, including acupuncturists, osteopaths, chiropractors, massage therapists, personal trainers, faith healers, homeopaths, naturopaths, herbalists, diet counsellors, hypnotists, colour therapists, iridologists, and energy healers. Some sufferers took up Yoga, Tai chi, macrobiotic and other diets, and primal screaming. Others tried reiki, shiatsu, zero balancing and craniosacral therapy. A few were treated with exotic machines such as the vibratoner and the Reumark3 machine. It caused ongoing frustration that alternative therapies were not funded by either the NHS or by private health insurance

for ‘CFS/ME’. Alternative therapies were especially likely to be mentioned by participants from ethnic minorities.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to serious limitations in one study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings) and nothing to lower our confidence in the other study; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to different research aims and limited detail on interventions received in both studies; minor concerns about adequacy as there were no clear statements of findings in one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations due to serious limitations in one study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings) and nothing to lower our confidence in the other study; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance with serious concerns in both contributing studies due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM in one study lack of details on diagnosis of the purposive sample used in the other study (including weather it was based on PEM) and due to different research aims and limited detail on interventions received in both studies; minor concerns about adequacy as there were no clear statements of findings in one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Holistic approach

People with ME/CFS were attracted to diverse healers by a common element - a holistic approach. They found these healers were largely unconcerned with labels but they tended to both ‘mind and body’ whether they were offering a cure or symptom relief. Their approach of combining concrete action with empathy resonated with sufferers’ ideas of what a health care practitioner should be. Alternative care practitioners also exposed sufferers to various philosophies and fresh perspectives on the source and meanings of illness. The most common new idea gleaned from many of these therapies was that energy blockage could be a source of illness.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to different research aim and limited detail on interventions received; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study and due to the diagnosis being made by a medical doctor but it being unclear if it had also been based

on PEM ; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Positive therapist approach

Therapists' positive approaches gave sufferers hope that it was possible to overcome the illness. In some respects, they were similar to supportive doctors, but they had no authority to legitimate illness and grant certification that some sufferers required.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to different research aim and limited detail on interventions received; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study and due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM ; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Effectiveness

Evaluations of these therapies were mixed. Some were found to be helpful, some were declared "absolutely useless", "not helpful" and "possibly harmful". Others experienced temporary effectiveness which reinforced their beliefs in these therapies.

Explanation of quality assessment: moderate concerns regarding methodological limitations due to serious limitations in one study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings) and nothing to lower our confidence in the other study; moderate concerns regarding coherence as effectiveness was mixed in one study, but alternative therapies were reported to be helpful overall in the other study; moderate concerns regarding relevance due to different research aims and limited detail on interventions received in both studies; minor concerns about adequacy as there were no clear statements of findings in one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, coherence, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations due to serious limitations in one study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings) and nothing to lower our confidence in the other study; moderate concerns regarding coherence as effectiveness was mixed in one study, but alternative therapies were reported to be helpful overall in the other study; serious concerns regarding relevance with serious concerns in both contributing studies due to the diagnosis

being made by a medical doctor but it being unclear if it had also been based on PEM in one study lack of details on diagnosis of the purposive sample used in the other study (including PEM) and due to different research aims and limited detail on interventions received in both studies; minor concerns about adequacy as there were no clear statements of findings in one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, coherence, relevance and adequacy.

Review finding: Follow up

Several sufferers were impressed with the fact that unlike their regular doctors, these therapists called periodically to find out how they were managing.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to different research aim and limited detail on interventions received; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (identification of HCPs by patients with ME/CFS may have meant that recruitment of HCPs with particular views was favoured; unclear relationship between participants and researcher; data analysis by a single researcher; no clear statement of findings); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study and due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM ; moderate concerns regarding adequacy (no clear statement of finding and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

2.1.5.9 Narrative summary of review findings for adults (severity mixed or unclear) who have had pharmacological interventions

Review finding: Antidepressants

In those who did not attend specialist ME services, key themes included antidepressants-being prescribed for ME symptoms by health care professionals, and the experiencing of negative side effects.

Explanation of quality assessment: serious concerns regarding methodological limitations in the contributing study (recruitment through a single ME charity potentially meaning participants were more likely to be those who had not improved/recovered; unclear detail on specific interventions received; unclear consideration of ethical issues; limited detail reported on methods of data analysis, no clear statement for all findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics or interventions; moderate concerns regarding adequacy (no clear statement of finding with elaboration and examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: serious concerns regarding methodological limitations in the contributing study (recruitment through a single ME charity potentially meaning participants were more likely to be those who had not improved/recovered; unclear detail on specific interventions received; unclear consideration

of ethical issues; limited detail reported on methods of data analysis, no clear statement for all findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to lack of information on participant characteristics including PEM which was self-reported in the contributing study; moderate concerns regarding adequacy (no clear statement of finding with elaboration and examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

2.1.5.10 Narrative summary of review findings for children/young people (severity mixed or unclear) who have had cognitive behavioural therapy

Review finding: Relationship with the therapist

Most young people found the therapy sessions acceptable or even enjoyable; they were not as intimidating as expected. The therapist's personality and interpersonal skills were important. Often the young people did not perceive the sessions a formal therapy, rather they were just a 'chat'. Nearly all young people and parents emphasised that having somebody to talk to who was interested in and understood CFS was a key positive feature of therapy sessions.

Explanation of quality assessment: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Acceptability of FITNET-NHS platform/ e-consultations

People liked that they could complete the platform in their own time rather than having to attend appointments. Emails gave them time to think about their answers and some participants found it easier to talk about personal topics over email. However, others found it difficult to portray things in writing and would have preferred some face to face contact.

Explanation of quality assessment: very minor methodological limitations in the contributing study (unclear relationship between the interviewers and participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

Explanation of quality assessment after PEM reanalysis: very minor methodological limitations in the contributing study (unclear relationship between the interviewers and participants); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance as participants fulfilled criteria where PEM was not compulsory; minor concerns about adequacy as the evidence is sufficiently

deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Validation

Recognition, validation and emotional support were almost always cited as important. These benefits were appreciated regardless of whether other aspects of the therapy were deemed useful.

Explanation of quality assessment: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Behavioural aspects

The behavioural aspects of the therapy emerged as being particularly valued and accepted by the young people who found these easy to ‘latch on to’. Help with setting goals for physical activity and implementing sleep routines were frequently cited as the most useful aspects. This was often perceived as the key element in helping to combat CFS. Although behavioural aspects of therapy were found to be useful, many young people struggled putting them in to practice. Tasks were often initially very hard to achieve, and parents found it challenging to watch their children push themselves.

Explanation of quality assessment: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Personalised care

Some parents felt the agenda during the sessions was too narrow and rigid and therefore unresponsive to families’ idiosyncratic issues. People using the FITNET-NHS platform valued

the individual tailored advice from a 'specialist' 'CFS/ME' therapist as they hadn't had the support before.

Explanation of quality assessment: no or very minor concerns regarding methodological limitations in both contributing studies with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; minor concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in one study, but no concerns in the other study; no or very minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples). There was a judgement of moderate confidence in this finding due to concerns regarding relevance.

Explanation of quality assessment after PEM reanalysis: no or very minor concerns regarding methodological limitations in both contributing studies with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance with serious concerns in one study due to findings for both CBT and psychoeducation interventions being combined in one study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis and moderate concerns in the other contributing study as participants fulfilled criteria where PEM was not compulsory; no or very minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples). There was a judgement of low confidence in this finding due to serious concerns regarding relevance.

Review finding: Inclusion of the family

In addition to the sessions functioning as support for the parent, young people felt that they needed their parent/s at the sessions for emotional support or 'back-up' in this novel or daunting situation. Young people and parents both felt family involvement was important so that parents could understand the approach and could be involved practically by implementing advice and strategies and enforcing rules. It was also important that parents were present to absorb the advice since young people often reported extreme fatigue during sessions. Most young people reported being comfortable talking about issues in front of their parents. Many referred to the fact that parents were intensely involved in their illness and its management so issues raised were not new or surprising to them. Despite this, many young people and a few parents felt that there were certain situations where the young person should have been seen alone and some issues that would be better discussed separately.

Explanation of quality assessment: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Psychological aspects

Several young people disliked the 'psychological' or 'emotional' aspects, finding them irrelevant or inappropriate. Some young people and parents felt pigeonholed and subjected

to generalisations. In particular, several young people felt they were being wrongly categorised as somebody with mental rather than physical health problems. The anxiety and depression questionnaire administered as part of the RCT contributed to this perception. Several young people and parents found the setting of the service within 'Psychological Medicine' inappropriate, in some cases upsetting the patient or inducing hostility. A small minority of participants from the psychoeducation group displayed frustration and fundamental disagreement with the approach and felt that the therapy overall was useless or even counterproductive. These participants had strong preferences for physiological explanations of CFS and deemed physiological approaches more useful and relevant. Others felt that the therapy was somehow incomplete and failed to tackle all aspects of the illness and psychological and emotional aspects appeared to be one area perceived to be ineffectively addressed.

Explanation of quality assessment: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Effectiveness

The therapy was useful to some extent, the family was thankful for the help, but improvements were modest and this was not a magic cure. However, participants particularly in the CBT group commonly reported that the therapy was a principle factor in allowing them to regain normality in their lives. The idea of therapy as a 'starting block' on a gradual journey to recovery was often mentioned. Participants described trying other treatments post-therapy and found these useful in different ways and for different aspects of the illness, but usually complementary to the therapy received. Other life changes such as personal growth, learning for maturity were deemed necessary for further improvement. Very few participants reported being 100% free from CFS. The majority experienced ongoing symptoms and limitations on activities and continued to see themselves as CFS patients with certain vulnerabilities. All of the young people's health had dramatically improved post-therapy and most participants found the extent of improvement acceptable. A minority, mostly parents, felt the therapy was insufficiently successful.

Explanation of quality assessment: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: no or very minor methodological limitations in the contributing study with nothing to lower our confidence; no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns

regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding relevance and adequacy.

Review finding: Effectiveness

Some young people with 'CFS/ME' and depression talked about finding CBT helpful. The combination treatment of CBT and medication was also discussed. One participant talked specifically about how they continue to use CBT in their lives, demonstrating a clear understanding of the cognitive behaviour therapy model and principles.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (insufficient data presented to support all findings, with some supported by single quotes and no clear statement of all findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance study population (ME/CFS with comorbid depression); minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations in the contributing study (insufficient data presented to support all findings, with some supported by single quotes and no clear statement of all findings); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to the study population having comorbid depression and no details available on PEM; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

2.1.5.11 Narrative summary of review findings for children/young people (severity mixed or unclear) who have had the Lightning Process

Review finding: Relationship with the therapist

Therapists and staff were mostly described as positive and encouraging. There were different opinions about the therapists; some had only good experiences, while others found their therapist too controlling and not open for critical questions. Alternative viewpoints brought up by the young people were not well-received and a few experienced a normative pressure to be happy all the time and not express any negative feelings, which they found difficult. Those who did not recover from the treatment felt that they were blamed for the lack of treatment success and consequently struggled with feeling of guilt and anger.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not

improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns about relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Dishonesty

People criticised the impression that staff gave about the Lightning Process always involving a quick recovery. Participants mentioned the dishonesty staff showed when they claimed the treatment had a 100% success rate.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns about relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Theory behind the Lightning Process

Several people highlighted that the educational part of the treatment, where they learned the theory behind the Lightning Process and which included practical examples of previous success stories, gave them a rationale they could believe in. Particular parts of the theory they found helpful were the association between thoughts, emotions and body, and how negative thoughts and emotions can affect the body directly. Some were unsure whether the theory was scientifically valid, but they still found it logical and believable.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor

concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance, and adequacy.

Review finding: Confusing

The information given in the first session was described as difficult to understand and challenging. The educational part of the intervention was considered complicated and difficult to understand, but necessary and helpful. The information given conflicted with that of other therapists. In particular, advice that participants could do anything they wanted conflicted with previous advice they had been given around activity pacing. Some found the teaching confusing and incomplete and not well-organised.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Peer support

The support from others and the group setting that allowed the participants to learn from each other was highlighted as helpful as aspects leading to engagement and treatment commitment.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns about relevance due the majority of

participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance, and adequacy.

Review finding: Goal setting

The focus on specific goals and identifying barriers from reaching them was considered a helpful part of treatment.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; moderate concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples and only based on one study). There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; moderate concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Practice and application

People had the opportunity to practice the process and apply it in their everyday life and they also realised that it was their own choice that would really help them recover. The behavioural aspects of the treatment stood out as the most important factor for symptom alleviation and continuing recovery.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low

confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Intensity

Several comments were raised regarding the intensity of treatment being too high. The length of the sessions was thought to be too long and intense, especially since many participants struggled with focus and concentration.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Follow up

Some described the whole treatment as too short; with too little follow up afterwards.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; moderate concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples and only based on one study). There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; moderate concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Effectiveness

Some participants experienced an instant healing, some experienced a gradual improvement that continued after treatment ended and some did not find the treatment helpful. One participant’s experience was dominated by a negative experience with one particular provider

who was described to be too evangelical about the treatment and not sufficiently understanding and supportive.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Secrecy

The secrecy surrounding the Lightning Process was criticised and thought to result in unnecessary sceptical and prejudiced attitudes from people. Participants were specifically encouraged not to talk to anyone about it and they found this unhelpful and difficult.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (recruitment through a single charity potentially meaning that participants were more likely to be those who had not improved/recovered; insufficient data presented to support all findings); no or very minor concerns regarding coherence; moderate concerns over relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

2.1.5.12 Narrative summary of review findings for children/young people (mild/moderate) who have had the Lightning process

Review finding: Validation

The service recognised and acknowledged the young person's condition, resulting in a sense of relief and reassurance. Mothers felt that symptoms were now being understood and they would receive help.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between the researcher and participants; some findings supported by single quotes only); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Personalised care

Referral to a specialist service gave families access to an informative team of experts, for some a formal diagnosis, and for all a tailored, patient centred specialist medical intervention that had not been available earlier. This enabled positive change and steps towards a managed recovery.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between the researcher and participants; some findings supported by single quotes only); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Professional support

Some mothers felt that the 'CFS/ME' service reinforced symptom management strategies that they had been trying to get their child to follow, and that they felt their child would be more likely to listen if techniques were legitimised by a health-care professional. Half the adolescents reported that specialist medical care was positive, as it enabled them to talk about their illness and gave guidance on how to manage their condition, which brought structure and a sense of normality back into their lives.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between the researcher and participants; some findings supported by single quotes only); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Challenges of a new routine

Some reported that, although specialist medical care resulted in better symptom management, accepting that for a time they must reduce activity levels and adopt a routine was challenging. A few mothers also noted that specialist medical care strategies had an impact on the whole family and could be difficult to integrate with their lifestyle.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between the researcher and participants; some findings supported by single quotes only); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Dialogue between healthcare professionals and education providers

Mothers discussed the beneficial way in which the 'CFS/ME' service opened channels of dialogue between health-care professionals and education providers in a variety of ways. A letter provided by the 'CFS/ME' service confirming a diagnosis enabled mothers to legitimately take their child out of school, request funding for home schooling and more generally inform and gain support from teachers when managing reduced attendance.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (unclear relationship between the researcher and participants; some findings supported by single quotes only); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep (with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

No change in quality assessment after PEM reanalysis.

2.1.5.13 Narrative summary of review findings for children/young people (severity mixed or unclear) who have had graded exercise therapy/other exercise interventions

Review finding: Exercise enjoyable

Despite mixed preconceptions, most were positive about GET once they entered treatment and reported positive experience of the exercises.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; moderate concerns regarding adequacy due to there being no elaboration or examples of positive experiences and the finding only being based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Routine and structure

Many families explained that the program introduced routine, which they experienced as important. People also described benefits of a more consistent routine from GET, including a regular waking/getting up pattern.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Relationship with therapist

Many families valued the support they received from their clinician. Some comments recognised the helpful support of the clinician in dealing with the young person's school. Many families acknowledged the importance of the relationship in terms of having someone listen and understand and feeling cared for.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Personalised care

Families consistently praised the way the program was implemented in a tailored way in which the clinician identified the individual needs of the young person and collaboratively developed a tailored treatment plan. Families commented that the GET program was tailored around the child's interests and activities and taking into account individual needs. Many commented on the program being adapted to the child's capabilities. Families felt that therapists delivering treatment recognised the fluctuating nature of 'CFS/ME' and that physical capabilities change, including setbacks and "crashes", and that the program included flexibility with recommendations. Families also reported that they gained extra advice beyond the central focus on activity, such as sleep or diet, when these came up.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Pacing benefits

Some families commented that the treatment set helpful boundaries to avoid a pattern of overexertion. Many families explained that the clinician worked closely with them to make sure that activity and any increases were done at a manageable pace for the child. Some reported that clinicians were flexible in reducing the activity if the increase had been too rapid/ too much.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants);

no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Pacing challenges

Some families reported that limiting activity was challenging, with evidence that the young person resisted this advice, wanting to do more physical exercise. Concerns about activity reduction included social effects and difficulties with limiting walking in school.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Setbacks

A number of families described that the young person had a setback or “crash” during the course of treatment. Families reported that crashes or setbacks happened as a result of the young person exceeding their recommended limits of physical activity. Young people reported dealing with setbacks by adapting their activity levels to a lower level, supported by their clinician. There were reports that travel to the hospital site for appointments contributed to setbacks, which worsened fatigue in some young people.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: FITBITS and physical monitoring

Participants commented positively on the use of wearables to accurately detect physical activity, as this demonstrated when they were doing too much, making the participant aware of over-exercising. Participants enjoyed using the Fitbit, often finding other functionality such as sleep or steps monitoring useful in addition to heart rate monitoring. Some issues with Fitbits were identified including inconsistent availability: one was the wrong size, two participants reported not receiving Fitbits, one participant purchased one independently. Some comments indicated that the measurements were not always accurate, for example under-reporting numbers of stair climbs in a day.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); no or very minor concerns regarding coherence or relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of moderate confidence in this finding due to concerns regarding adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Positive outcomes

There were many positive reports of treatment outcomes from families, with overall recognition that the young person had benefitted from GET. Families commented on improvements to the young person's 'CFS/ME' symptoms, including reductions in fatigue and tiredness, improved sleep and ability to concentrate. Several comments indicated improvements to the young person's functioning attributed to GET. Several families reported that treatment led to mood improvements in the young person.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); moderate concerns regarding coherence as another finding from the same study showed uncertain/lack of difference from treatment; no or very minor concerns regarding relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding coherence and adequacy.

No change in quality assessment after PEM reanalysis.

Review finding: Uncertain/lack of difference from treatment

Some families did not notice a difference with treatment, either reporting uncertainty, or lack of impact, often related to school and cognitive activities.

Explanation of quality assessment: very minor concerns regarding methodological limitations in the contributing study (unclear relationship between the interviewer and the participants); moderate concerns regarding coherence as another finding from the same study showed positive outcomes; no or very minor concerns regarding relevance with nothing to lower our confidence; minor concerns about adequacy as the evidence is sufficiently deep (clear statement of finding with elaboration and examples), but only based on one study. There was a judgement of low confidence in this finding due to concerns regarding coherence and adequacy.

No change in quality assessment after PEM reanalysis.

2.1.5.14 Narrative summary of review findings for children/young people (severity mixed or unclear) who have had complementary and alternative therapies

Review finding: Complementary and alternative therapies

Some families sought diverse treatments such as acupuncture, dietician input, sickness bands and the emotional freedom technique, while others spoke to their 'CFS/ME' clinician for advice. External support varied greatly in perceived accessibility and helpfulness; therefore, outcomes across participants were inconsistent.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (involvement of clinicians in determining participant eligibility that may have introduced selection bias; lack of data richness); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties (findings may not be equally relevant to the wider population of ME/CFS who did not experience such difficulties); moderate concerns regarding adequacy (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (involvement of clinicians in determining

participant eligibility that may have introduced selection bias; lack of data richness); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties (findings may not be equally relevant to the wider population of ME/CFS who did not experience such difficulties) and it being unclear whether diagnosis had been based on PEM; moderate concerns regarding adequacy (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

2.1.5.15 Narrative summary of review findings for children/young people (severity mixed or unclear) who have had pharmacological interventions

Review finding: Sickness/stomach acid relief medication

Some adolescents took prescribed sickness or stomach acid relief medication which they found helpful. However, it was not common to have been offered medication to relieve their symptoms which frustrated some adolescents.

Explanation of quality assessment: moderate concerns regarding methodological limitations in the contributing study (involvement of clinicians in determining participant eligibility that may have introduced selection bias; lack of data richness); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties (findings may not be equally relevant to the wider population of ME/CFS who did not experience such difficulties); moderate concerns regarding adequacy (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: moderate concerns regarding methodological limitations in the contributing study (involvement of clinicians in determining participant eligibility that may have introduced selection bias; lack of data richness); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties (findings may not be equally relevant to the wider population of ME/CFS who did not experience such difficulties) and it being unclear if participants had PEM; moderate concerns regarding adequacy (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Review finding: Attitude toward medication

Young people generally did not mind taking medication providing they found it helpful.

Explanation of quality assessment: minor concerns regarding methodological limitations in the contributing study (insufficient data presented to support all findings; no clear statement of all findings); no or very minor concerns regarding coherence with nothing to lower our confidence; moderate concerns about relevance due to study population (ME/CFS with comorbid depression); moderate concerns regarding adequacy (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

Explanation of quality assessment after PEM reanalysis: minor concerns regarding methodological limitations in the contributing study (insufficient data presented to support all findings; no clear statement of all findings); no or very minor concerns regarding coherence with nothing to lower our confidence; serious concerns about relevance due to study population being limited to participants with ME/CFS who also had comorbid depression and

it being unclear if they had PEM; moderate concerns regarding adequacy (no elaboration or examples and only based on one study). There was a judgement of very low confidence in this finding due to concerns regarding methodological limitations, relevance and adequacy.

2.1.6 Qualitative evidence summary

See Appendix F- PEM reanalysis in evidence review H for details on the methods followed

Adults (severity mixed or unclear)

Table 82: Summary of evidence: Cognitive behavioural therapy

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Hopes and expectations					
1	Semi-structured interviews	Feelings of confusion and apprehension at the beginning of therapy were replaced by feeling as ease. Some felt that the treatment exceeded expectations.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Validation					
1	Semi-structured interviews	Treatment was perceived as a source of validation. CBT helped people to feel understood and to reaffirm that their suffering is real and recognised.	Limitations	Moderate concerns about methodological limitations[a]	LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [a]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
CBT as support					
1	Semi-structured interviews	The simple act of talking to someone was of benefit and people were comforted by the knowledge that the therapist was available if they needed help as a form of safeguard.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [a]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Relationship with the therapist					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi-structured interviews	People valued building a relationship with the therapist and reported a preference for face-to-face consultations, which were found by some to be more personal and enabling.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Personalised care					
1	Semi-structured interviews	People felt that treatment was shaped by both the client and the therapist, which made them feel in control and able to contribute.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Motivation and engagement					
1	Semi-structured interviews	People recognised that they must be ready to invest effort and motivation must come from within. However, this might depend on illness severity and personal circumstances at the time.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Self-monitoring/management support					
2	Semi-structured interviews (1 study), survey including closed and open-ended questions (1 study)	Improvement was closely linked to a mastery of self-monitoring. People valued the support to learn skills and strategies to self-manage, specifically through CBT and mindfulness meditation approaches.	Limitations	Moderate concerns about methodological limitations[b]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [b]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Adequacy	No or very minor concerns about adequacy	
Behavioural aspects					
1	Semi-structured interviews	Behavioural tasks such as activity or sleep monitoring were found to be helpful in facilitating the development of self-awareness.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Cognitive aspects					
1	Semi-structured interviews	Feedback on the cognitive aspects was mixed, with some perceiving it as crucial and others finding it less useful, especially for physical symptoms.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Relevance (PEM)	Moderate concerns about relevance [a]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Negative perceptions					
1	Unstructured interviews	Some perceived CBT as controlling, patronising and a form of brainwashing.	Limitations	Moderate concerns about methodological limitations[c]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[c]	PEM reanalysis:
			Relevance (PEM)	Serious concerns about relevance [c]	VERY LOW
			Adequacy	Minor concerns about adequacy[c]	
Effect on symptoms					
3	Semi-structured interviews (1 study), survey including closed ended and open-	Response was mixed, with some reporting a gradual improvement which did not reach a pre-morbid level of functioning, some reporting no change and some reporting a worsening of symptoms. There were criticisms of the therapy being used as a 'treatment' for ME.	Limitations	Moderate concerns about methodological limitations[d]	LOW
			Coherence	Moderate concerns about coherence[d]	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	ended questions (2 studies)		Relevance (PEM)	Moderate concerns about relevance [d]	VERY LOW
			Adequacy	No or very minor concerns about adequacy	
Ongoing support					
1	Semi-structured interviews	Many felt they would have liked the support of additional sessions; many feared a relapse and did not know how they would cope without CBT.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	

[a]One study with moderate methodological limitations due to only participants who had completed treatment being recruited, unclear relationship between the researcher and participants and unclear consideration of ethical issues (Picariello 2017); minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: moderate concerns about relevance with participants fulfilling diagnostic criteria where PEM was not compulsory (Picariello 2017).

[b]Two studies with moderate methodological limitations due to only participants who had completed treatment being recruited and unclear consideration of ethical issues in one study (Picariello 2017), unclear methods of data analysis in one study (NHS North Bristol, 2019) and an unclear relationship between the researcher and participants in both studies (Picariello 2017; NHS North Bristol 2019); PEM reanalysis: moderate concerns over relevance with moderate concerns in one study with participants fulfilling diagnostic criteria where PEM was not compulsory (Picariello 2017) and serious concerns in the other study due to a lack of information on participant characteristics including PEM and a lack of information on which interventions were received (NHS North Bristol 2019)..

[c]One study with moderate methodological limitations due to recruitment through ME/CFS charities, unclear interventions and insufficient data presented to support all findings (Ward 2008); minor concerns regarding relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: serious concerns regarding relevance due to unclear interventions (finding relates to interventions which participants perceived to be CBT, but no details) and diagnosis made by a medical practitioner, but with no information on PEM (Ward 2008).
[d]Two studies with moderate methodological limitations due to only participants who had completed treatment being recruited, unclear relationship between the researcher and participants and unclear consideration of ethical issues (Picariello 2017), recruitment through ME/CFS charities and issues regarding methods of data collection and analysis (Oxford Clinical Allied Technology and Trials Services Unit 2019) and one study with serious methodological limitations due to unclear interventions, recruitment through an ME/CFS charity, unclear consideration of ethical issues, unclear methods of data analysis and no clear statement of some findings (Leary 2019); moderate concerns about the coherence of the finding with one study reporting worsening of symptoms (Oxford Clinical Trials Services Unit 2019) and the other two reflecting subtle or minimal differences (Picariello 2017; Leary 2019); PEM reanalysis: moderate concerns over relevance with moderate concerns across contributing studies due to lack of details on diagnosis and PEM being self-reported in one study (Leary 2019), with participants fulfilling diagnostic criteria where PEM was not compulsory in one study (Picariello 2017) and diagnosis made by a clinician but the percentage of participants who had PEM being self-reported in the third contributing study (Oxford Clinical Allied Technology and Trials Services Unit 2019).

Table 83: Summary of evidence: other psychological therapies (counselling)

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Activity related counselling interventions					
1	Unstructured interviews	Pacing was the most valued aspect, although in the early stages, people often got this wrong, resulting in periods of crushing fatigue and pain. There was often a delay before the full impact of activity was felt and for these people, exercise regimes and sometimes activity programmes were viewed negatively. People often felt pushed to overdo it, leading to significant relapse.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Stress-management counselling interventions					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Unstructured interviews	Relaxation and meditation techniques were viewed positively, with people talking of reduced stress levels in terms of the impact of their condition and their life activities.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Thought management counselling interventions					
1	Unstructured interviews	Responses to thought management strategies were mixed. Some found suggestions of negative thoughts being counterproductive to be patronising and negative; some found such notions simplistic; some found the interventions useful, for example in helping them to counter unrealistic or catastrophizing reactions.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Examining the influence of the past counselling interventions					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Unstructured interviews	Very few people experienced this approach. Those who had felt very negatively about it because they thought the suggestion was that the cause of their ME might be rooted in the past and they firmly rejected any psychological cause for their condition.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Relationship with the therapist					
1	Unstructured interviews	Positive reflections involved counsellor listening, understanding and offering appropriate challenge, whereas negative reactions to counsellors involved poor communication and non-empathic responding.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Physical impact					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Unstructured interviews	Several people mentioned the physical impact of counselling on someone with severe ME, describing the difficulty of making their way to and from the session each week and the strain of keeping up a session of 50 minutes.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	

[a]One study with moderate methodological limitations due to recruitment through ME/CFS charities, unclear interventions based on participant recall and insufficient data presented to support all findings (Ward 2008); minor concerns about relevance due to unclear interventions in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study.
[b] serious concerns about relevance due to unclear interventions in the contributing study and it being unclear if participants had PEM.

Table 84: Summary of evidence: Graded exercise therapy/other exercise interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Baseline activity levels and false starts					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
2	Semi structured interviews (1 study), qualitative data submitted as "free text" in an online survey (1 study)	Most people found stabilising their routine, choosing physical activity and setting their baseline level to be straightforward, but baseline levels were not experienced as sustainable. Some experienced 'false starts' as they commenced the programme.	Limitations	Minor concerns about methodological limitations[a]	MODERATE
			Coherence	Minor concerns about coherence[a]	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	Minor concerns about relevance[a]	
			Adequacy	No or very minor concerns about adequacy	
The indeterminate phase of GES					
2	Semi-structured interviews	Most people noticed no immediate difference in symptoms, or an exacerbation during the initial phase which resulted in them not knowing if the programme was helping or hindering their condition and during this 'indeterminate phase', it was found to be difficult to maintain motivation.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[b]	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	Minor concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[b]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Too difficult					
3	Semi-structured interviews (2 studies), qualitative data submitted as "free text" in an online survey (1 study)	Most found following the programme to be 'hard work'. The level of exercise was selected by the therapist and experienced by patients as too difficult.	Limitations	Minor concerns about methodological limitations[c]	LOW
			Coherence	Minor concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	
			Relevance (PEM)	Moderate concerns about relevance [c]	PEM reanalysis: LOW (no change)
			Adequacy	Minor concerns about adequacy[c]	
'Push-crash' and worsening of symptoms					
6	Semi-structured interviews (2 studies), focus groups (1 study), survey including closed ended and open-ended questions (2	People experienced a lack of control over their bodies after exertion subsequent to non-customised activity. For some, debilitating exacerbations of symptoms were a reason for discontinuation. For others, trying to persist with rehabilitation led to a worsening of their symptoms in the longer term.	Limitations	Moderate concerns about methodological limitations [d]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Relevance (PEM)	Moderate concerns about relevance [d]	PEM reanalysis:

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	studies), qualitative data submitted as "free text" in an online survey (1 study)		Adequacy	No or very minor concerns about adequacy	LOW
Competing commitments					
1	Semi-structured interviews	People needed enough 'capacity' in their lives to experience an exacerbation of symptoms and for this not to interfere with essential life activities. Higher functioning participants had more to do in their lives and reported more challenges in fitting the programme in to busier lifestyles.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance[e]	
			Adequacy	Minor concerns about adequacy[e]	
Comorbid conditions					
1		People who reported their condition to be 'a little worse' following treatment reported more comorbid conditions and greater	Limitations	No or very minor concerns about	MODERATE

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	Semi-structured interviews	interferences from these conditions when following the programme.		methodological limitations	
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance [e]	
			Adequacy	Minor concerns about adequacy[e]	
Therapist approach					
4	Semi-structured interviews (2 studies), qualitative data submitted as "free text" in an online survey (2 studies)	Approaches and attitudes taken by physiotherapists that were enthusiastic, gentle, understanding and patient centred generally facilitated a positive experience and engagement with them and the programme. Conversely miscommunication and not having their opinions taken into account left people feeling unsupported.	Limitations	Minor concerns about methodological limitations[f]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[f]	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concern about relevance[f]	
			Adequacy	No or very minor concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Conflict in beliefs					
1	Qualitative data submitted as "free text" in an online survey	There were therapist-patient differences in beliefs about the nature of their condition and the role of rehabilitation with consequences for the appropriateness of treatment and expertise of therapists needed to provide this.	Limitations	Minor concerns about methodological limitations[g]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [g]	
			Adequacy	Minor concerns about adequacy[g]	
Pressure to comply with treatment					
2	Qualitative data submitted as "free text" in an online survey	People felt unreasonably pressured to comply with the rehabilitation therapy, especially when asked to ignore symptoms and continue trying to do more activity than they felt was sensible. People tried in vain to convey to therapists their sense that GET was not successful.	Limitations	Minor concerns about methodological limitations[h]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[h]	PEM reanalysis:
			Relevance	Serious concerns about relevance [h]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Adequacy	No or very minor concerns about adequacy	LOW
Feeling blamed					
1	Qualitative data submitted as "free text" in an online survey	Some experienced difficulties in their relationship with the therapist when they reported finding the therapy unhelpful, and the blame was shifted onto them.	Limitations	Minor concerns about methodological limitations[g]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [g]	
			Adequacy	Minor concerns about adequacy[g]	
Booklet information resource					
1	Semi-structured interviews	Some found the information booklet helpful, whereas others found it patronising, having the feel of marketing material or seemingly designed for participants with a higher level of functioning. The statement suggesting that there should be no ill effects from the programme was not accurate in their experience.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy [e]	
Personalised care					
4	Semi-structured interviews (1 study), focus groups (1 study), qualitative data submitted as "free text" in an online survey (2 studies)	Being allowed to choose activities supported motivation and individually adapted advice was perceived to be helpful. People described experiences of becoming extremely ill after organised exercise, whereas similar exercise undertaken in a non-organised way was helpful, enjoyable and easier to adapt to individual energy level.	Limitations	Moderate concerns about methodological limitations[i]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[i]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [i]	
			Adequacy	No or very minor concerns about adequacy	
Overall approach					
1	Semi-structured interviews	Some felt that the remit of graded exercise self-help was too narrow and that it needed a broader approach which included CBT or took into account mental activity.	Limitations	No or very minor concerns about methodological limitations	MODERATE

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	No or very minor concerns about relevance	MODERATE (no change)
			Adequacy	Minor concerns about adequacy [e]	
Knowledge and understanding					
1	Semi-structured interviews	An understanding of the theory behind graded exercise helped understanding and engagement in the programme.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	No or very minor concerns about relevance	MODERATE (no change)
			Adequacy	Minor concerns about adequacy[e]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Support for self-management					
2	Focus groups (1 study), qualitative data submitted as "free text" in an online survey (1 study)	Reviewing the daily workload with an occupational therapist, baseline setting and pacing was found to be helpful. Mapping exercises helped to prioritise tasks and reviewing activities, putting expectations aside and letting things happen diminished stress.	Limitations	Moderate concerns about methodological limitations[j]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[j]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance [j]	
			Adequacy	No or very minor concerns about adequacy	
Routines and goals					
1	Qualitative data submitted as "free text" in an online survey	Some found treatments that encouraged development of routines and setting of goals to be helpful.	Limitations	Minor concerns about methodological limitations[g]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [g]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy[g]	
Additional benefits					
1	Semi-structured interviews	Social benefits of group exercise were found to be extremely important and encouraged attendance and compliance. Additional benefits were enjoyment, better ability to self-manage, increased fitness or use of muscles, enhanced breathing, regulation of body temperature, the engaging mixture and pacing of exercises and improved cognitive symptoms.	Limitations	Minor concerns about methodological limitations[k]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[k]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance [k]	
			Adequacy	Minor concerns about adequacy	
Practical limitations					
1	Semi-structured interviews	Aspects of an aquatic exercise intervention that some participants did not like included travelling, the time it took to get undressed and dressed, the energy needed to remove wet swimsuits and heart rate monitors, the discomfort of wearing a heart rate monitor and the possible need for more space in the pool.	Limitations	Minor concerns about methodological limitations[k]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[k]	PEM reanalysis:
			Relevance (PEM)	Serious concerns about relevance [k]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy	VERY LOW
Other sources of support					
1	Semi-structured interviews	People with who reported their condition to be 'much better' following treatment reported use of other complementary therapies such as counselling, CBT, self-help or peer support.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[e]	

[a]*One study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014) and very minor limitations in one study due to unclear consideration of ethical issues (Cheshire 2020); minor concerns about the coherence of the finding, with some description related to ease and benefits of setting baselines (Gladwell 2014) and some related to unsustainability and 'false starts' (Cheshire 2020); PEM reanalysis: minor concerns about relevance with moderate concerns over one study due to participants being a self-selected sample and it was unclear if they experienced PEM (Gladwell 2014) and no concerns over the other contributing study (Cheshire 2020)*

[b]*Minor concerns regarding relevance due to one study only including female participants (Broadbent 2020) and no concerns regarding the other study (Cheshire 2020); minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but mainly based on one study; PEM reanalysis: minor concerns regarding relevance with serious concerns in one study due to unclear PEM and the study only including female participants (Broadbent 2020) but no concerns in the other contributing study (Cheshire 2020) and the majority of the information supporting the theme coming from the study with no concerns.*

[c]*Two studies with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014), unclear relationship between researchers and participants and data analysis (Broadbent 2020) and very minor limitations in one study due to unclear consideration of ethical issues (Cheshire 2020); minor concerns about the coherence of the finding, with it being unclear whether 'hard work' reported in one study (Cheshire 2020) has the same meaning*

as 'too difficult' reported in the other (Gladwell 2014) and concerns regarding one study reporting participants wanting longer/more frequent sessions being explained by differences in the type of exercise intervention (Broadbent 2020); minor concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples in any of the contributing studies); PEM reanalysis: moderate concerns about relevance with moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014), serious concerns in one study due to unclear PEM and the study only including female participants (Broadbent 2020) and no concerns in the other contributing study (Cheshire 2020)

[d]Two studies with moderate methodological limitations due to recruitment through ME/CFS charities, issues regarding methods of data collection and analysis (Oxford Clinical Allied Technology and Trials Services Unit 2019), recruitment through self-selection and clinic staff and unclear relationship between researcher and participants (Larun 2011); one study with serious methodological limitations due to unclear interventions, recruitment through an ME/CFS charity, unclear consideration of ethical issues, unclear methods of data analysis and no clear statement of some findings (Leary 2019); two studies with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014), unclear relationship between researchers and participants and data analysis in the other study (Broadbent 2020); one study with no or very minor limitations (Cheshire 2020); PEM reanalysis: moderate concerns about relevance with serious concerns in two studies due to one study including only female participants and it being unclear if they had PEM (Broadbent 2020) and one study including participants with unclear PEM and conducted in a rural area raising concerns over the applicability of the setting (Larun 2011), but moderate concerns in three studies due to participants being a self-selected sample and it being unclear if they had PEM in one study (Gladwell 2014), due to PEM being unclear or self-reported (Oxford Clinical Allied Technology and Trials Services Unit 2019; Leary 2019) and no concerns in one contributing study (Cheshire 2020).

[e]Minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only mainly based on one study.

[f]Two studies with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014), unclear relationship between researchers and participants and data analysis (Broadbent 2020); one study with very minor limitations due to unclear consideration of ethical issues (Cheshire 2020); one study with serious methodological limitations due to no clear statement of research aim, recruitment through a ME/CFS charity, unclear relationship between researcher and participants, unclear consideration of ethical issues, no information on method of qualitative data analysis and key themes only with no data presented to support findings (Physios for M.E.); minor concerns regarding relevance due to a lack of information on participant characteristics and interventions in one study (Physios for M.E.) and one study only including female participants (Broadbent 2020); PEM reanalysis: moderate concerns regarding relevance with serious concerns in two studies due to a lack of information on participant characteristics including PEM but also on the interventions received in one study (Physios for M.E.) and due to unclear PEM and the study only including female participants (Broadbent 2020) but moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014) and no concerns in the fourth contributing study (Cheshire 2020).

[g] One study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014); minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: moderate concerns over relevance with participants being a self-selected sample and it being unclear if they had PEM (Gladwell 2014)

[h]One study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014) and one study with no or very minor limitations (McManimen 2019); minor concerns about relevance due to one study with a different research aim and limited detail on interventions (McManimen 2019); PEM reanalysis: serious concerns about relevance with moderate concerns in one study with participants being a self-selected sample and it being unclear if they had PEM (Gladwell 2014) and serious concerns in the other study due to limited detail on interventions and concerns over the relevance of the population with the analysis being based only on people who had experienced a dismissive attitude from a health care professional and whose diagnosis and experience of PEM were self-reported rather than confirmed by specific criteria or professional (McManimen 2019).

[i]One study with serious methodological limitations due to no clear statement of research aim, recruitment through a ME/CFS charity, unclear relationship between researcher and participants, unclear consideration of ethical issues, no information on method of qualitative data analysis and key themes only with no data presented to support findings (Physios for M.E.); one study with moderate methodological limitations due to recruitment through self-selection and clinic staff and unclear relationship between researcher and participants (Larun 2011); one study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014) and one study with very minor limitations due to unclear consideration of ethical issues (Cheshire 2020); minor concerns regarding relevance, with one study having a different aim to the review question (Larun 2011) and a lack of information on participant characteristics and interventions in another (Physios for M.E.); PEM reanalysis: moderate concerns regarding relevance, with serious concerns in two studies due the inclusion of participants with unclear PEM and one study being conducted in a rural area raising concerns over the applicability of the setting (Larun 2011) and a lack of information on participant characteristics including PEM but also on the

interventions received in one study (Physios for M.E.) but moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014) and no concerns in the other contributing study (Cheshire 2020)

[j]*One study with moderate methodological limitations due to recruitment through self-selection and clinic staff and unclear relationship between researcher and participants (Larun 2011) and one study with minor limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014); minor concerns regarding relevance due to one study having a different aim to the review question (Larun 2011); PEM reanalysis: serious concerns over relevance due to serious concerns in one study contributing the majority of the information to this theme as it included participants with unclear PEM and was conducted in a rural area raising concerns over the applicability of the setting (Larun 2011) and moderate concerns in the other contributing study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014)*

[k]*One study with minor limitations due to unclear relationship between researchers and participants and data analysis in the other study (Broadbent 2020); moderate concerns regarding relevance due to the contributing study only including female participants (Broadbent 2020); PEM reanalysis: Serious concerns regarding relevance due to unclear PEM and the contributing study only including female participants (Broadbent 2020).*

Table 85: Summary of evidence: Education/information interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Validation					
2	Semi structured interviews (1 study), service evaluation forms (1 study)	The provision of reliable evidence-based information meant that their GP was validating people's CFS/ME, which enabled them to self-manage their condition. People appreciated meeting health care professionals with knowledge of CFS.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: LOW (No change)
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	No or very minor concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Knowledge and understanding					
3	Semi structured interviews (1 study), focus groups (1 study), service evaluation forms (1 study)	Learning about the diagnosis, symptoms, possible causes and prognosis increased understanding and confidence. DVD case studies helped people to understand that others shared their experiences, and the format allowed those who found it difficult to read to access the information. As a result of this information some patients felt that they needed to visit their practice less frequently. It was considered helpful to learn that deterioration may occur even when doing everything 'right'.	Limitations	Minor concerns about methodological limitations[b]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[b]	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [b]	
			Adequacy	No or very minor concerns about adequacy	
Sources of information					
2	Semi structured interviews (1 study), focus groups (1 study)	An evidence-based source of information was welcomed due to issues with identifying reliable information on the internet. Some felt more able to assess information about the illness and treatments more critically.	Limitations	Minor concerns about methodological limitations[c]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [c]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Adequacy	No or very minor concerns about adequacy	
Acceptance					
1	Focus groups	Some people with ME/CFS realised that they had to focus on acceptance and coping with the illness rather than curing it. People experienced increased acceptance, although at times still felt that acceptance was equivalent to giving up hope of getting better.	Limitations	Minor concerns about methodological limitations[d]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [d]	LOW
			Adequacy	Minor concerns about adequacy[d]	
Coping					
2	Focus groups (1 study), service evaluation forms (1 study)	People found it especially helpful to learn about pacing and energy conservation, relaxation exercises, how to deal with difficult feelings, economic and public support systems, nutrition and sleep management. They experienced better coping with their illness and increased feeling of control but did not experience better health.	Limitations	Minor concerns about methodological limitations[e]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Relevance (PEM)	Moderate concerns about relevance [e]	LOW
			Adequacy	No or very minor concerns about adequacy	
Activity management and diaries					
1	Service evaluation forms	People valued the use of a diary, which gave people a visual representation of their daily activities, which led to more awareness of triggers for setbacks. Help with understanding and setting baselines was also identified as an important outcome.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Difficulties accessing and engaging in seminars					
1	Service evaluation forms	Practical issues related to location, environment, timing and duration made accessibility and engagement difficult for some. Managing fatigue in order to attend the seminar was also an issue for some and a common difficulty experienced was CFS/ME symptoms during the seminars.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Peer support					
2	Focus groups (1 study), service evaluation forms (1 study)	People found it helpful to meet others in that they no longer felt alone and were able to exchange coping experiences and beneficial coping strategies. The presence of a peer counsellor increased the feeling of safety and fellowship and was valued as an important role model.	Limitations	Moderate concerns about methodological limitations[e]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[e]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [e]	
			Adequacy	No or very minor concerns about adequacy	
Group participation					
1	Service evaluation forms	Group participation was identified as an important part of the seminar delivery as it contributed to creating a collaborative and accepting atmosphere.	Limitations	Serious concerns about methodological limitations[g]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[g]	
			Adequacy	Moderate concerns about adequacy[g]	
Problems with the group setting					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Service evaluation forms	Issues raised included a lack of personal focus, difficulty in "opening up" in front of the group, feeling as if others were not as severely affected, information not being shared with the family, some attendees talking more than others and some negative comments made by other attendees.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Impact on friends, family and colleagues					
1	Semi structured interviews	The resources had an impact on the friends, family and colleagues. In some cases, the provision of evidence-based information improved relationships and strengthened support networks.	Limitations	Minor concerns about methodological limitations[h]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[h]	
			Adequacy	Moderate concerns about adequacy[h]	
Emotional impact					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Service evaluation forms	There were challenges inherent in confronting the reality of CFS/ME in the seminars; in particular information about prognosis was experienced as difficult.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Difficulty putting theory into practice					
1	Service evaluation forms	Some thought that applying the strategies into practice would be difficult as it depends on work, lifestyle and the severity of their CFS/ME.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Ongoing support					
2	Focus groups (1 study),	Several people wanted more guidance or follow-up to maintain the coping strategies after an education programme. Some mentioned	Limitations	Moderate concerns about methodological limitations[e]	LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	service evaluation forms (1 study)	that they were unsure about what happened next after the seminars.	Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[e]	PERM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [e]	
			Adequacy	No or very minor concerns about adequacy	

[a]*One study with serious methodological limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service) and one study with minor limitations due to unclear relationship between researcher and participants and no clear statement of findings (Bayliss 2016); minor concerns regarding relevance due to the lack of information on participant characteristics in one study (Bristol CFS/ME Service); PEM reanalysis: moderate concerns over relevance in both contributing studies due to the lack of information on participant characteristics including PEM in one study (Bristol CFS/ME Service) and participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM in the other study (Bayliss 2016).*

[b]*Two studies with minor methodological limitations due to no clear statement of findings in one study (Bayliss 2016), data analysis mainly by a single researcher in one study (Pinxsterhuis 2015) and an unclear relationship between researcher and participants in both studies (Bayliss 2016; Pinxsterhuis 2015) and one study with serious limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); minor concerns regarding relevance due to the lack of information on participant characteristics in one study (Bristol CFS/ME Service); PEM reanalysis: moderate concerns about relevance with moderate concerns across contributing studies due to the lack of information on participant characteristics including PEM (Bristol CFS/ME Service), participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM in one study (Bayliss 2016) and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (for Fukuda 1994) criteria where (Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria (Pinxsterhuis 2015)*

[c]*Two studies with minor methodological limitations due to no clear statement of findings in one study (Bayliss 2016), data analysis mainly by a single researcher in one study (Pinxsterhuis 2015) and an unclear relationship between researcher and participants in both studies (Bayliss 2016; Pinxsterhuis 2015); PEM reanalysis: moderate concerns over relevance in both contributing studies due to participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM (Bayliss 2016) and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria (Pinxsterhuis 2015)*

[d]One study with minor methodological limitations due to unclear relationship between researcher and participants and data analysis mainly by one researcher (Pinxsterhuis 2015); minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: moderate concerns over relevance due to participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria in the contributing study (Pinxsterhuis 2015)

[e]One study with minor methodological limitations due to unclear relationship between researcher and participants and data analysis mainly by one researcher (Pinxsterhuis 2015) and one study with serious limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); minor concerns regarding relevance due to lack of information on participant characteristics reported in one study (Bristol CFS/ME Service); PEM reanalysis: moderate concerns regarding relevance in both studies, due to lack of information on participant characteristics including PEM in one study (Bristol CFS/ME Service) and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria (Pinxsterhuis 2015)

[f]One study with serious methodological limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); moderate concerns regarding relevance due to lack of information on participant characteristics in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study. PEM reanalysis: moderate concerns regarding relevance due to lack of information on participant characteristics including PEM (Bristol CFS/ME service)

[g]One study with serious methodological limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); moderate concerns regarding relevance due to lack of information on participant characteristics in the contributing study; moderate concerns about adequacy as the evidence is not sufficiently deep and only based on one study; PEM reanalysis: moderate concerns regarding relevance due to lack of information on participant characteristics including PEM (Bristol CFS/ME service)

[h]One study with minor limitations due to an unclear relationship between researcher and participants and no clear statement of findings (Bayliss 2016); moderate concerns about adequacy as the evidence is not sufficiently deep and only based on one study; PEM reanalysis: moderate concerns about relevance due to participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM (Bayliss 2016).

Table 86: Summary of evidence: Rehabilitation/condition management programmes

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Accessibility					
1	Mixed methods (focus	Timing of the sessions in the afternoon and a venue which had a lift and high-backed chairs made the programme accessible.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	groups and questionnaire)		Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Accessibility					
1	Online survey	Travel required to access the clinic and carpark and waiting time were found to be less helpful/beneficial.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	
Validation					
1	Online survey	Obtaining a diagnosis and validation of symptoms was a key process.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Coherence	No or very minor concerns about coherence	(no change after PEM reanalysis)
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	
Lack of attendance pressure					
1	Mixed methods (focus groups and questionnaire)	There had been no pressure when people missed a week; they felt welcome and appreciated how encouraged they felt to return to the programme.	Limitations	Serious concerns about methodological limitations[c]	VERY LOW
			Coherence	Moderate concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [c]	
			Adequacy	Moderate concerns about adequacy[c]	
Handouts					
1	Mixed methods (focus groups and questionnaire)	Having handouts was helpful, especially if they were given out at the beginning of the session as it saved energy used to take notes.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Video conferencing					
1	Mixed methods (focus groups and questionnaire)	It was suggested that incorporating video calls for example through Skype, Facetime or webcam would be useful for patients who were housebound at the time of the programme.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Duration					
1	Mixed methods (focus	There were mixed opinions on the duration of each session. Some felt that the sessions were too long and that 1.5 hours would be a more manageable duration than 2 hours.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	groups and questionnaire)		Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Self-management					
2	Mixed methods (focus groups and questionnaire) (1 study), online survey (1 study)	It was beneficial to learn about the use of diaries, boom and bust patterns, knowing limits, prioritising, planning ahead, time management and pacing, how to rest properly, diet, learning 'not to be so hard on yourself' and the practicalities and the help available to return to work. Additional topics people would like to be covered included benefits, the impact of sunny weather, pain management and stress recognition and management.	Limitations	Serious concerns about methodological limitations[d]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [d]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[d]	
Signposting					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Online survey	Some referred to the signposting process as a beneficial aspect.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	
Science behind ME/CFS					
2	Mixed methods (focus groups and questionnaire) (1 study), online survey (1 study)	Some people appreciated learning the science behind ME/CFS, although some requested less medical content.	Limitations	Serious concerns about methodological limitations[e]	VERY LOW
			Coherence	Moderate concerns about coherence[e]	
			Relevance	Minor concerns about relevance[e]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[e]	
			Adequacy	Moderate concerns about adequacy[e]	
Relationships					
1	Mixed methods (focus	Some emphasised the value of discussing the impact of ME on relationships with people who understand.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	groups and questionnaire)		Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Exercise/physical activity					
1	Mixed methods (focus groups and questionnaire)	Views on physical activity advice were mixed.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Group setting					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
2	Mixed methods (focus groups and questionnaire) (1 study), online survey (1 study)	People placed great value on meeting other patients and hearing others' stories, which helped create a support network. Those who had one-on-one sessions in addition to the group sessions also deemed this as helpful.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[f]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[f]	
			Adequacy	Moderate concerns about adequacy[f]	
Additional and ongoing support					
1	Mixed methods (focus groups and questionnaire)	People appreciated having follow-up at three and six months. Several would have liked one-off crisis-type access for during a deterioration or relapse and suggested that some people would require longer-term support.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	
Staffing					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Online survey	People found staff support, knowledge and individual approaches to be helpful/beneficial. People wanted nutritionist support and counselling services to be provided.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	

[a]*One study with serious methodological limitations due to only those who completed the programme being recruited, unclear relationship between the interviewer and the participants, unclear consideration of ethical issues, data analysis by individual researcher, insufficient data presented to support all findings and no clear statement of some findings (Snounou); moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study; PEM reanalysis: moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study (Snounou)*

[b]*One study with serious methodological limitations due to recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants, unclear methods of data analysis and no clear statement of findings (Pemberton 2019); moderate concerns regarding relevance due to lack of information on participant characteristics including PEM in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study.*

[c]*One study with serious methodological limitations due to only those who completed the programme being recruited, unclear relationship between the interviewer and the participants, unclear consideration of ethical issues, data analysis by individual researcher, insufficient data presented to support all findings and no clear statement of some findings (Snounou); moderate concerns about the coherence of the finding with description of lack of pressure, but also anxiety about missing sessions in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study; PEM reanalysis: moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study (Snounou)*

[d]*Two studies with serious methodological limitations due to unclear consideration of ethical issues, data analysis by an individual researcher and insufficient data presented to support all findings in one study (Snounou), unclear methods of data analysis in one study (Pemberton 2019) and recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants and no clear statement of some findings in both studies (Snounou; Pemberton 2019); moderate concerns regarding adequacy, with no clear statement of the finding in either study; PEM reanalysis: moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies (Pemberton 2019; Snousnou)*

[e]*Two studies with serious methodological limitations due to unclear consideration of ethical issues, data analysis by an individual researcher and insufficient data presented to support all findings in one study (Snounou), unclear methods of data analysis in one study (Pemberton 2019) and recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants and no clear statement of some findings in both studies (Snounou; Pemberton 2019); moderate*

concerns about the coherence of the finding with one study suggesting that science was beneficial (Snounou) and the other suggesting that people wanted less medical content (Pemberton 2019); minor concerns regarding relevance due to lack of information on participant characteristics in one study (Pemberton 2019); moderate concerns regarding adequacy, with no clear statement of the finding in either study; PEM reanalysis: moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies (Pemberton 2019; Snousnou)

[f]Two studies with serious methodological limitations due to unclear consideration of ethical issues, data analysis by an individual researcher and insufficient data presented to support all findings in one study (Snounou), unclear methods of data analysis in one study (Pemberton 2019) and recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants and no clear statement of some findings in both studies (Snounou; Pemberton 2019); minor concerns regarding relevance due to lack of information on participant characteristics in one study (Pemberton 2019); moderate concerns regarding adequacy, with no clear statement of the finding in either study; PEM reanalysis: moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies (Pemberton 2019; Snousnou)

Table 87: Summary of evidence: Complementary and alternative therapies

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Range of complementary and alternative therapies					
1	Mixture of structured and semi structured questions interviews	People desperate for relief of symptoms tried a wide range of different alternative therapies.	Limitations	Moderate concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Holistic approach					
1	Mixture of structured and semi	People with ME/CFS were attracted to alternative therapies by a holistic approach.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	structured questions interviews		Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[b]	
Positive therapist approach					
1	Mixture of structured and semi structured questions interviews	Therapists' positive approaches gave people hope that it was possible to overcome the illness.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[b]	
Effectiveness					
2	Mixture of structured and semi	Evaluations of the effectiveness of alternative therapies were mixed. Some experienced temporary effectiveness which reinforced their beliefs in these therapies.	Limitations	Moderate concerns about methodological limitations[c]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	structured questions interviews		Coherence	Moderate concerns about coherence[c]	
			Relevance	Moderate concerns about relevance[c]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [c]	
			Adequacy	Minor concerns about adequacy[c]	
Follow up					
1	Mixture of structured and semi structured questions interviews	Several people with ME/CFS were impressed that unlike their regular doctors, alternative therapists called periodically to find out how they were managing.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[b]	

[a]*One study with serious methodological limitations due to identification of HCPs by patients with ME/CFS, unclear relationship between participants and researcher, data analysis by a single researcher and no clear statement of findings (Beaulieu 2000) and nothing to lower our confidence in the other contributing study (de Carvalho Leite 2011); moderate concerns regarding relevance due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011); minor concerns about adequacy as there were no clear statements of findings in one study (Beaulieu 2000); PEM reanalysis: serious concerns regarding relevance with serious concerns in both contributing studies due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM in one study (Beaulieu 2000), lack of details on diagnosis (including PEM) of the purposive sample used in the other study (de Carvalho Leite 2011) and due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011)*

[b]One study with serious methodological limitations due to identification of HCPs by patients with ME/CFS, unclear relationship between participants and researcher, data analysis by a single researcher and no clear statement of findings (Beaulieu 2000); moderate concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study; PEM reanalysis: serious concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study and due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM (Beaulieu 2000).
[c]One study with serious methodological limitations due to identification of HCPs by patients with ME/CFS, unclear relationship between participants and researcher, data analysis by a single researcher and no clear statement of findings (Beaulieu 2000) and nothing to lower our confidence in the other contributing study (de Carvalho Leite 2011); moderate concerns regarding coherence as effectiveness was mixed in one study (Beaulieu 2000), but alternative therapies were reported to be helpful overall in the other study (de Carvalho Leite 2011); moderate concerns regarding relevance due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011); minor concerns about adequacy as there were no clear statements of findings in one study (Beaulieu 2000); PEM reanalysis: serious concerns regarding relevance in the contributing studies due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM in one study (Beaulieu 2000), lack of details on diagnosis (including PEM) of the purposive sample used in the other study (de Carvalho Leite 2011) and due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011)

Table 88: Summary of evidence: Pharmacological interventions

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Antidepressants					
1	Survey including open ended questions	Antidepressants were prescribed for ME symptoms by health care professionals, and people experienced negative side effects.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[a]	

[a]One study with serious methodological limitations due to recruitment through a single ME/CFS charity, unclear detail on specific interventions received, unclear consideration of ethical issues, limited detail reported on methods of data analysis and no clear statement for all findings (Leary 2019); moderate concerns regarding relevance due to lack

of information on participant characteristics in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding with elaboration and examples and evidence only based on one study.

[b] Moderate concerns regarding relevance due to lack of information on participant characteristics including PEM which was self-reported in the contributing study.

Children/young people (severity mixed/unclear)

Table 89: Summary of evidence: Cognitive behavioural therapy

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Relationship with the therapist					
1	Semi structured interviews	The therapist's personality and interpersonal skills were important. Having somebody to talk to who was interested in and understood CFS was a key positive feature of therapy sessions.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Acceptability of FITNET-NHS platform/ e-consultations					
1	Semi structured interviews	People liked that they could complete the platform in their own time and think about their answers. Some found it easier to talk about personal topics over email, whereas others found it difficult	Limitations	No or very minor concerns about methodological limitations	MODERATE

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
		to portray things in writing and would have preferred some face to face contact.	Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[b]	
Validation					
1	Semi structured interviews	Recognition, validation and emotional support were almost always cited as important and benefits were appreciated regardless of whether other aspects of the therapy were deemed useful.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Behavioural aspects					
1		The behavioural aspects of the therapy were particularly valued and accepted by the young people, although many struggled	Limitations	No or very minor concerns about	LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	Semi structured interviews	putting them in to practice. Tasks were often initially very hard to achieve and parents found it challenging to watch their children push themselves.		methodological limitations	
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Personalised care					
2	Semi structured interviews	Some parents felt the agenda during the sessions was too narrow and rigid and therefore unresponsive to families' idiosyncratic issues. Participants valued the individual tailored advice from a specialist CFS/ME therapist.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[c]	PEM reanalysis: LOW
			Relevance (PEM)	Serious concerns about relevance[c]	
			Adequacy	No or very minor concerns about adequacy	
Inclusion of the family					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Semi structured interviews	Sessions functioned as support for parents and young people felt they needed their parent/s at the sessions for emotional support. Despite this, many felt that there were certain situations and issues where the young person should have been seen alone.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Psychological aspects					
1	Semi structured interviews	Several disliked the 'psychological' or 'emotional' aspects, finding them irrelevant or inappropriate. Some felt pigeonholed and subjected to generalisations.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Effectiveness					
1	Semi structured interviews	The therapy was useful to some extent, the family was thankful for the help, but improvements were modest. However, the therapy was a principle factor in regaining normality and viewed as a 'starting block' on a gradual journey to recovery.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Effectiveness					
1	Semi structured interviews	Some young people with ME/CFS and depression found CBT helpful and the combination treatment of CBT and medication was also discussed.	Limitations	Minor concerns about methodological limitations[d]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[d]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[d]	
			Adequacy	Minor concerns about adequacy[d]	

[a]*Moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study (Dennison 2010); minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study; PEM reanalysis: serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis (Dennison 2010).*
[b]*Minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study (Anderson);* PEM reanalysis: m*oderate concerns regarding relevance as participants fulfilled criteria where PEM was not compulsory (Anderson).*
[c]*Minor concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in one study (Dennison 2010), but no concerns in the other study (Anderson);* PEM reanalysis: *serious concerns regarding relevance with serious concerns in one study due to findings for both CBT and psychoeducation interventions being combined in one study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis (Dennison 2010), and moderate concerns in the other study as participants fulfilled criteria where PEM was not compulsory (Anderson). .*
[d]*One study with minor methodological limitations due to insufficient data presented to support all findings, with some supported by single quotes and no clear statement of all findings (Taylor 2017); moderate concerns regarding relevance due to the study population having comorbid depression in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study; PEM reanalysis: serious concerns regarding relevance due to the study population having comorbid depression and no details available on PEM (Taylor 2017).*

Table 90: Summary of evidence: The Lightning Process

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Relationship with the therapist					
1	Semi structured interviews	Therapists and staff were mostly described as positive and encouraging. There were different opinions about the therapists; some had only good experiences, while others found their therapist too controlling and not open for critical questions. Alternative viewpoints brought up by the young people were not well-received and a few experienced pressure to be happy all the time and not express any negative feelings. Those who did not recover felt that they were blamed for the lack of treatment success and consequently struggled with feelings of guilt and anger.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Dishonesty					
1	Semi structured interviews	People criticised the impression that staff gave about the Lightning Process always involving a quick recovery and the dishonesty staff showed when they claimed the treatment had a 100% success rate.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Theory behind the Lightning Process					
1	Semi structured interviews	The educational part of the treatment, including the theory behind the Lightning Process and practical examples of previous success stories, gave people a rationale they could believe in.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy[a]	
Confusing					
1	Semi structured interviews	The educational part of the intervention was considered as complicated and difficult to understand, but necessary and helpful. Some found the teaching incomplete and not well-organised. Advice that participants could do anything they wanted conflicted with previous advice they had been given around activity pacing.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Peer support					
1	Semi structured interviews	The support from others and the group setting that allowed people to learn from each other was highlighted as helpful aspects leading to engagement and treatment commitment.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Goal setting					
1	Semi structured interviews	The focus on specific goals and identifying barriers from reaching them was considered a helpful part of treatment.	Limitations	Moderate concerns about methodological limitations[b]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Moderate concerns about adequacy[b]	
Practice and application					
1	Semi structured interviews	The practical assignments were described as important for rapid recovery. People realised that it was their own choice that would really help them recover and the behavioural aspects of the treatment stood out as the most important factor for symptom alleviation and continuing recovery.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Intensity					
1	Semi structured interviews	The length of the sessions was thought to be too long and intense, especially since many participants struggled with focus and concentration.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Follow up					
1	Semi structured interviews	Some described the whole treatment as too short; with too little follow up afterwards.	Limitations	Moderate concerns about methodological limitations[b]	LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Moderate concerns about adequacy[b]	
Effectiveness					
1	Semi structured interviews	Some experienced an instant healing, some experienced a gradual improvement that continued after treatment ended and some did not find the treatment helpful.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Secrecy					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	The secrecy surrounding the Lightning Process was criticised and thought to result in unnecessary sceptical and prejudiced attitudes from people. Participants were specifically encouraged not to talk to anyone about it and they found this unhelpful and difficult.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	

[a]*One study with moderate methodological limitations due to recruitment through a single charity and insufficient data presented to support all findings (Reme 2013); minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study.*
[b]*One study with moderate methodological limitations due to recruitment through a single charity and insufficient data presented to support all findings (Reme 2013); moderate concerns about adequacy as the evidence is not sufficiently deep and only based on one study.*
[c] Moderate concerns about relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met.

Table 91: Summary of evidence: The Lightning Process (mild/moderate severity)

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Validation					
1	Semi structured interviews	The service recognised and acknowledged the young person's condition, resulting in a sense of relief and reassurance that symptoms were now being understood and they would receive help.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Personalised care					
1	Semi structured interviews	Families had access to an informative team of experts, for some a formal diagnosis, and for all a tailored, patient centred specialist medical intervention that had not been available earlier. This enabled positive change and steps towards a managed recovery.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Professional support					
1	Semi structured interviews	Some found specialist medical care to be positive, as it enabled them to talk about their illness and gave guidance on how to	Limitations	Minor concerns about methodological limitations[a]	LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
		manage their condition, which brought structure and a sense of normality back into their lives.	Coherence	No or very minor concerns about coherence	(PEM reanalysis: no change)
			Relevance	Moderate concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Challenges of a new routine					
1	Semi structured interviews	Some people reported that, although specialist medical care resulted in better symptom management, accepting that for a time they must reduce activity levels and adopt a routine was challenging. Mothers also noted that specialist medical care strategies had an impact on the whole family and could be difficult to integrate with their lifestyle.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Minor concerns about adequacy[a]	
Dialogue between healthcare professionals and education providers					
1	Semi structured interviews	The service opened channels of dialogue between health-care professionals and education providers.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy[a]	

[a] *One study with minor methodological limitations due to an unclear relationship between the researcher and participants and some findings supported by single quotes only (Beasant 2014); moderate concerns regarding relevance as the contributing study aimed to understand the experiences of accessing as well as using a specialist service and some participants had not yet used the service and it was unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study.*

Table 92: Summary of evidence: Graded exercise therapy/other exercise interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Exercise enjoyable					
1	Semi structured interviews	Despite mixed preconceptions, most participants were positive about GET once they entered treatment and reported positive experience of the exercises.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy[a]	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Routine and structure					
1	Semi structured interviews	Many families explained that the program introduced routine, which they experienced as important.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Relationship with therapist					
1	Semi structured interviews	Many families valued the support they received from their clinician in terms of having someone listen and understand and feeling cared for.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Personalised care					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Families praised the way the program was tailored so that the clinician identified the individual needs of the young person and collaboratively developed a tailored treatment plan, recognising the fluctuating nature of 'CFS/ME' and that physical capabilities change. Families also reported that they gained extra advice beyond the central focus on activity, such as sleep or diet, when these came up for participants.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Pacing benefits					
1	Semi structured interviews	Some commented that the treatment set helpful boundaries to avoid a pattern of overexertion and that clinicians were flexible in reducing the activity if the increase had been too rapid/ too much.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Pacing challenges					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Some found limiting activity was challenging, with evidence that the young person resisted this advice, wanting to do more physical exercise. Concerns about activity reduction included social effects and difficulties with limiting walking in school.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Setbacks					
1	Semi structured interviews	Families described that the young person had a setback or "crash" during the course of treatment, as a result of exceeding the recommended limits of physical activity. Travel to the hospital site for appointments contributed to setbacks.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
FITBITS and physical monitoring					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Participants commented positively on the use of wearables to accurately detect physical activity, as this demonstrated when they were doing too much and provided other useful functionality such as sleep or steps monitoring in addition to heart rate monitoring. Some comments indicated that the measurements were not always accurate.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Positive outcomes					
1	Semi structured interviews	There was overall recognition that the young people had benefitted from GET, including reductions in fatigue and tiredness, improved sleep, ability to concentrate, functioning and mood.	Limitations	No or very minor concerns about methodological limitations	LOW (no change after PEM reanalysis)
			Coherence	Moderate concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[c]	
Uncertain/lack of difference from treatment					
1			Limitations	No or very minor concerns about	LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	Semi structured interviews	Some families did not notice a difference with treatment, either reporting uncertainty, or lack of impact, often related to school and cognitive activities.		methodological limitations	(no change after PEM reanalysis)
			Coherence	Moderate concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[c]	

[a]*Moderate concerns regarding adequacy due to there being no elaboration or examples of positive experiences and the finding only being based on one study (Brigden (Beasant)).*
[b]*Minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study (Brigden (Beasant)).*
[c]*Moderate concerns regarding coherence as the finding conflicts with another finding from the same study (Brigden (Beasant)); minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study.*

Table 93: Summary of evidence: Complementary and alternative therapies

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Alternative therapies					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Some families sought treatments such as acupuncture, dietician input, sickness bands and the emotional freedom technique, while others spoke to their CFS/ME clinician for advice. External support varied greatly in perceived accessibility and helpfulness.	Limitations	Moderate concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	

[a]*One study with moderate methodological limitations due to involvement of clinicians in determining participant eligibility that may have introduced selection bias and lack of data richness (Harris 2017); moderate concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties in the contributing study; moderate concerns regarding adequacy, with no elaboration or examples and evidence only based on one study; PEM reanalysis: serious concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties in the contributing study and it being unclear whether diagnosis had been based on PEM.*

Table 94: Summary of evidence: Pharmacological interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Sickness/stomach acid relief medication					

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Some took prescribed sickness or stomach acid relief medication which they found helpful. However, it was not common to have been offered medication to relieve their symptoms which frustrated some people.	Limitations	Moderate concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[a]	
Attitude toward medication					
1	Semi structured interviews	Young people generally did not mind taking medication providing they found it helpful.	Limitations	Minor concerns about methodological limitations[c]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[c]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance [d]	
			Adequacy	Moderate concerns about adequacy[c]	

[a]*One study with moderate methodological limitations due to involvement of clinicians in determining participant eligibility that may have introduced selection bias and lack of data richness (Harris 2017); moderate concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties in the contributing study;; moderate concerns regarding adequacy, with no elaboration or examples and evidence only based on one study.*

[b] *serious concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties and it being unclear if participants had PEM (Harris 2017)*

[c]*One study with minor methodological limitations due to insufficient data presented to support all findings and no clear statement of all findings (Taylor 2017); moderate concerns about relevance due to the study population having comorbid depression;; moderate concerns regarding adequacy, with no elaboration or examples and only based on one study.*

[d] *Serious concerns about relevance due to the study population having comorbid depression and it being unclear if participants had PEM (Taylor 2017)*

3 The committee's discussion and interpretation of the evidence

The committee's discussion on the evidence reviews for the clinical and cost-effectiveness of non-pharmacological interventions and the experiences of people who have had interventions for ME/CFS are included here.

The committee discussed this evidence with the findings from the review on access to care (report C), diagnosis (report D), multidisciplinary care (report I) and the reports on Children and Young people (Appendix 1) and people with severe ME/CFS (Appendix 2). Where relevant this is noted.

3.1 The outcomes that matter most

Review of clinical and cost effectiveness

Mortality, quality of life, general symptom scales, fatigue/fatigability, physical function, cognitive function, psychological status, pain, sleep quality, treatment-related adverse events, activity levels, return to school/work and exercise performance measures were agreed by the committee to be critical outcomes for decision making.

The committee was aware of concerns from the ME/CFS community that delays in diagnosis and the potential for inappropriate advice on activity and rest could result in deterioration of symptoms and poorer prognosis for people who are later diagnosed with ME/CFS. Fatigue/fatigability, unrefreshing sleep and physical and cognitive dysfunction are recognised as key symptoms of ME/CFS. The worsening or improvement of these symptoms reflect the impact of an intervention or strategy. The committee agreed that pain though not key to the diagnosis of ME/CFS, is a common symptom in people with ME/CFS and should be considered by the committee in their decision making. The committee agreed that any decisions on interventions and strategies should be informed by treatment related adverse events as a possible indicator of harm.

Care needs, impact on families and carers and ability to resume occupation, school or study were considered important outcomes for decision making reflecting the effectiveness of an intervention.

The committee acknowledged the lack of existing objective outcome measures of effectiveness of interventions for ME/CFS and the limitations of subjective measures (see Professor Edwards expert testimony – Appendix 3: Expert testimonies). Only validated outcome measurement scales were included in the evidence review.

No evidence was identified for mortality, care needs or impact on families and carers.

Qualitative review of experiences of interventions

Themes emerging from qualitative data regarding experiences of people that have had interventions for ME/CFS and the benefits and harms they experienced. Themes were derived from the evidence identified and were not pre-specified by the committee.

Only findings that were relevant to the review question were included; findings related to people's experiences of general ME/CFS services rather than specific interventions were not extracted.

3.2 The quality of the evidence

3.2.1 Summary of quality for review of clinical and cost effectiveness

Evidence from 55 studies was identified for the following non-pharmacological interventions; self-management (n=4), behavioural/psychological support (including cognitive behavioural therapy (n=19), buddy/mentor programmes (n=2), pragmatic/other rehabilitation programmes (n=1), mindfulness (n=3), group therapy (n=1), education and support groups (n=1), cognitive therapy (n=1), and the Lightning Process (n=1)),exercise therapies (including graded exercise therapy (n= 3), intermittent exercise (n=1), orthostatic training (n=1), qigong (n=1) and anaerobic exercise (n=1), complementary therapies (n=6), dietary strategies (n=1), and dietary supplementation (n=8). No evidence was identified for aids/adaptations/occupational therapy, occupational/school advice, repetitive transcranial magnetic stimulation, compression socks, hyperbaric oxygen, lifestyle advice, sleep interventions, or non-pharmacological pain management interventions.

Most of the interventions were compared with usual care. There was substantial variation in the completeness of descriptions of the interventions and comparators between the studies. The study populations were mainly adults with 6 studies identified in children and young people. The severity of ME/CFS was mixed or unclear in most of the studies for both adults and children; only two studies defined populations, one had a severe ME/CFS population and the other a moderate ME/CFS population.

The overall quality of the evidence for the interventions is described here. Where there are differences in the quality of evidence for individual interventions they are described below.

The majority of the evidence was of low and very low quality. The main reasons for downgrading were risk of bias, indirectness and imprecision. There was a lack of blinding of participants in the studies due to the nature of the interventions. This, combined with the mostly subjective outcomes, resulted in a high risk of performance bias. Performance bias occurs when knowledge of which intervention was received affects outcomes, rather than the intervention itself, and subjective outcomes are particularly at risk of being affected by performance bias (for example based on expectations or resulting changes in behaviour). The committee acknowledged the difficulty in blinding non-pharmacological trials; however, this was still an important limitation they considered when interpreting the evidence. This is not a limitation which is unique to non-pharmacological trials in ME/CFS.

After considering the stakeholder comments the committee agreed to revisit the evidence for the intervention reviews, further scrutinising the information on PEM reported in the trials and the application of indirectness in the evidence. For outcomes that were reanalysed, this did not result in any changes to the overall quality rating of the evidence. Further information on this analysis is briefly summarised elsewhere in this section (full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence Appendix G in Evidence Review H). Most of the comparisons only included one study. Therefore, evidence for most outcomes was based on single studies, many of which included small sample sizes. This resulted in imprecision around the point estimates.

Population indirectness

The committee discussed the CDC 1994 diagnostic criteria used in the studies to recruit eligible participants. The committee have identified PESE as an essential symptom that is central to the diagnosis of ME/CFS (see evidence report D: diagnosis) and the CDC 1994 criteria does not include this as a compulsory requirement. It should be noted that PESE is referred to as post exertional malaise (PEM) in the criteria, but PESE is the committee's preferred term. The committee agreed that a population diagnosed with such criteria may not accurately represent the ME/CFS population and that people experiencing PEM/PESE may respond differently to treatment than those who do not experience PEM/PESE and this

raised concerns over the generalisability of findings to the ME/CFS population. It was therefore agreed to downgrade the evidence for population indirectness.

After considering the stakeholder comments the committee agreed to revisit the evidence for the intervention reviews further scrutinising the information on PEM reported in the trials and the application of indirectness in the evidence. As part of this they agreed that any evidence with a population ≥ 95% with PEM would be considered direct. Studies where < 95% of participants had PEM, or where the percentage of participants with PEM was not reported would be considered indirect. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Evidence was not stratified by diagnostic criteria used, so theoretically, studies including potentially different populations could have been combined. In practice, for the majority of outcomes, meta-analysis was not appropriate due to important differences between the types of interventions, comparators, population strata, or multiple relevant measures of the same outcome being reported within the same study. Therefore, potentially different populations were rarely combined. Where they were combined, no serious heterogeneity was identified.

Evidence quality by intervention

Self-management (pacing)

Adults

Evidence from 4 randomised controlled trials were identified for self-management interventions. Three studies compared self-management to usual care and one to relaxation. The quality of the evidence ranged from moderate to very low. No evidence was identified for mortality, cognitive function, activity levels, care needs or impact on families and carers. The severity of ME/CFS was mixed or unclear in most of the studies, with one study in a population of people with severe ME/CFS.

Children

One randomised controlled trial was identified. The quality of the evidence was low to very low. No evidence was identified for mortality, physical function, cognitive function, pain, sleep quality, treatment-related adverse events, activity levels, exercise performance measures, care needs and impact on families and carers. The population included children with severe ME/CFS.

Cognitive behavioural therapy

Adults

Evidence from 15 randomised controlled trials were identified for CBT. Eight studies compared CBT to usual care, and single studies compared CBT to psychoeducation, education and support group, multidisciplinary rehabilitation, relaxation, adaptive pacing therapy, graded exercise therapy, counselling and cognitive therapy and anaerobic activity therapy. The quality of the evidence ranged from low to very low quality. No evidence was identified for mortality, care needs and impact on families and carers. The severity of ME/CFS was mixed or unclear in most of the studies, with one study in a population of people with moderate ME/CFS.

Children and young people

Evidence from 4 randomised controlled trials were identified for CBT. Three studies compared CBT to usual care/waiting list and one study to psychoeducation and pacing. The quality of the evidence ranged from low to very low quality. No evidence was identified for

mortality, quality of life, psychological status, sleep quality, activity levels, exercise performance measures, care needs and impact on families and carers.

Other psychological/behavioural interventions

Adults

Buddy mentor programmes

Evidence from two randomised controlled trials compared buddy mentor programmes to no intervention and a waiting list. The quality of the evidence was very low quality. No evidence was identified for mortality, fatigue/fatigability, cognitive function, pain, sleep quality, treatment-related adverse events, activity levels, return to school/work, exercise performance measures, care needs and impact on families and carers.

Pragmatic/ rehabilitation programmes

Evidence from one randomised controlled trial compared a programme of graded return to activity based on a physiological dysregulation model to usual care and with supportive listening. The quality of the evidence was low to very low quality. No evidence was identified for mortality, quality of life, general symptom scales, cognitive function, pain, treatment-related adverse events, activity levels, return to school/work, care needs and impact on families and carers.

Mindfulness

Evidence from one randomised controlled trial compared mindfulness and medical qigong to usual care. Evidence from two randomised controlled trials compared mindfulness based cognitive therapy to waiting list control. The quality of the evidence was very low quality. No evidence was identified for mortality, quality of life, general symptom scales, cognitive function, pain, sleep quality, activity levels, return to school/work, exercise performance measures, care needs and impact on families and carers.

Group therapy

Evidence from one randomised controlled trial compared focused group therapy to waiting list control. The quality of the evidence was very low quality. No evidence was identified for mortality, general symptom scales, fatigue/fatigability, physical function, cognitive function, psychological status, pain, sleep quality, treatment-related adverse events, activity levels, return to school/work, exercise performance measures, care needs and impact on families and carers.

Education and support groups

Evidence from one randomised controlled trial compared an education and support group with usual care. The quality of the evidence was very low quality. No evidence was identified for mortality, general symptom scales, fatigue/fatigability, physical function, pain, sleep quality, treatment-related adverse events, activity levels, return to school/work, care needs and impact on families and carers.

Cognitive therapy versus relaxation

Evidence from one randomised controlled trial with adults with moderate severity ME/CFS compared cognitive therapy to relaxation. The quality of the evidence was very low quality. No evidence was identified for mortality, cognitive function, sleep quality, treatment-related adverse events, activity levels, care needs and impact on families and carers.

Children

Lightning Process

Evidence from one randomised controlled trial compared the Lightning Process in addition to specialist medical care to specialist medical care. The quality of the evidence was low to very low quality. No evidence was identified for mortality, quality of life, general symptom scales, cognitive function, sleep quality, activity levels, exercise performance measures, care needs and impact on families and carers.

Graded exercise therapy

Adults

Evidence from 12 randomised controlled trials were identified for graded exercise therapy. Six studies compared graded exercise therapy to usual care, two studies to flexibility/relaxation, and single studies compared graded exercise therapy to heart rate variability feedback, adaptive pacing, intermittent exercise, and activity dairies. The quality of the evidence ranged from low to very low quality. No evidence was identified for mortality, care needs and impact on families and carers. The severity of ME/CFS was mixed or unclear in all of the studies and one study included young people and adults.

Other exercise interventions

Evidence from 3 randomised controlled trials compared types of exercise (intermittent exercise, orthostatic training and qigong) to non-active controls (usual care, sham, no treatment) and 1 randomised controlled trial compared anaerobic activity therapy to cognitive therapy or relaxation. The quality of the evidence was very low quality. No evidence was identified for mortality, cognitive function, psychological status, pain, sleep quality, treatment-related adverse events, activity levels, care needs and impact on families and carers.

Complementary and alternative therapies

Evidence from 6 randomised controlled trials compared different complementary therapies in single studies; isometric yoga to usual care, Chinese music therapy in combination with traditional Chinese medicine to traditional Chinese medicine alone, homeopathy compared with placebo, acupuncture and sham acupuncture, and abdominal tuina massage with acupuncture. The quality of the evidence was low to very low quality. No evidence was identified for mortality, general symptom scales, physical function, cognitive function, pain, sleep quality, activity levels, return to school/work and exercise performance measures were considered by the committee to be critical outcomes for decision making. Care needs and impact on families and carers were also considered to be important outcomes.

Dietary strategies

Evidence from one small randomised controlled trial compared a low sugar, low yeast diet to healthy eating advice. The quality of evidence was very low. There was no evidence for mortality, general symptom scales, physical function, cognitive function, pain, sleep quality, treatment-related adverse events, activity levels, return to school/work and exercise performance measures were considered by the committee to be critical outcomes for decision making, care needs and impact on families and carers.

Dietary supplementation

Evidence from 8 randomised controlled trials compared different supplements to placebo in single studies; acclydine with amino acids, poly-nutrient supplement, aribinoxylane (biobran), vitamin D supplement, coenzyme Q10 with NADH, guanidinoacetic acid an myelophil. The evidence was very low to low quality. No evidence was identified for mortality, physical function, return to school/work and exercise performance measures, care needs and impact on families and carers.

3.2.2 The quality of the evidence - qualitative review of experiences of interventions

Evidence was identified on experiences of CBT, counselling, the Lightning Process, GET, education/information interventions, rehabilitation/condition management programmes and alternative therapies for ME/CFS. This included evidence identified from database searching (n=13) and from a call for evidence (n=13).

The majority of studies were of adults and the severity of ME/CFS was mixed or unclear in the majority of the studies for both adults and children. A variety of qualitative methodologies were used to inform the research. Confidence in the review findings was mainly rated as moderate to very low. The main reasons for downgrading were concerns regarding methodological limitations and adequacy.

Several studies had limitations around the recruitment strategies, such recruitment solely from one source, such as a ME/CFS charity. There was a lack of detail reported on the relationship between the researchers and the participants in many of the studies, making it unclear whether the relationship could have influenced the data gathered. In some studies, the methods of data analysis were not clearly reported making it unclear if the methods used were sufficiently rigorous. Presentation of findings was also limited in some studies, where for example, a clear statement of the finding was not presented, or the finding was supported by a single quote only.

Data were stratified by adults and children/young people, condition severity and type of intervention, therefore the evidence for several of the strata was based on individual studies. This led to concerns regarding data adequacy, as some studies had small sample sizes and may not be adequately represent the wider context. However, understanding the experience of different groups about the different interventions was considered important when review was planned.

Some studies were based on subpopulations, so findings were downgraded due to concerns regarding relevance. For example, one study included only people who experienced eating difficulties, so the findings may not be applicable to the wider ME/CFS population.

In general, the committee placed greater weight on moderate confidence findings than low and very low confidence findings during discussion of the evidence, although they acknowledged that some lower confidence findings reflected their own experience and should not be disregarded. The committee also acknowledged that some common themes were identified across multiple review strata and that lower confidence findings contributing to these themes could be interpreted with higher confidence when considered across studies.

After considering the stakeholder comments about the inclusion of PEM in the diagnostic criteria of ME/CFS being applied differently across the quantitative and the qualitative evidence, the committee agreed to revisit the evidence for the intervention reviews further scrutinising the information on PEM reported in the studies and its impact on concerns over applicability at the individual study level and in turn, on the relevance rating given to the findings that the studies contributed to. The committee agreed the requirement of PEM was particularly important in the studies evaluating interventions as they considered that the response to an intervention is likely to be different in people who have PEM compared to those who do not, and this should be taken into account when interpreting the evidence (full details of the approach taken, and the impact on the results and interpretation of the evidence are in Appendix F- PEM reanalysis in Evidence Review H).

3.3 Benefits and harms

Benefits and harms of each non-pharmacological intervention were reviewed and discussed by the guideline committee. These are outlined below by intervention with the clinical and cost-effectiveness evidence and discussion followed by the experience of the intervention concluding with an overall summary.

The interventions (in this order are): self-management, cognitive behaviour therapy, other psychological/behavioural interventions, graded exercise therapy, other exercise interventions, complementary therapy, dietary strategies and dietary supplements.

Self-management

Review of clinical and cost effectiveness

Adults

The self-management programmes used activity pacing to support people to regulate and balance their energy levels. The delivery and the content of the interventions varied. Delivery of the programmes included training sessions, online booklets and videos. Diaries and step counters were used to monitor activity in two studies.

Most of the evidence showed no clinical difference between self-management strategies and any of the comparison groups (usual care or relaxation). The evidence on the SF36 quality of life was mixed, with clinical benefit being shown on the physical, social functioning, emotional, mental health and subscales a small study comparing self-management to relaxation and no difference on the mental and physical components when compared to usual care. The difference in reporting the SF36 was noted. Fatigue (as measured on the fatigue severity scale) showed no clinical difference in the evidence compared to usual care in a population of mixed severity and a benefit for self-management strategies in one study with a population of people with severe ME/CFS.

Serious adverse events were reported in one study with harm identified in the adaptive pacing group, the committee noted that adverse events were any new health related event reported by the participant in any context (treatment related or not) and could not be easily attributed to the intervention and this was from very low quality evidence. There was no clinical difference between the study arms in non-serious adverse events (treatment related or not) and adverse reactions (treatment-related) reported in the same study.

The committee discussed the lack of standardisation of techniques in the programmes and concerns were raised about the term 'pacing' as there is no standard definition and there are a range of different interpretations. The committee noted that most of the evidence was of very low quality showing no difference and where clinical benefits were identified for quality of life and fatigue there was other evidence showing no difference. In addition, the evidence for clinical benefit was low to very low quality evidence and the committee was not confident about the effect.

The committee considered why the evidence showed no difference between adaptive pacing therapy and usual care. It was suggested that a possible explanation was that the extra information in the adaptive pacing group was beneficial but negated by the extra effort it took to take part. Some committee members felt that the adaptive pacing therapy intervention trialled encouraged an increase in activity and therefore was not a true 'pacing' intervention. In addition, the definition of specialist medical care in the trial was considered by the committee to include elements of pacing, such as a patient leaflet which included avoiding extremes of activity, which may have led to an underestimation of the effect of the intervention.

Children and young people

The evidence came from one small study evaluating the Stairway to health programme to adaptive pacing. The effects were inconsistent. No clinical difference was found for psychological status (both depression and anxiety). Clinical benefit for the programme was shown for quality of life, functional ability and return to school and the fatigue scores increased in the programme group. The committee noted that the evidence was low to very low quality and the committee was not confident about using this evidence to make any recommendations for children and young people.

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of self-management interventions

No evidence was identified on people's experiences of self-management interventions for ME/CFS, however evidence identified for other interventions included findings related to self-management support.

Adults who had experienced interventions that encouraged self-management techniques, such as reviewing activities, use of diaries, knowing their limits, prioritisation, valued the support to learn these skills and strategies. They reported these techniques helped them to feel more in control, cope with their illness, reduce stress and manage expectations. Help with understanding and setting baselines was also identified as an important outcome. Conversely, some people reported that in the in the early stages of activity related counselling interventions people reported that they could make errors resulting in in periods of crushing fatigue and pain.

Although most of the evidence was low quality the committee agreed it reflected their experience. As well as recognising the benefits of teaching self-management strategies it is important that people have access to support if they overexert themselves.

Overall – self management

The committee considered that the interventions included in the effectiveness review were of mostly low to very low quality, heterogeneous in terms of their composition, duration, intensity and personnel, which made drawing conclusions about the overall effectiveness of self-management interventions difficult. The committee discussed the findings in the qualitative review. The committee noted the importance of individualised and symptom dependent advice, the inclusion of families and carers, reminding people that it is okay not to push themselves, having permission and support to say 'no', and an appropriate level of monitoring and review.

The committee discussed that pacing is the main self-management tool used by many people with ME/CFS and noted pacing is often used as one of the first steps of interventions such as cognitive behavioural therapy (CBT) to stabilise a person's activity levels. The committee considered the evidence regarding the best self-management strategy is unclear and that in their experience people with ME/CFS use their own individual self-management strategies without the need for a specific intervention. Taking this into account the committee did not make a recommendation for any particular self-management strategy identified in the evidence included in this review, but recognised the benefits of self-management strategies for people with ME/CFS and the importance of having access to personalised advice as part of their care and support plan that supports them to learn to use the amount of energy they have while reducing their risk of post-exertional malaise or worsening their symptoms by exceeding their limits. The committee agreed it is important that people with ME/CFS are

offered information about self-management strategies and the qualitative evidence showed that people valued this type of information and support. The committee noted that energy management includes some of the components that are identified in this type of intervention (such as, activity monitoring) and reflected these components in the recommendations on energy management and flare-ups and relapse.

The committee acknowledged that some people found that technologies, such as activity trackers helpful and recommended that people could use the tools they already have. In response to the lack of research in activity management strategies and the high interest in how tools can be used to support people with ME/CFS the committee made a research recommendation.

Cognitive behavioural therapy (CBT)

Review of clinical and cost effectiveness

Adults

CBT versus usual care

The interventions comparing CBT to usual care varied in their delivery from one to one therapy, group therapy and web-based interventions. The present evidence review did not look at studies comparing different modes of intervention delivery and the current evidence base was not sufficient to allow us to draw conclusions about the benefit of any particular mode of delivery over another.-.

One study compared CBT with GET to usual care and showed no clinical difference in quality of life, general symptom scales, physical functioning, or pain. Most of the evidence showed no clinical difference for CBT compared to usual care or waiting list for quality of life, cognitive function, physical function, psychological status, pain, and sleep quality.

There was benefit of CBT for activity levels in two studies (actigraphy score, days in bed per week, and interference with activities). There was some, but not consistent, evidence across the studies showing both clinical benefit and no clinical difference for general symptom scales (benefit for Sickness Impact Profile-8 but not for Clinical Global Impression Scale), fatigue (mixed results with various scales), physical functioning (mixed results with SF-36 sub-scale), exercise performance (benefit for walking speed and shuttles walked but not 6 minute walk test), and return to work (mixed results for Work and Social Adjustment Scale).

Adverse event reporting came from two studies. One study showed a higher rate of adverse events (fatigue, pain, distress and other) in the waiting list/usual care arm. The other study showed no clinical difference between study arms for non-serious and serious adverse events (treatment-related or not), and adverse reactions (treatment-related).

CBT versus other interventions

Most of the evidence for CBT versus other studies came from small single studies.

-
- Psychoeducation
    - There was no clinically important difference for quality of life (Quality of life inventory), general symptom scales (CFC symptom inventory), psychological status (Profile of mood states and Perceived stress scale).
- Education and support
    - There was no clinically important difference for quality of life (SF36 physical and mental components and HUI3), fatigue (Chalder fatigue scale), cognitive function (word recall and reaction time), psychological status (Hospital anxiety and

depression scales and General health questionnaire), and exercise performance (walking speed, shuttles walked, and perceived exertion during physical activity).

- Multidisciplinary rehabilitation
  - Clinical benefit of CBT was seen for fatigue (Checklist individual strength fatigue severity).
  - There was no clinically important difference for quality of life (SF36 physical and mental components), general symptom scales (Sickness impact profile), psychological status (symptom checklist-90), and activity levels (measured by accelerometer).
- Relaxation
  - In two studies, one with a population of mixed severity and one with a population of moderate severity, clinical benefit of CBT was seen for general symptom scales (global impression of change rating) and return to work (number in employment). In the study with a mixed severity population clinical benefit was also seen for fatigue (chalder fatigue scale and fatigue problem rating) and physical functioning (SF36 sub scale). In the study with a moderate severity population clinical benefit of CBT was also seen for exercise performance (6 minute walk test), and clinical benefit of relaxation was seen for pain (muscle pain).
  - No clinically important difference was seen for psychological status in either study (Beck depression and anxiety inventories and general health questionnaire). In the study with a moderate severity population no clinical difference was seen for quality of life (quality of life scale), fatigue (fatigue severity scale), physical functioning (SF36 sub scale), and pain (brief pain inventory severity and interference sub scales, and joint pain).
- Adaptive pacing therapy and graded exercise therapy
  - One study compared CBT to adaptive pacing therapy and graded exercise therapy. There was no clinically important difference for either comparison for quality of life (EQ5D), general symptom scales (global impression of change scale) fatigue (Chalder fatigue scale), physical functioning (SF36 sub scale), psychological status (Hospital anxiety and depression scales), pain (joint and muscle pain), sleep (Jenkin's sleep scale), return to school/work (Work and social adjustment scale), exercise performance (6 minute walk test)
  - One small study in a mixed/unclear age group (mean age suggests mostly adults) showed a benefit of CBT for fatigue (Chalder fatigue scale).
- Cognitive therapy
  - Clinical benefit of CBT was seen for general symptom scales (global impression of change rating) and fatigue (fatigue severity scale). Clinical benefit of cognitive therapy was seen for pain (muscle pain).
  - No clinically important difference was seen for quality of life (quality of life scale), physical functioning (SF36 sub scale), psychological status (Beck depression and anxiety inventories), pain (brief pain inventory severity and interference sub scales, and joint pain), exercise performance (6 minute walk test), and return to work (number in employment).
- Anaerobic therapy
  - Clinical benefit of CBT was seen for general symptom scales (global impression of change rating), fatigue (fatigue severity scale), physical functioning (SF36 sub scale), exercise performance (6 minute walk test), and return to work (number in employment).
  - No clinically important difference was seen for quality of life (quality of life scale), psychological status (Beck depression and anxiety inventories), and pain (brief pain inventory severity and interference sub scales, and muscle and joint pain),
- Counselling
  - In one small study with mixed/unclear age (mean age suggests mostly adults) there was clinical benefit of CBT for psychological status (Hospital anxiety and depression scale – depression sub scale)

- No clinically important difference was seen was for fatigue (Chalder fatigue scale), and psychological status (Hospital anxiety and depression scale – anxiety sub scale).

Additionally, adverse event reporting from one study comparing CBT to adaptive pacing therapy and graded exercise therapy showed no clinical difference between study arms for non-serious and serious adverse events (treatment-related or not) and adverse reactions (treatment-related).

Children and young people

CBT versus usual care/waiting list

Evidence from 2 studies in children and young people showed evidence of clinical benefit for CBT for general symptom scales (self-rated improvement), fatigue (Checklist Individual Strength fatigue severity sub-scale), and physical function (SF36 sub-scale). This benefit was seen for both individual face to face and web based CBT. No clinically important difference was seen for return to school (measured in hours attended) in the study of individual face to face CBT, but benefit was seen for return to school (measured as the proportion of classes attended) in the study of web based CBT. There were mixed results for cognitive function and pain outcomes reported in the trial of individual face to face CBT, with some suggesting benefit (concentration sub-scale of Checklist Individual strength, joint pain) and some no clinically important difference (reaction time tests, daily pain, and muscle pain). Adverse event reporting from one trial showed no clinical difference in serious adverse events between study arms.

CBT versus other interventions

Evidence from 1 small study in children and young people showed a clinical benefit of individual face to face CBT compared with psychoeducation and pacing for general symptom scales (strengths and difficulties questionnaire) and return to school on the work and social adjustment scale but no clinically important difference in fatigue, physical function or percentage in school attendance over 2 weeks. There was evidence of harm for CBT compared to psychoeducation/pacing in serious adverse events, but the committee noted this was a small study (n=63) with 1 reported event in the CBT group.

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of CBT

Evidence was identified for both adults' and children and young people's experiences of CBT. Themes of validation, relationship with the therapist, individualised care, self-management support and ongoing support were identified for CBT but were also common across other interventions. There were some findings that were specific to CBT, including hopes and expectations, CBT as support, the importance of motivation and engagement, experiences of the behavioural and cognitive aspects of the therapy, negative perceptions and effectiveness and these are discussed below. People recognised the importance of investing effort and motivation in the intervention, but this was dependant on illness severity and personal circumstances at the time.

Positive experiences of CBT were described as providing support for people. Feelings of confusion and apprehension reported at the beginning of therapy were replaced by feeling as ease and that some felt that the treatment exceeded expectations. The simple act of talking to someone was of benefit and people were comforted by the knowledge that the therapist

was available if they needed help as a form of safeguard. It was noted that this finding was closely related to the theme of the relationship with the therapist and likely to be dependent on the establishment of a good therapeutic relationship.

Evidence from the experiences of children and young people of an online CBT programme suggested that they liked that they could complete the platform in their own time and think about their answers. Some participants found it easier to talk about personal topics over email, whereas others found it difficult to portray things in writing and would have preferred some face to face contact.

The feedback on the cognitive aspects of CBT was mixed, with some adults perceiving it as crucial and others finding it less useful, especially for physical symptoms.

Behavioural tasks as part of the CBT such as activity or sleep monitoring were found to be helpful in facilitating the development of self-awareness in adults but although behavioural aspects were particularly valued and accepted by children and young people many struggled putting them in to practice. Tasks were often initially very hard to achieve, and parents found it challenging to watch their children push themselves.

Regarding the effect of CBT on symptom improvement, the response in adults was mixed, with some reporting a gradual improvement which did not reach a pre-morbid level of functioning, some reporting no change and some reporting a worsening of symptoms. There were also criticisms of the therapy being used or promoted as a cure for ME[a].

In children and young people, evidence showed that CBT was useful to some extent, the family was thankful for the help, but improvements were modest. However, the therapy was described by parents as a principle factor in regaining normality and viewed as a 'starting block' on a gradual journey to recovery. CBT sessions were described as support for parents. Some young people reported that there were times when they needed their parents at the sessions for emotional support but also many felt that there were certain situations and issues where the young person should have been seen alone.

Negative experiences of CBT were described as a dislike of the 'psychological' or 'emotional' aspects finding them irrelevant or inappropriate. Some people felt pigeonholed and subjected to generalisations. Some people perceived CBT as controlling, patronising and a form of brainwashing. The committee noted that this finding may have been limited by recall bias, as it came from a study on the past experiences of counselling interventions where participants were asked to recall what type of counselling they had received.

PEM re-analysis

After further scrutinising the information on PEM, studies from which findings for CBT in adults emerged were downgraded for moderate and serious concerns over applicability due to a lack of details on PEM across studies. This resulted in the overall confidence in the findings being downgraded from low to very low.

After further scrutinising the information on PEM, studies from which findings for CBT in children and young people emerged were downgraded for moderate and serious concerns over applicability due to a lack of details on PEM across studies. This did not impact the overall assessment confidence in the majority of findings that remained low but changed the confidence in two findings on the acceptability of the FITNET platform and personalised care from moderate to low.

Overall – cognitive behavioural therapy

[a] ME as written in the study.

The committee considered the clinical and cost effectiveness evidence alongside the qualitative evidence on the positive and negative experiences of CBT. The committee reflected that most of the clinical evidence showed no clinical difference but there was some benefit of CBT. They acknowledged there was some, but not consistent, evidence of benefit across the studies for general symptom scales, fatigue, physical functioning, exercise performance, return to work and adverse events when comparing CBT to usual care. The committee discussed potential reasons for this and noted the limitations of the clinical evidence including, the low to very low quality and the committee was not confident about the effects, the heterogeneity in the CBT interventions, the lack of clarity over the intervention components, potentially different recruited populations and outcomes being measured differently across the studies and the difficulty in combining any of the studies.

This was also reflected in the evidence that compared CBT to other interventions. The committee agreed that the same limitations applied and in addition the heterogeneity in the other comparisons made it difficult to make confident conclusions about the evidence. The committee noted that no harms were identified but also noted these were rarely included as an outcome and reported.

The committee were familiar with many of the themes that emerged from the qualitative evidence. The committee noted the criticisms reported in the qualitative studies of CBT being used as a 'treatment' for ME/CFS and felt it important to highlight that CBT is not a curative intervention, but that it is one type of supportive psychological therapy which aims to improve wellbeing and quality of life and may be useful in supporting people who live with ME/CFS to manage their symptoms and cope with having a chronic illness. The committee discussed why benefits to quality of life and psychological status were not demonstrated in the clinical effectiveness evidence. It was suggested that summative benefits across other outcomes such as general symptom scales, fatigue, physical function, activity levels and return to school/work may lead to longer term improvements in quality of life and psychological distress. The committee concluded that CBT has a role in helping to manage the impacts of having a chronic illness such as ME/CFS and can be particularly helpful for improving associated symptoms such as sleep, depression, and dietary issues.. Therefore, the committee made a 'do not' recommendation for the use of CBT as a cure for ME/CFS but recognised that CBT could be useful for people in supporting them to manage their symptoms of ME/CFS and reduce the distress associated with having a chronic illness.

The committee discussed the importance of the therapist in the context of the qualitative evidence showing that people with ME/CFS have found CBT useful when delivered by a therapist who understands ME/CFS but also the potential for harm when inappropriately delivered. To avoid this the committee made a recommendation that CBT should be delivered only by a healthcare professional with appropriate training and experience in CBT for ME/CFS, and under the clinical supervision of someone with expertise in CBT for ME/CFS.

To support this, recommendations were made to explain the principles of CBT for people with ME/CFS and what people should expect if they decided to consider CBT. This included explaining that CBT for people with ME/CFS is a collaborative time limited intervention that is designed to improve wellbeing and quality of life, reduce psychological distress associated with having a chronic illness, provide support in helping the person work towards establishing strategies that help the person work towards meaningful goals and priorities that they have defined.

The committee also agreed and reflected in the recommendations the importance of explaining what CBT for people with ME/CFS is not. The committee discussed the different types of CBT delivered and agreed that the narrative underpinning them is key to their effectiveness. The committee agreed that CBT manuals developed for other conditions should not be applied to ME/CFS, rather that CBT for ME/CFS should be specifically developed. There was concern, particularly from the lay members of the committee, about

the wording of CBT manuals that make suppositions about 'wrong' cognitions. The committee considered that the narrative around fear avoidance and false illness beliefs can deny patient experience, as fears can be completely rational and protective against harm. Therefore, the committee decided to specify in the recommendations that CBT does not assume people with ME/CFS have 'abnormal' illness beliefs and behaviours as an underlying cause of ME/CFS, but recognises thoughts, feelings, behaviours and physiology and how they interact with each other.

The committee discussed the mixed response to CBT reflected by the qualitative evidence and accepted that CBT may not be appropriate for everybody. The committee considered it important that the principles of CBT, along with the potential benefits and risks are discussed with the person with ME/CFS, in order for them to make an informed decision on whether or not to consider CBT. The committee recommended that the principles of CBT are discussed with the person with ME/CFS, its role in supporting them to adapt to and manage the symptoms of ME/CFS and the potential benefits and risks they should expect.

Validation and non-blaming attitudes emerged as a strong theme throughout the qualitative reviews (see Evidence review A: Information and support for people with ME/CFS and Evidence review B: Information and support for health and social care professionals) and the committee agreed this needed to be highlighted in the recommendations for people with ME/CFS over and above what is outlined in the NICE patient experience guideline. Related to CBT, the committee agreed the approach should be non-judgemental, supportive and compassionate when taking account of the person's experience of their symptoms and the complex challenges these might present. This was included in the recommendations.

Benefits of tailored care to people with ME/CFS also emerged as a clear theme throughout the qualitative review. The committee agreed that tailoring of therapy to individual goals, preferences and abilities is crucial in people with ME/CFS. Therefore, the committee made recommendations to explain the CBT is collaborative and takes into account how symptoms are individual to the person and can fluctuate in severity and may change over time. The committee also addressed the theme of tailored care through the recommended components of CBT, including a shared understanding between the person with ME/CFS and the CBT therapist about the difficulties and main challenges, an exploration of the personal meaning of symptoms and illness and how this might relate to how they manage their symptoms, the development of a self-management plan with strategies and prioritisation of goals chosen by the person with ME/CFS and regular reassessment of the self-management plan (see other considerations section for overall discussion on plans and assessment).

The committee discussed different modes of delivery of CBT, including individual one to one, group-based and web/written formats and the advantages and disadvantages of each. They noted that the evidence for mode of delivery did not highlight any one mode as better. The committee considered that individual face to face CBT is tailored to individuals and often more appropriate for people with complex conditions/comorbidities, whereas group-based CBT focusses more on general principles that work for most people.

The committee considered the theme of ongoing support from the qualitative evidence and agreed that specific recommendations should be made for end of CBT treatment planning ensuring people are upskilled during treatment. A widely used tool in CBT for this purpose is a therapy blueprint, which includes the person's therapy journey and the skills learned. The committee recommended that CBT include a therapy blueprint collaboratively developed between the therapist and person with ME/CFS at the end of the course of therapy.

Children and young people

There was less evidence for use of CBT for children and young people, although the evidence identified was mostly positive, particularly regarding benefits to general symptom scales, fatigue, physical function and school attendance. The committee discussed whether there were any specific considerations for CBT in this group.

The committee considered that while there is no agreed lower age limit for the application of CBT for children and young people their cognitive and emotional stage of development should be taken into account if CBT is considered. CBT is considered generally appropriate for children of school age. In the committee's experience CBT based interventions in young children would include parents and be behavioural in focus. The committee discussed the theme of inclusion of the family of children and young people identified in the qualitative review. The importance of finding balance between involving carers and family members for both adults and children and young people for emotional and practical support and including one-on-one time between the patient and therapist/health care professional was highlighted. Safe-guarding concerns are discussed in Evidence review B: Information and support for health and social care professionals.

The committee discussed appropriate adaptations that should be made to CBT to ensure children are fully supported and able to engage with the intervention. These included:

- Detailed holistic assessment and formulation to establish both the individual and systemic circumstances of the child and how these might relate to the child's symptoms, self-management and treatment
- The formulation and intervention should be tailored according to their cognitive and emotional development and monitored throughout the intervention
- Extended time should be spent socialising the child (and carer/family where appropriate) to the CBT model so they fully understand the treatment and implications of treatment
- The child should be supported to develop skills in differentiating thoughts and feelings prior to the intervention to ensure they can fully engage with CBT
- Psychoeducational support for emotional literacy should be considered to ensure the child is able to understand and respond to the CBT model
- The therapist should ensure the child has appropriate support to implement self-management, behavioural change and homework tasks where appropriate (this may include school or care/family involvement).

- The intervention itself should consider the following adaptations:
    - Involvement of carers/families/school where indicated in the formulation
    - Developmentally appropriate materials and tasks
    - Creative approaches to engagement including narrative, pictorial and externalising techniques
    - Use of concrete language where useful
    - Use of metaphors
    - Simplified / developmentally appropriate language use.

The committee concluded there was enough positive evidence to support this as a recommendation. Therefore, the committee decided to make the recommendation that CBT is only offered for children and young people with ME/CFS (and their parents and carers) who have been fully informed about the principles and aims of CBT and that their cognitive and emotional maturity is taken into account.

People with severe or very severe ME/CFS

The committee noted that none of the evidence included or reflected the needs of people with severe or very severe ME/CFS. They recognised that CBT could be supportive for people with severe or very severe ME/CFS but because of the severity of their symptoms it is important to be more flexible and adapt the delivery of CBT to accommodate the limitations of those with severe or very severe ME/CFS. This might include shorter, more infrequent sessions and longer-term goals.

Other psychological/behavioural interventions

Review of clinical and cost effectiveness

Adults

Buddy/mentor programmes

Evidence from 2 studies showed clinical benefit for a buddy/mentor programme in compared with waiting list control for improving fatigue (Fatigue Severity Scale) and no clinically important difference for quality of life (Quality of Life Index), general symptom scales (CFS Symptom Rating Form), physical function (SF26 sub-scale) or psychological status (Perceived Stress Scale and CORE-E scale).

Pragmatic/ rehabilitation programmes

Evidence from 1 study showed a clinical benefit of a programme of graded return to activity based on a physiological dysregulation model for fatigue (Chalder Fatigue scale) compared with both usual care and supportive listening. There was no clinically important difference between the programme compared with usual care or supportive listening for physical function (SF36 sub-scale), psychological status (Hospital Anxiety & Depression scales), sleep quality (Jenkin's Sleep Scale) or exercise performance. There was also clinical difference for exercise performance (the step test, and perceived exertion during physical activity – Borg scale), reported only for the comparison with usual care.

Mindfulness and mindfulness based cognitive therapy (MBCT)

Evidence from 1 study showed a harm of mindfulness and medical qigong compared with usual care for quality of life (SF36 health transition score). Evidence from two studies showed a clinical benefit of mindfulness based cognitive therapy compared with waiting list control for return to school/work (Work and Social Adjustment scale) and no clinically important difference in fatigue (Chalder Fatigue scale), physical functioning (SF36 sub-scale), psychological status (Hospital Anxiety & Depression scales). Evidence from one study on 'substantive' adverse events (not further defined) showed no clinical difference between study arms.

Group therapy

Evidence from 1 small study showed a clinical benefit of focused group therapy compared with waiting list control for quality of life measured by visual analogue scale with uncertainty, but no clinically important difference in quality of life measured by the Gothenburg Quality of Life Scale.

Education and support groups

Evidence from 1 study showed a benefit of an education and support group compared with usual care for exercise performance (shuttles walked), but no clinically important difference in quality of life (SF36 and HUI3 scales), fatigue (Chalder fatigue scale), cognitive function (reaction time and recall), psychological status (Hospital Anxiety & Depression scales) or exercise performance (normal walking speed). There was some evidence of harm for exercise performance (perceived fatigue during physical exertion – Borg scale).

Cognitive therapy versus relaxation

Evidence from 1 study in adults with moderate severity ME/CFS showed a benefit of cognitive therapy over relaxation for general symptom scales (self-rated global impression scale), pain (brief pain inventory severity and interference sub scales, and muscle and joint pain) and return to work (number employed), although there was uncertainty around the effect estimates. The evidence also showed no clinically important difference in quality of life (Quality of Life Scale), fatigue (Fatigue Severity Scale), physical function (SF36 sub-scale), psychological status (Beck depression & anxiety inventories) or exercise performance (6 minute walk test).

Lightning Process

Evidence from 1 study with moderate severity ME/CFS showed a benefit of the Lightning Process in addition to specialist medical care compared with specialist medical care alone for fatigue (Chalder Fatigue scale), physical function (SF36 sub-scale), psychological status (anxiety - Hospital anxiety and depression anxiety sub-scale and Spence Children's Anxiety scale) and school/college attendance (over the previous week), and no clinically important difference in psychological status (Hospital anxiety and depression scale – depression) or pain (visual analogue scale). There was no clinical difference between study arms for serious treatment-related adverse events (study authors reported no serious adverse events attributable to either treatment).

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of other psychological/behavioural interventions

Counselling interventions

Evidence of adults' experiences of counselling interventions was based on one study. Identified themes were activity related, stress management, thought management, examining the influence of the past counselling interventions and physical impact. There was low confidence in the findings due to methodological limitations, relevance and adequacy. The committee noted the limited details reported on the interventions and the potential recall bias, as the study was on past experiences of counselling interventions and participants were asked to recall what type of counselling they had received. Overall, themes related to the importance of self-management support and the relationship with the therapist identified across other review strata were echoed. Relaxation and meditation techniques were viewed positively, responses to thought management strategies were mixed and those who had experienced examining the influence of the past interventions felt very negatively because they thought the suggestion was that the cause of ME/CFS might be rooted in the past and they firmly rejected any psychological cause for their condition.

PEM re-analysis: After further scrutinising the information on PEM reported in the studies, evidence was downgraded for serious concerns over applicability due to a lack of information of PEM. This resulted in the overall confidence of themes for counselling interventions being downgraded from low to very low.

Educational/information interventions

There was moderate confidence in the finding that learning about the diagnosis, symptoms, possible causes and prognosis increased understanding and confidence in adults who had experienced education/information interventions. There was moderate confidence in the finding that an evidence-based source of information was welcomed due to issues with identifying reliable information on the internet and some felt more able to assess information about the illness and treatments more critically. There was moderate confidence in the finding that some people realised that they had to focus on acceptance and coping with the illness rather than curing it. There was very low confidence in the finding that practical issues related to location, environment, timing and duration made accessibility and engagement difficult for some. There was very low confidence in the finding that group participation was identified as an important part of the seminar delivery as it contributed to creating a collaborative and accepting atmosphere, however other issues were raised about a lack of personal focus, difficulty in "opening up" in front of the group, feeling as if others were not as severely affected, information not being shared with the family, some attendees talking more than others and some negative comments made by other attendees. There was low

confidence in the finding that the resources had an impact on the friends, family and colleagues and that in some cases, the provision of evidence-based information improved relationships and strengthened support networks. There was very low confidence in the finding that there were challenges inherent in confronting the reality of ME/CFS in the seminars, in particular information about prognosis and that some thought that applying the strategies into practice would be difficult as it depends on work, lifestyle and the severity of their ME/CFS. Other themes emerging were validation, self-management, peer support, ongoing support. These themes were also common to other interventions and are discussed elsewhere.

PEM re-analysis: After further scrutinising the information on PEM reported in the studies, evidence for education/information interventions was downgraded for moderate concerns over applicability due to a lack of information of PEM. This resulted in moderate confidence themes being downgraded to low confidence.

Rehabilitation/condition management

There was very low confidence in findings from two studies on adults' experiences of rehabilitation/condition management programmes. Overarching themes of validation, self-management, relationships, peer support and ongoing support emerged from this evidence. Other findings specific to rehabilitation/condition management programmes were related to barriers and facilitators to accessibility, lack of attendance pressure, utility of handouts and video conferencing, mixed opinions on duration and including the science behind ME/CFS, signposting as beneficial, mixed views on physical activity and benefits of staff support. The committee noted that there were serious concerns regarding methodological limitations of the studies and very limited detail on some of the findings.

PEM re-analysis: After further scrutinising the information on PEM reported in the studies relevant to rehabilitation/condition management programs, there was no change in the overall assessment of confidence in the themes.

Lightning Process

Evidence on children/young people's experiences of the Lightning Process showed that the educational part of the treatment, including the theory behind the Lightning Process and practical examples of previous success stories, gave people a rationale they could believe in, although it was also considered as complicated and difficult to understand and advice that participants could do anything they wanted conflicted with previous advice they had been given around activity pacing. There was low confidence in these findings. There was low confidence in the findings that the focus on specific goals and identifying barriers from reaching them was considered a helpful part of treatment and that the practical assignments were described as important for rapid recovery. There was low confidence in the finding that the length of the sessions was found by participants to be too long and intense, especially since many struggled with focus and concentration. A theme of dishonesty emerged, with people criticising the impression that staff gave about the process always involving a quick recovery and the dishonesty staff showed when they claimed the treatment had a 100% success rate. Evidence also showed that participants were specifically encouraged not to talk to anyone about the therapy and they found this unhelpful and difficult. There was low confidence in these findings. Regarding effectiveness of the therapy, experiences were mixed, with some experiencing an instant healing, some experiencing a gradual improvement that continued after treatment ended and some not finding the treatment helpful.

PEM re-analysis

After further scrutinising the information on PEM reported in the studies, the study from which findings emerged was downgraded for moderate concerns over applicability with study participants reported to meet the Oxford (Sharpe 1991) criteria prior to undergoing the

Lightning Process, where PEM is not a compulsory feature for the diagnosis of ME/CFS and there were no further details on the population to suggest they experience PEM. This resulted in the overall confidence in the findings being downgraded from low to very low.

Mild/moderate severity

Evidence identified in children/young people with mild/moderate severity ME/CFS showed some found specialist medical care to be positive, as it enabled them to talk about their illness and gave guidance on how to manage their condition, which brought structure and a sense of normality back into their lives. Some people reported that, although specialist medical care resulted in better symptom management, accepting that for a time they must reduce activity levels and adopt a routine was challenging. Mothers also noted that specialist medical care strategies had an impact on the whole family and could be difficult to integrate with their lifestyle. Finally, evidence showed that the service opened channels of dialogue between health-care professionals and education providers. There was low confidence in these findings due to methodological limitations, relevance and adequacy. The committee noted that the study included participants taking part in the Specialist Medical Intervention and Lightning Evaluation (SMILE) study, but findings seemed to be more relevant to the specialist service in general rather than the Lightning Process.

Other themes emerging from the evidence on children and young people's experiences of the Lightning Process were relationship with the therapist, peer support, ongoing support, validation and individualised care. These themes were also common to other interventions and are discussed elsewhere.

PEM re-analysis

Further scrutinising the information on PEM reported in the studies did not change the confidence in the findings relevant to children and young people with mild/moderate severity.

Overall – other psychological/behavioural interventions

The committee considered the clinical and cost effectiveness evidence alongside the qualitative evidence on the benefits and harms experienced. The committee considered that the clinical and cost effectiveness evidence for each type of psychological intervention was of low and very low quality and based mainly on single studies.

The committee considered the clinical evidence from the buddy/mentor programmes, pragmatic rehabilitation programmes, mindfulness, group therapy, education and support groups, cognitive therapy and noted although some benefit was reported for each intervention this was mainly based on single studies and the evidence was low to very low quality. The committee agreed that there was insufficient evidence to make any recommendations for any of the interventions.

The committee discussed the qualitative evidence on experiences of interventions. Evidence on adults' experiences of counselling interventions was based on a single study with several limitations and there was no clinical effectiveness evidence identified. Therefore, the committee decided that there was insufficient evidence to make a recommendation for counselling interventions.

Evidence on adults' experiences of education/information interventions showed some benefits, in particular to understanding, confidence, acceptance and coping with ME/CFS. The committee considered that provision of information, education and support is covered in the recommendations on providing information for people with ME/CFS (see Evidence review A: Information and support for people with ME/CFS).

Evidence on adults' experiences of rehabilitation/condition management programmes was based on a single study with very serious limitations. Therefore, the committee decided that there was insufficient evidence to make a recommendation for rehabilitation or condition management programmes.

Children and young people

The committee did not consider there were any specific considerations for children and young people with ME/CFS related to other psychological/behavioural interventions.

Severe or very severe ME/CFS

The committee did not consider there were any specific considerations for people with severe or very severe ME/CFS related to other psychological/behavioural interventions.

The Lightning Process

Evidence on children and young people's experiences of the Lightning Process showed that although some aspects of the therapy such as goal setting, practical examples and applications and peer support were found to be helpful, experiences varied and some negative experiences were reported around the confusing nature of the educational component, the intensity of the sessions, the secrecy surrounding the therapy, the approach of some therapists which led to feelings of pressure and blame and dishonesty about the success rate. The committee were particularly concerned around the secrecy of the Lightning Process and the lack of public information on the components and implementation of the process. The committee discussed concerns that the Lightning Process encourages people to ignore their symptoms and push through them and this could potentially result in harm for people with ME/CFS. The committee noted they had made clear recommendations on the principles of energy management and this is at odds with the principles of energy management in the guideline. In addition, the committee were aware that some children had been told not to discuss the therapy with their carer or parents. The committee agreed this was an inappropriate and harmful message to give to children and young people. The committee considered these findings were applicable to adults as well as children and young people and therefore, the committee decided to make a recommendation not to offer therapies based on the Lightning Process for ME/CFS.

Graded exercise therapy (GET)

Review of clinical and cost effectiveness

GET versus usual care

After further scrutinising the information on PEM reported in the trials, a subgroup analysis was performed where data was available separately for studies where ≥ 95% of participants had PEM and those where < 95% of participants had PEM, or this was not reported. The GETSET trial was the only study for this comparison in which more than 95% of study participants were considered to have PEM (all met the NICE 2007 criteria). Where outcomes from this trial were pooled with trials where less than 95% of participants had PEM (PACE trial) or an unclear percentage of participants had PEM (Moss-Morris 2005), a subgroup analysis was performed to explore the results from these trials separately. These outcomes included general symptom scales, fatigue, physical functioning, psychological status (anxiety & depression), and adverse events (serious, non-serious, and adverse reactions), and results are briefly summarised below alongside the summary from the original analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

The original analysis comparing GET to usual care showed a benefit of GET for general symptom scales (Clinical Global Impression of change in CFS at 12-42 weeks and clinical global impression of change in overall health at 12 weeks), fatigue (Chalder fatigue questionnaire at 12 weeks), activity levels (International Physical Activity questionnaire), and exercise performance (VE peak), There was no clinically important difference for quality of life (EQ5D), general symptom scales (Clinical Global Impression scale at 134 weeks), fatigue (Chalder fatigue questionnaire at 134 weeks), physical functioning (SF36 sub-scale), psychological status (Hospital Anxiety & Depression scales), pain (muscle & joint pain), sleep quality (Jenkin's sleep scale), return to school/work (Work & Social Adjustment scale), or exercise performance (6 minute walk, VO2 peak, peak power, elapsed exercise test time).There was no clinical difference between study arms for non-serious and serious adverse events (treatment-related or not), and adverse reactions (treatment-related).In the PEM re-analysis benefit of GET remained for general symptom scales in the PEM subgroup, but not the unclear PEM subgroup. For fatigue benefit remained in both subgroups. For physical functioning there remained to be no clinical benefit in the PEM subgroup, but benefit was seen in the unclear PEM subgroup. For psychological status and adverse events there remained to be no clinical difference in both subgroups.

The one study with young people and adults showed a benefit for fatigue, physical function, psychological status and sleep, psychological status (Hospital anxiety and depression scale anxiety) and sleep.

GET versus other interventions

- Flexibility and relaxation
    - Evidence from two studies (one included 16 and 17 year olds; mean age not reported) showed a benefit of GET for general symptom scales (Global Impression of Change scale), physical functioning (SF36 sub scale), and psychological status (Hospital Anxiety and Depression scales). There was no clinical difference for cognitive function (Stroop test), or exercise performance (treadmill walking test duration and VO2 peak).
    - Results for fatigue were inconclusive, as the Chalder fatigue scale total score from one study (adults) showed a benefit of GET, but neither the mental or physical fatigue sub scales from the other study (including 16 and 17 years) showed a clinical difference.
- Adaptive pacing therapy
    - There was a no clinical difference for any of the outcomes measured: quality of life (EQ5D), general symptom scales (Global impression of change score), fatigue (Chalder fatigue scale), physical functioning (SF36 sub scale), psychological status (Hospital anxiety and depression scales), pain (muscle and joint pain), sleep (Jenkin's sleep scale), return to school/work (Work and social adjustment scale), and exercise performance (6 minute walk test).
    - Additionally, adverse event reporting showed no clinical difference between study arms for non-serious and serious adverse events (treatment-related or not), and adverse reactions (treatment-related).
- Heart rate variability biofeedback
    - In one small study there was a benefit of heart rate variability feedback for quality of life (SF36 mental component), fatigue (Multidimensional fatigue inventory), and psychological status (Patient health questionnaire-9). There was no clinical difference for the SF36 physical component.
- Activity diaries
    - Results from one small study showed benefit of GET for exercise performance (VO2 peak). There was no clinical difference for fatigue (Chalder fatigue scale) or psychological status (Hospital anxiety and depression scale depression sub scale).
- Intermittent exercise

- Results from one small study showed benefit of intermittent exercise for some exercise performance measures (peak power), but no clinical difference between study arms for others (cycle ergometer test duration, VE peak, VO2 peak, and Borg perceived exertion during physical activity).

After further scrutinising the information on PEM reported in the trials no new information on PEM was identified that required re-analysis apart from the results noted above for the GET versus usual care comparison. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of graded exercise therapy

Evidence was identified for both adults' and children/young people's experiences of GET.

Adults Themes specific to GET in adults included false starts, an indeterminate phase, difficulty, 'push-crash' and worsening of symptoms, competing commitments, comorbid conditions, conflict in beliefs, pressure to comply with treatment, feeling blamed, information resources, the overall approach, improved knowledge and understanding, routines and goals, additional benefits, practical limitations and other sources of support. Confidence in these findings was moderate to low.

PEM re-analysis: After further scrutinising the information on PEM reported in the studies, the overall assessment of confidence in themes including the worsening of symptoms, conflict in beliefs, pressure to comply with treatment, feeling blamed, routines and goals was downgraded from moderate to low, and confidence in themes on additional benefits and practical limitations was downgraded from low to very low. Confidence in themes on comorbid conditions, the overall approach, improved knowledge and understanding, other sources of support remained moderate.

The evidence showed that most people found stabilising their routine, choosing physical activity and setting their baseline level to be straightforward, but baseline levels were not experienced as sustainable and some experienced 'false starts' as they commenced the programme. Most people noticed no immediate difference in symptoms, or an exacerbation during the initial phase which resulted in them not knowing if the programme was helping or hindering their condition and during this 'indeterminate phase', it was found to be difficult to maintain motivation. Contrastingly, this was not experienced by those who participated in an aquatic exercise intervention, with evidence showing that approximately three weeks after commencing the programme, the severity of post-exercise symptoms declined and that aquatic exercises were experienced to produce less fatigue than other types of exercise that participants had previously experienced, including Tai Chi, yoga, stretching, cycling and running.

Another finding suggested that most found following the programme to be 'hard work'. The level of exercise was selected by the therapist and experienced by patients as too difficult. People experienced a lack of control over their bodies after exertion subsequent to non-customised activity. For some, debilitating exacerbations of symptoms were a reason for discontinuation. For others, trying to persist with rehabilitation led to a worsening of their symptoms in the longer term.

People reported needing enough 'capacity' in their lives to experience an exacerbation of symptoms and for this not to interfere with essential life activities. Higher functioning participants had more to do in their lives and reported more challenges in fitting the programme in to busier lifestyles. People who reported their condition to be 'a little worse'

following treatment reported more comorbid conditions and greater interferences from these conditions when following the programme.

Evidence suggested a conflict in beliefs between therapists and people with ME/CFS about the nature of their condition and the role of rehabilitation with consequences for the appropriateness of treatment and expertise of therapists needed to provide this. People felt unreasonably pressured to comply with the rehabilitation therapy, especially when asked to ignore symptoms and continue trying to do more activity than they felt was sensible. People tried in vain to convey to therapists their sense that GET was not helping them. Some experienced difficulties in their relationship with the therapist when they reported finding the therapy unhelpful, and the blame was shifted onto them.

Some found the information booklet helpful, whereas others found it patronising, having the feel of marketing material or seemingly designed for participants with a higher level of functioning. The statement suggesting that there should be no ill effects from the programme was not accurate in their experience. However, another finding showed that an understanding of the theory behind graded exercise helped understanding and engagement in the programme.

Those who had participated in an aquatic exercise intervention reported that the social benefits of group exercise with people with the same medical condition were extremely important and encouraged attendance and compliance. Additional benefits of the intervention were enjoyment of the exercise, better ability to self-manage, increased fitness or use of muscles, enhanced breathing, better regulation of body temperature, the engaging mixture and pacing of exercises and improved cognitive symptoms.

In terms of the overall approach, some felt that the remit of GET was too narrow and that it needed a broader approach which included CBT or took into account cognitive activity. People who reported their condition to be 'much better' following treatment reported use of other therapies such as counselling, CBT, self-help or peer support.

Children and young people

Themes specific to GET in children/young people included exercise being enjoyable, the importance of routine and structure, setbacks, physical monitoring, positive outcomes and uncertain or lack or difference from treatment. Confidence in these findings ranged from moderate to low. Evidence showed that despite mixed preconceptions, most participants were positive about GET once they entered treatment and reported positive experience of the exercises.

Many families explained that the program introduced routine, which they experienced as important. Participants also commented positively on the use of wearables to accurately detect physical activity, as this demonstrated when they were doing too much and provided other useful functionality such as sleep or steps monitoring in addition to heart rate monitoring.

Families described that the young person had a setback or "crash" during the course of treatment, as a result of exceeding the recommended limits of physical activity. Travel to the hospital site for appointments contributed to setbacks.

In terms of the participants' view of effectiveness, evidence was conflicting, with one finding showing that there was overall recognition that the young people had benefitted from GET, including reductions in fatigue and tiredness, improved sleep, ability to concentrate, functioning and mood. Another finding showed that some families did not notice a difference with treatment, either reporting uncertainty, or lack of impact, often related to school and cognitive activities.

PEM re-analysis: After further scrutinising the information on PEM reported in the study relevant to children and young people, the overall assessment of confidence in the themes remained the same.

Overall – graded exercise therapy

The committee noted that overall, the clinical effectiveness evidence for GET was of low to very low quality and the committee was not confident about the effects. The committee noted the outcomes showing benefit were mainly measured at a relatively short follow up period of around 12 weeks. The benefits may have been a result of initial improvements in energy management and then potentially not been sustained. This was supported by outcomes measured at longer term follow up points not demonstrating the same benefits. The committee concluded there was no clear picture of benefit, and the evidence was inconsistent with outcomes that showed benefit in one study showing no clinically importance difference in other studies. The committee discussed potential reasons for this and noted the limitations of the clinical evidence including, the low to very low quality, the heterogeneity in the GET interventions, the lack of clarity over the intervention components, potentially different recruited populations and outcomes being measured differently across the studies and the difficulty in combining any of the studies. This picture was also reflected in the evidence that compared GET to other interventions. The committee agreed that the same limitations applied and in addition the heterogeneity in the other comparisons made it difficult to make confident conclusions about the evidence. The committee discussed that no harms were identified in the clinical evidence but also noted these were rarely included as an outcome and reported. Some committee members noted the CGI change score were reported in the PACE and GETSET trials. The committee reflected that in contrast, people with ME/CFS reported harms such as worsening of their symptoms in the qualitative evidence and took this into consideration when making recommendations on physical activity and exercise.

Concerns were raised regarding the definition of GET, as there is no standard definition and there have been a range of different interpretations. This was reflected by the heterogeneity in the interventions described in the studies, although they do have in common setting a baseline, incrementally increasing it, and if heart rate reaches maximum or increased fatigue occurs, staying at that activity level until symptoms improve. Wallman[99] and Broadbent[12,13,14] also include advice for when symptoms worsen. Taking this into account GET is defined in the guideline as a therapy based on the deconditioning and exercise avoidance theories of chronic fatigue syndrome. These theories assume that ME/CFS is perpetuated by reversible physiological changes of deconditioning and avoidance of activity. These changes result in the deconditioning being maintained and an increased perception of effort, leading to further inactivity. Graded exercise therapy consists of establishment of a baseline of achievable exercise or physical activity, followed by fixed incremental increases in the duration of time spent physically active.

The committee agreed that the term 'GET' should be avoided as it has significant negative connotations amongst people with ME/CFS, largely due to GET programmes that have fixed continued increases in activity despite patients reporting a worsening of their symptoms. The committee concluded that any programme based on fixed incremental increases in physical activity or exercise, for example graded exercise therapy should not be offered to people with ME/CFS.

Members of the committee considered that the term 'exercise' should also be avoided as this could easily be misinterpreted by patients and practitioners and could lead to people undertaking non-ME/CFS-specific exercise programmes that could be harmful to them. However, the committee concluded that not mentioning exercise could be confusing and should be added to the recommendations on physical activity where appropriate. The distinction between exercise and physical activity was highlighted in the terms used in the guideline.

Understanding energy management

The committee discussed that the controversy over GET had resulted in confusion over what services and support should be available to safely manage activity in people with ME/CFS. They discussed the requirement to provide clarity and clear guidance around activity. The committee noted that activity refers to cognitive, physical, emotional and social activity. The committee agreed that energy management is one of key tools that people with ME/CFS have to support them in managing and living with the symptoms of ME/CFS and people with ME/CFS should have access to support from a ME/CFS specialist team to develop a plan for energy management. The committee made a recommendation that energy management is discussed with the person with ME/CFS as part of their care and support plan. The committee noted that energy management is not a physical activity or exercise programme although the principles of energy management apply to physical activity or exercise programmes (these programmes are discussed in the following subsection).

The committee concluded that with the controversy surrounding activity management for people with ME/CFS it was important to define energy management and to have recommendations that listed the principles and components of energy management and what an assessment and plan would include.

The committee recommended a detailed assessment that took into account all areas of current activity and evaluation of rest and sleep, this is important to establish an individual activity pattern within their current energy limit that minimises their symptoms.

The key component of energy management is understanding that each person has an 'energy limit'. This is defined as the amount of energy a person has to do any activity without triggering an increase in symptoms and/or in symptom severity. In turn energy management is the management of a person's activities to stay within their energy limits. The committee noted energy management is an active self-management approach that reduces the risk of over exertion leading to a worsening of symptoms and potentially their condition. It is a collaborative person-centred approach that is led by the person with ME/CFS and helps to understand the potential risks if the person goes beyond their energy limits. It recognises each person has a different energy limit and that this limit can fluctuate within a person. It respects that the person with ME/CFS is the best judge of this limit, but that they might need guidance from a health care professional on recognising when they are approaching their limit to avoid over-reaching themselves. The committee noted that children and young people may find it harder to judge their limits and can overreach their limits.

Based on this an energy management plan can be developed with the awareness that a flexible, tailored approach is used so that activity is never automatically increased but is progressed during periods when symptoms are improved. The committee made a recommendation that the plan should be regularly reviewed and revised when needed.

The committee were keen to avoid potential harms through energy management being wrongly applied to people with ME/CFS without adequate support and expertise and recommended that people with ME/CFS should be referred to a specialist ME/CFS physiotherapy and/or occupational therapy service if the person with ME/CFS has problems with their physical activity or mobility or has experienced reduced physical activity or mobility levels for a prolonged period.

The committee considered the overarching themes throughout the qualitative reviews that identified positive components of self-management and activity programmes and incorporated these into the recommended energy management plan. The elements of GET that were reported by people with ME/CFS to be beneficial, such as development of routines, establishing realistic expectations and meaningful goals, and physical monitoring were included.

The committee discussed the balance of benefits in setting of goals with the findings in the qualitative evidence that described following a programme that was too hard and resulted in worsening of symptoms. Another finding highlighted the need for programmes to fit into people's lives accounting for essential life activities. The committee noted that where goals are rigid and unrealistic this can result in false starts, flare-ups and relapses. The committee commented on the findings in the qualitative evidence that people had felt pressured and blamed when they could not complete the programme even though it was making their symptoms worse. The committee acknowledged the controversy around the setting of fixed unrealistic goals and the importance of understanding realistic goal setting by both the person with ME/CFS and the healthcare professional supporting any programme. The committee made a recommendation that when developing any energy management intervention the person with ME/CFS should be supported to develop realistic expectations and goals that are meaningful to them.

The committee discussed the balance between the benefits of wearables to demonstrate when people with ME/CFS are doing too much activity and the provision of other useful functionality such as sleep or steps monitoring with the potential harms of increasing burden on the person and causing them additional anxiety about activity level. Therefore, the committee decided to recommend that activity recording/self- monitoring should be as easy as possible and should take advantage of tools the person is already using, (for example, activity trackers, phone heart-rate monitor, diary).

Approach to physical activity and to exercise programmes

It was the opinion of the committee that a physical activity or exercise programme can be beneficial for people who have chronic fatigue (not ME/CFS) and in a subset of people with ME/CFS who have already begun to improve and feel they want to do more. Due to some people with ME/CFS reporting harms in the qualitative review, as well as the committee's experience of the effects of exceeding individual limitations in exercise capacity the committee concluded that it would be misleading and potentially harmful to advise people with ME/CFS that a physical activity programme will be appropriate for them except in certain circumstances. They described this as people who are able and feel ready to progress their physical activity beyond their current activities of daily living, and as such would like to focus on their ME/CFS energy management around physical activity and exercise. The committee agreed the expertise of the person delivering the intervention is of high importance to prevent potential harm, they agreed that any physical activity or exercise programme should only be overseen under the supervision of a physiotherapist working in a ME/CFS specialist team. The committee recognised certain interventions should only be delivered or overseen by healthcare professionals who are part of a specialist team. The committee recognise there is a crossover in skills within specialist teams, occupational therapists and physiotherapists both support people with ME/CFS with activity management and support with symptoms. They noted that in specific circumstances the expertise of a specific professional role may be needed, for example a ME/CFS specialist physiotherapist to oversee physical activity programmes or to support colleagues where there are concerns around the physical effects of illness, injury or comorbidities with developing physical activity or exercise. The committee made a recommendation to reflect this.

The committee discussed that people with ME/CFS react significantly differently to physical activity compared to healthy people and people with other medical conditions. The concept of an 'anaerobic threshold' was found to be useful by some committee members to describe the limitations in energy capacity experienced by many people with ME/CFS, however other committee members thought it was not easily understood and refers to something that cannot be readily measured in clinical practice. The committee thought it was important to note that this 'threshold' is different for different people, is not fixed (that is, it can fluctuate moving up or down), and is usually identified through trial and error, therefore people with ME/CFS may not be able to readily assess risk of harm. 'Energy limits' and 'energy envelope' were preferred terms as they were considered to be more practical and more widely

understood. However, the committee agreed that 'energy envelope' could be interpreted differently by different people given existing definitions in the literature, therefore they agreed to use 'energy limits'.

The committee agreed their recommendations should emphasise that any activity, including physical activity programmes, should not assume that increasing activity is standard requirement but rather that activity should be graded down, towards stabilisation, or up, taking into account individual symptoms and stage of illness. Therefore, the committee concluded they would make a 'do not' recommendation to offer advice to undertake generalised physical activity or exercise programmes, physical activity or exercise programmes that are based on deconditioning and exercise avoidance theories and any programme based on fixed incremental in physical activity or exercise (for example, graded exercise therapy). The importance of acknowledging ME/CFS as a complex, chronic medical condition is raised throughout the guideline and the principles of care for people with ME/CFS state that people with ME/CFS should be believed and they should be reassured their condition is real.

In developing more specific recommendations regarding the content, approach and delivery of physical activity or exercise programmes , the committee considered the experiences of the benefits and harms associated with GET interventions identified in the qualitative review, as well as evidence from other qualitative reviews and reports and their own experiences of these types of interventions. The committee noted that some people with ME/CFS have found physical activity programmes can make their symptoms worsen, for some people it makes no difference and others find them helpful. The committee considered it important to discuss this with people with ME/CFS and made a recommendation to reflect the risks and benefits. The committee also outlined what a personalised physical activity or exercise programme should look like based on their experience. The programme included establishing the person's physical activity baseline at a level that does not worsen their symptoms, starts by reducing the person's activity to within their energy limit, can be maintained successfully before attempting to increase physical ability, uses flexible increments for people who want to focus on improving their physical abilities while remaining within their energy limit, recognises flare-ups and relapses early and outlines how to manage them and incorporates reviews regularly as well as whenever the person requests one. The committee stated the importance of flexible increments that were sensitive to the person's energy limit and emphasised that fixed increments were not part of a programme. The committee recommended the plan should only be delivered or overseen by a physiotherapist who has training and expertise in ME/CFS.

The committee noted the positive experiences of people who had participated in an aquatic exercise intervention. Session duration gradually increased over time, although the intervention was based on a model of adapted pacing therapy where patients are active only within their symptom limits and 'energy limit'. The committee considered the low quality of the evidence, which was based on one small study and the lack of any clinical outcome data from randomised controlled trials and decided that there was not enough evidence to recommend this type of exercise intervention.

Physical functioning and mobility

The committee discussed that it is important to acknowledge that people with ME/CFS can have reduced and limited mobility and in their experience this can lead to health problems. They noted it is important that where appropriate people with ME/CFS have plans for physical functioning, symptom control or restoration of physical ability included in the care and support plan. The plans should consider the following components: joint mobility, muscle flexibility, balance, postural and positional support, muscle function, bone health and cardiovascular health. The committee included a definition of physical functioning and mobility in the terms used in the guideline to clarify this is the process of incorporating in daily

activity, a level of movement that helps to maintain joint and muscle flexibility which does not exacerbate symptoms.

The committee recommended that people with severe or very severe ME/CFS or those with prolonged periods of immobility should be given information about the recognition and prevention of the possible complications of long-term immobility such as bone health and skin problems. Some of the committee members with personal experience of caring for people with limited mobility commented on the lack of support or information they had received in these areas of care (for example, how to transfer someone from a bed to a chair) and how it would have helped them. The committee supported this and made a recommended that families and carers are given advice on support on how to help a person with ME/CFS follow their agreed physical maintenance plans.

Children and young people

The committee did not consider that there were any specific considerations for children and young people with ME/CFS related to activity and energy support programmes.

Severe or very severe ME/CFS

The committee discussed the sensitivities and difficulties of implementing energy management in people with severe or very severe ME/CFS due to the severity and impact of their symptoms. The committee made general recommendation on the principles of caring for people with severe or very severe ME/CFS - this is discussed in Evidence report C:Access to care. The committee emphasised the importance of referring people with severe or very severe ME/CFS to a specialist ME/CFS physiotherapy and/or occupational therapy service for support on developing energy management strategies.

In addition, the committee noted that when agreeing energy management strategies with people with severe ME/CFS (and their families and carers as appropriate) that changes in activity are smaller and any increases (if possible) much slower. The committee noted that people with severe or very severe ME/CFS have limited mobility and are often house or bedbound and agreed that it is important that they are assessed at every contact for DVT's pressure ulcers and risk of contractures.

Other exercise interventions

Review of clinical and cost effectiveness

All the evidence came from small single studies.

- There was a clinical benefit of isometric yoga for fatigue (Chalder fatigue scale). The committee noted that isometric yoga is a specific type of yoga and that the evidence could not be generalised to other types of yoga.
- There was a clinical benefit of intermittent exercise compared with usual care for exercise performance measures (aerobic capacity, peak power, VEpeak and exercise duration on a cycle ergometer) and for orthostatic training compared to sham for fatigue (Fatigue Impact Scale).
- There was clinical benefit of qigong compared with no treatment for some SF36 quality of life sub scales (mental health, bodily pain), fatigue exercise performance (VO2 max), but no clinically important difference for the majority of SF36 sub scales (vitality, social functioning, role emotional, physical functioning, role physical) or exercise performance (max workload) and a harm of qigong for the general health sub scale on SF36.
- There was no clinically important difference between anaerobic activity therapy and cognitive therapy or between anaerobic activity therapy and relaxation for fatigue (Fatigue Severity scale), psychological status (Beck Depression & Anxiety

inventories), exercise performance (6 minute walk test) or pain (Brief Pain inventory severity and interference sub scales, and muscle and joint pain). Evidence showed a benefit of both cognitive therapy and relaxation over anaerobic activity therapy for quality of life (Quality of Life scale), general symptom scales (Self-rated global impression scale), physical function (SF36 sub-scale) and return to work (number employed).

The committee noted that all the evidence was very low quality and they were not confident of the effects.

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of other exercise interventions

No qualitative evidence was identified on people's experiences of other exercise interventions.

Overall – other exercise interventions

The committee considered that there was not enough robust evidence to make a recommendation for any of the types of exercise intervention.

Complementary and alternative therapies

Review of clinical and cost effectiveness

All the evidence came from small single studies.

- There was a clinical benefit of Chinese music therapy in combination with traditional Chinese medicine compared with traditional Chinese medicine alone for fatigue (scale based on Chalder fatigue scale) and psychological status (Hamilton anxiety scale) but no difference in psychological status (Hamilton depression scale). The committee noted the cultural context of the evidence and considered the limitations in the generalisability to the wider ME/CFS population.
- There was clinical benefit of homeopathy compared with placebo for one subscale of the Multidimensional fatigue inventory and no clinically important difference between homeopathy and placebo for other fatigue subscales of the Multidimensional fatigue inventory or Fatigue impact scale, or quality of life (Funtional limitations profile).
- There was no clinically important difference between acupuncture and sham acupuncture for quality of life (SF12), fatigue (Chalder fatigue scale), or psychological status (GHQ12). There was no clinical difference in adverse events reported in the two study arms.
- There was benefit for abdominal tuina massage compared to acupuncture for improving fatigue (Fatigue Scale 14) and psychological status (anxiety), but there was no clinically important difference for psychological status (depression). There was no clinical difference in adverse events or serious adverse events reported in the two study arms. The committee noted that the evidence was all of low or very low quality and they were not confident of the effects.
- There was no clinical difference for myelophil compared to placebo for any of the three fatigue scales reported. There was no clinical difference in adverse events or serious adverse events reported in the two study arms.

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of complementary therapies

There was very low confidence in the finding that adults with ME/CFS, desperate for relief of symptoms tried a wide range of different complementary/alternative therapies and for some, it caused ongoing frustration that these therapies were not funded by either the NHS or by private health insurance for ME/CFS.

There was very low confidence in the finding that people valued practitioners that took a holistic approach to the condition and showed empathy and therapists' positive approaches gave people hope that it was possible to overcome ME/CFS. The committee considered this finding alongside the finding identified in the evidence review of the information, education and support needs of people with ME/CFS (see report A) that a positive direction for the future and the ME/CFS diagnosis being framed in a positive way was important to people with ME/CFS and enabled them to maintain hope for improvement. The committee's discussion of the ethical considerations regarding health care professionals taking 'positive' or 'optimistic' approaches and resulting recommendations are outlined in report A.

Evaluations of the therapies was mixed, with some found to be helpful, some were not helpful, and some were experienced to be possibly harmful. People were impressed that the therapists called periodically to check how they were managing. There was very low confidence in these findings.

There was very low confidence in the finding that some families of children/young people with ME/CFS sought treatments such as acupuncture, dietician input, sickness bands and the emotional freedom technique, while others spoke to their ME/CFS clinician for advice. External support varied greatly in perceived accessibility and helpfulness. It was noted that this finding was based on one study which included children/young people who had eating difficulties; therefore, applicability may be limited.

PEM reanalysis: Further scrutinising the information of PEM did not raise further concerns over the applicability of the evidence in adults. Further concerns over applicability were raised for studies relevant to children and young people, however the overall confidence in the themes on complementary and alternative therapies remained the same in both adults and children and young people as it was deemed very low based on the concerns and limitations identified prior to the PEM reanalysis.

Overall – complimentary therapies

The committee considered that there was not enough robust evidence to recommend any type of complementary therapy for ME/CFS.

Dietary strategies

Review of clinical and cost effectiveness

One small study showed no clinically important difference between a low sugar, low yeast diet and healthy eating advice for the majority of the SF36 quality of life subscales, fatigue (Chalder Fatigue scale) or psychological status (Hospital Anxiety & Depression scales) and a clinical benefit of healthy eating advice for the bodily pain subscale on SF36 with uncertainty. The committee noted the evidence was very low quality and they were not confident of the effects.

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of dietary strategies

No qualitative evidence was identified on people's experiences of dietary strategies.

Overall – dietary strategies

The committee considered that there was not enough evidence to make a recommendation for any dietary strategy for ME/CFS and made a research recommendation. However, the committee agreed some general recommendations to ensure that people with ME/CFS receive appropriate support related to diet. These include ensuring that a dietary assessment is carried out as part of the baseline assessment (including weight history, pre- and post-diagnosis of ME/CFS, use of restrictive and alternative diets and access to shopping and cooking) and dietary strategies are included in the care and support plan. This included general recommendations on the importance of adequate fluid intake and a well-balanced diet according to the NHS Eat well diet; working with the person to develop strategies to minimise complications caused by nausea, swallowing problems, sore throat or difficulties buying, preparing and eating food; and referring people who are losing weight and at risk of malnutrition, weight gain or have a restrictive diet, to a dietitian with a special interest in ME/CFS. The committee noted that addressing weight gain in people with ME/CFS may require different strategies to those addressing weight gain in people without ME/CFS, in particular exercise may not be appropriate.

In addition, the committee referred to the recommendations on screening for malnutrition, indications for nutrition support, and education and training of staff and carers related to nutrition, in NICE's guideline on nutrition support for adults.

Children and young people

The committee discussed whether there were any specific considerations for children and young people with ME/CFS related to dietary management/strategies. The committee agreed that children and young people who are losing weight, have faltering growth or dietary restrictions should be referred to a paediatric dietician with a special interest in ME/CFS and decided to make this recommendation. The committee noted it is important the referral is to a paediatric dietician that understands the impact ME/CFS symptoms can have on weight gain and weight loss and that these are not necessarily the result of an eating disorder.

In addition, the committee referred to the recommendations on food allergies, in the NICE guideline on food allergy in under 19s.

Severe or very severe ME/CFS

The committee discussed whether there were any specific considerations for people with severe or very severe ME/CFS related to dietary management/strategies. The committee considered that this group are particularly at risk of problems associated with eating and are likely to require additional support. Therefore, the committee recommended that people with severe or very severe ME/CFS are referred to a dietitian with a special interest in ME/CFS for a full dietetic assessment and monitored for t risk of malnutrition. The committee also discussed some general dietary strategies that could be helpful for people with severe or very severe ME/CFS from their own experience. These included eating little and often, having nourishing snacks and drinks, finding easier ways of eating to conserve energy and using modified eating aids. The committee noted that some people with severe and very severe ME/CS may not be able to feed themselves and need support from someone else. The committee noted that in their experience this could be a family member and they require support and education. The committee made a recommendation to be aware of the types of

dietary issues that people with severe or very severe ME/CFS may face and the possible strategies to support them including oral nutrition support and enteral feeding.

Nausea

In the committee's experience many people with ME/CFS suffer with nausea and this can impact on maintaining a healthy diet. The committee discussed that although in line with the protocol interventions may have identified nausea as an adverse event, the reduction in nausea was not included as an outcome in protocol. On reflection the committee considered this should have been included. In the absence of any evidence the committee made a consensus recommendation within in the dietary management and strategies section of the guideline. The recommendation advised that people with ME/CFS who have nausea should keep up adequate fluid intake and try to eat regularly, taking small amounts often. The committee discussed general strategies that could be useful to reduce nausea but recognised that different approaches worked for different people and decide to include their suggestions here and not in the recommendation. In their experience the strategies below might be helpful:

- *Eat "little and often". For example, aim to eat something 6 times a day. Particularly avoid going too long without eating or becoming over full*
- *Avoid drinking whilst eating. For example, drink half an hour after meals and aim to have sips and try cool drinks*
- *Avoid cooking smells. Cold foods have less smell than hot foods and might be better tolerated.*
- *Try salty or sharp-tasting foods. For example, crisps, pineapple, lemon and lime cordials, sorbet*
- *Try plain biscuits, crackers, or unbuttered toast*
- *Try foods containing ginger, for example, ginger ale, ginger biscuits, ginger tea*
- *Try peppermint flavoured foods or drinks, for example, peppermint tea.*

Dietary supplements

Review of clinical and cost effectiveness

All the evidence came from single studies compared to placebo. There was no clinically important difference for:

- acclydine with amino acids for general symptom scales (Sickness Impact profile), fatigue (Checklist Individual Strength fatigue severity subscale), activity levels (measured by actometer).
- poly-nutrient supplement for general symptom scales (Sickness Impact profile), fatigue (Checklist Individual Strength fatigue subscale), general symptom scales (self-reported change in symptoms), or activity levels (measured by actometer).
- aribinoxylane (Biobran) for quality of life (WHOQOL-BREF), general symptom scales (Self-rated global impression scale and Measure Yourself Medical Outcomes Profile 2), fatigue (Chalder fatigue scale), and psychological status (Hospital Anxiety & Depression scales).
- vitamin D supplement for fatigue (Piper fatigue scale), and psychological status (Hospital Anxiety & Depression scales).
- coenzyme Q10 with NADH for fatigue (fatigue index scale), sleep (Global Pittsburgh sleep quality index), exercise performance (VO2 max, max workload, and perceived exertion during physical activity – Borg scale), and pain (McGill pain questionnaire),
- coenzyme Q10 alone (ubiquinol-10) for cognitive function (Uchida-Kraepelin psychodiagnostic test).

- guanidinoacetic acid (GAA) for quality of life (SF36), general or physical fatigue on the Multidimensional fatigue inventory, or pain (visual analogue scale).

Clinical benefit was found for GAA for fatigue (mental, reduced activity and reduced motivation sub scales).

A clinically important difference in adverse events was reported for participants receiving the poly-nutrient supplement (they experienced more nausea compared to the placebo arm). There were no clinical differences in adverse events compared to the placebo arms for acclydine with amino acids ('important' adverse events, not further defined), Biobran (minor side effects causing withdrawal and serious adverse events), vitamin D (no deaths occurred in the study), coenzyme Q10 with NADH (moderate adverse events, treatment-related or not), coenzyme Q10 alone (serious adverse events), and GAA (self-reported side effects).

The evidence was low to very low quality and the committee was not confident of the effects.

PEM re-analysis

After further scrutinising the information on PEM reported in the trials, no new information on PEM was identified that required re-analysis. See Appendix G in Evidence Review H for full details of the approach taken, the analysis, and the impact on the results and interpretation of the evidence.

Qualitative review of experiences of dietary supplements

No qualitative evidence was identified on people's experiences of dietary strategies.

Overall – dietary supplements

The committee considered there was not enough evidence to recommend dietary supplements for ME/CFS. The committee considered that general guidelines regarding nutrition support should be followed and referred specifically to recommendations on screening for malnutrition, indications for nutrition support, and education and training of staff and carers related to nutrition, in NICE's guideline on nutrition support for adults.

The committee were aware from their experience and from the qualitative evidence on alternative therapies that many people with ME/CFS turn to alternative and complementary treatments in an attempt to alleviate symptoms. They agreed evidence of a potential benefit was very limited and unconvincing and acknowledging the financial cost of therapies such as those derived from osteopathy, life-coaching, and neuro-linguistic programming for people with ME/CFS, the committee agreed it was not appropriate to make a recommendation for their use. It was considered that, especially as there is a lot of misinformation available regarding effective treatments for ME/CFS, people should be aware of the potential risk and side effects of high doses of vitamins and minerals. Therefore, the committee made a recommendation to be aware that there is insufficient evidence for the use of other vitamin and mineral supplements. It is important to give advice about potential side effects associated with high doses of vitamins and minerals and that if a person's diet is inadequate or supplementation is advised, a multivitamin and mineral supplement within the recommended daily amount is advised.

The committee also discussed the increased risk of vitamin D deficiency in people who are unable to spend sufficient time outdoors to synthesise enough vitamin D from sunlight. People with severe or very severe ME/CFS are a population the committee considered to be particularly at risk and so recommended clinicians should be aware of this and monitor their levels. The committee also noted that as vitamin D is a fat-soluble vitamin, the administration of any supplementation should be monitored to prevent toxicity. Therefore, the committee decided to cross-refer to the NICE guideline on vitamin D.

Children and young people

The committee did not consider that there were any specific considerations for children and young people with ME/CFS related to dietary supplements.

Severe or very severe ME/CFS

The committee discussed whether there were any specific considerations for people with severe or very severe ME/CFS related to dietary supplements. They considered that people with severe or very severe ME/CFS are at a higher risk of vitamin D deficiency. However, the committee decided that the recommendations in the NICE guideline on vitamin D adequately deal with the management of deficiency and no additional recommendations specific to this population were required.

Overall summary of non-pharmacological interventions for ME/CFS

Overall, the evidence for non-pharmacological interventions as a treatment for ME/CFS is inconclusive with heterogenous treatment effects and uncertainty around the effect estimates being high. There is little evidence for most of the interventions identified and most of the evidence is not consistent showing some clinical benefit but also no clinical difference across outcomes and studies. The committee noted there was more evidence for CBT and graded exercise therapy, but this evidence had the same limitations. After discussing the clinical effectiveness of non-pharmacological interventions and people's experiences and considering the reports from the young people and people with severe ME/CFS the committee agreed there is no current non-pharmacological cure for ME/CFS. The committee discussed the claims that have been made about cures for people with ME/CFS and lack of conclusive evidence for this. The committee were aware of interventions that are promoted as cures and there is often a financial cost to people with ME/CFS when these are pursued. To address this the committee made a recommendation to raise awareness that there is no current non-pharmacological cure for people with ME/CFS. In addition, the committee made 'do not' offer recommendations for CBT, therapy based on physical activity or exercise therapies, therapies based on the Lightning Process, and supplements to cure ME/CFS.

3.4 Cost effectiveness and resource use

Self-management strategies

There was one published economic evaluation which evaluated adaptive pacing therapy (APT) in people with ME/CFS. This study was deemed to be partially applicable, for example, it could have included some patients who did not have post exertional malaise. It had potentially serious limitations, for example there was a lack of blinding.

APT had a very small improvement in quality of life compared with specialist medical care but the incremental cost-effectiveness ratio was above £30,000 per QALY gained. CBT was more cost effective in that study. The committee considered why the evidence showed little health gain APT. It was suggested that a possible explanation was that the extra information in the adaptive pacing group was beneficial but negated by the extra effort it took to take part. Some committee members thought that the adaptive pacing therapy intervention trialled encouraged an increase in activity and therefore was not a true 'pacing' intervention. In addition, the definition of specialist medical care in the trial was considered by the committee to include elements of pacing, such as a patient leaflet which included avoiding extremes of activity, which may have led to an underestimation of the effect of the intervention.

Overall, the committee considered that the evidence regarding the best self-management strategy is unclear and people with ME/CFS use their own individual self-management strategies without the need for a specific intervention, therefore the committee decided not to make a recommendation for any particular self-management strategy. However, the qualitative evidence showed that people valued support for self-management. The committee

thought that some level of support would be cost effective and this was reflected in the recommendations on cognitive behavioural therapy and energy management.

Cognitive behavioural therapy (CBT)

There were two published economic evaluations of CBT in people with ME/CFS. They were each deemed to be partially applicable, for example, they could have included some patients who did not have post exertional malaise. Both had potentially serious limitations: for example, they were all at potentially high risk of bias due to lack of blinding.

In one study, CBT was found to improve quality-adjusted life-years using the EQ-5D as an adjunct to specialist care. The patients were still experiencing relatively poor quality of life by the end of the study. However, the improvement was enough for CBT to be considered cost effective at £20,000 per QALY gain, although the probabilistic sensitivity analysis indicated substantial uncertainty around this result.

In another study, CBT had higher quality of life gain but was more costly than GP-led care. It had a smaller quality of life gain but less cost than education and support. The study sample size was very small, and the baseline differences were quite large, so it was difficult to draw any conclusions about cost effectiveness.

The committee considered this evidence in the context of the clinical effectiveness and qualitative reviews. They concluded that there is enough evidence that CBT is effective and cost effective as a means of helping some people with ME/CFS to cope with their symptoms. The committee made recommendations that describe the way that CBT should be conducted to ensure that it is of value to patients.

Whilst the evidence review did not show differences in benefit from one-to-one, group or web-based interventions, there will be differences in resource use and cost. For patients where it is of equal efficacy, web-based therapy would clearly be more cost effective followed by group-based therapy. Although some people with ME/CFS might get additional therapeutic benefits from meeting in a group, for many, the benefits might be greatest from web-based CBT, as it would not involve travel that could trigger post-exertional malaise.

Other psychological/behavioural interventions

There were four published economic evaluations for these types of intervention in people with ME/CFS. They were each deemed to be partially applicable, for example, they could have included some patients who did not have post exertional malaise. They all had potentially serious limitations: they were all at potentially high risk of bias due to lack of blinding.

One study evaluated the Lightning Process compared with specialist medical care for young people. The study found a substantial improvement in QALYs, which cost only £3,400 per QALY gained. However, in the evidence on people's experiences (noted above) some harms were reported around the confusing nature of the educational component, the intensity of the sessions, the secrecy surrounding the therapy, the approach of some therapists which led to feelings of pressure and blame and dishonesty about the success rate. These concerns are not likely to be fully captured in the QALYs. Therefore, the committee decided to make a recommendation against the use of the Lightning Process.

The second study evaluated both pragmatic rehabilitation and supportive listening compared with GP-led usual care. Both interventions were dominated by usual care (they had higher cost and lower QALYs). The committee did not recommend either intervention.

In the third study multidisciplinary rehabilitation yielded an improvement in fatigue and slightly more QALYs than CBT but at £106,000 per QALY gained, the cost was too high for multidisciplinary rehabilitation to be considered cost effective. The committee decided not to

recommend multidisciplinary rehabilitation but they did not find it necessary to make a 'do not' recommendation, as there was no evidence that the intervention is harmful.

In the fourth study, an 'education and support' programme had higher cost and better quality of life than GP-led usual care. The study sample size was very small, and the baseline differences were quite large, so it was difficult to draw any conclusions about cost effectiveness. However, the trend indicated that education and support would be cost effective. The committee did not specifically recommend this intervention.

Exercise interventions

There was one published economic evaluation which evaluated graduated exercise therapy (GET) in people with ME/CFS. This study was deemed to be partially applicable, for example, it could have included some patients who did not have post exertional malaise. It had potentially serious limitations, including lack of blinding.

In the study there was a small gain in quality of life associated with GET was not cost effective at £20,000 per QALY gained compared with specialist medical care. However, it was cost effective at a threshold of £30,000 per QALY gained. CBT was more cost effective in this study.

The committee considered this evidence along with the clinical effectiveness and qualitative evidence. Given the uncertainty around the health benefits of GET combined with the possibility of harm due to over-exertion, especially when GET is poorly implemented, the committee agreed to not recommend GET.

Flexible physical activity/exercise interventions are recommended but only in patients who are clearly on a recover trajectory, who desire an increase in physical activity levels and are aware of the potential risks. The committee recommended that this should be under the supervision of a specialist physiotherapy or occupational therapy service. In 2013, a survey ME/CFS services in England showed that of those that cared for people with severe ME/CFS most had a physiotherapist (18/30) and nearly all had an occupational therapist (26/30).[54]

Complementary and alternative therapies

There were no published economic evaluations for this type of intervention in people with ME/CFS.

Since there was not good quality evidence of clinical effectiveness for any of the interventions trialled, their cost effectiveness remains unproven.

Therefore, the committee did not recommend an intervention in this category.

Dietary strategies

There were no published economic evaluations for this type of intervention in people with ME/CFS.

Since there was not good quality evidence of clinical effectiveness for any of the interventions trialled, their cost effectiveness remains unproven.

Therefore, the committee did not recommend an intervention in this category.

Dietary supplements

There were no published economic evaluations for this type of intervention in people with ME/CFS.

Since there was not good quality evidence of clinical effectiveness for any of the interventions trialled, their cost effectiveness remains unproven.

Therefore, the committee did not recommend an intervention in this category.

3.5 Other factors the committee took into account

The committee noted that no clinical or cost effectiveness evidence was identified for interventions evaluating aids/adaptations/occupational therapy, occupational/school advice, repetitive transcranial magnetic stimulation, compression socks, hyperbaric oxygen, lifestyle advice, sleep interventions, or non-pharmacological pain management interventions for people with ME/CFS. The committee agreed that some of these interventions (such as, repetitive transcranial magnetic stimulation, hyperbaric oxygen) were considered to be experimental and very little could be commented about them at the moment.

The committee noted that although no clinical evidence was identified for aids and adaptions, occupational and school advice, sleep and pain these were all important areas of care that have been identified in the reports on children and young people and people with severe ME/CFS and in the evidence review on access to care. The committee discussion on aids and adaptions is in Evidence review C: Access to care. The committee discussion on supporting people with ME/CFS in work, education and training is in Evidence review A: The information and support for people with ME/CFS.

Sleep interventions and rest

The committee discussed the lack of evidence for sleep management recognising that difficulties with sleep was an area of concern for many people with ME/CFS. The committee discussed making consensus recommendations for providing advice for people with ME/CFS but agreed it was hard to be confident in recommending any advice when there was not any evidence and lack of consensus in the area. The committee agreed not to make any recommendations on sleep management but did consider that giving advice on planning rest and activity was important as a fundamental part of any management strategy. In their experience the committee had found that understanding the role of rest and how to introduce rest periods was important in successful energy management. The committee made a recommendation to give this advice and also noted that relaxation techniques at the beginning of rest periods could be helpful. The committee made a research recommendation to evaluate sleep strategies.

Pain management

The committee noted that pain was a common symptom in people with ME/CFS and particularly intense in people with severe or very severe ME/CFS. The committee acknowledged the lack of evidence meant they could not recommend any interventions but did cross refer to the NICE guidelines on neuropathic pain and headaches.

Orthostatic intolerance

In the suspecting ME/CFS section of the guideline orthostatic intolerance (OI) is identified as one of the symptoms that are commonly associated with but not exclusive to ME/CFS. In the committee's experience although not everyone with ME/CFS may experience OI it is very common, and the symptoms can be hard to differentiate from other ME/CFS symptoms. The committee made a consensus recommendation to raise awareness that people with ME/CFS may experience orthostatic intolerance, such as postural orthostatic tachycardia syndrome (POTS), and people with orthostatic intolerance should be referred to secondary care if their symptoms are severe or worsening, or there are concerns that another condition may be the cause. The committee did not make any recommendations on the management of OI noting

that although this can be straightforward it this can involve advice on diet, carrying out daily activities and activity support and should be tailored to the person taking into account their other ME/CFS symptoms. The committee noted medicines usually prescribed for OI can worsen other symptoms in people with ME/CFS and should only be prescribed or overseen by a clinician with expertise in orthostatic intolerance.

Assessments and care planning

The key to the successful management of ME/CFS and the symptoms people experience is assessment and personalised planning. The committee noted that assessment and planning is recommended in specific interventions in the guideline, such as social care assessments, energy management, physical maintenance, CBT and dietary management. Each of these assessments and plans outlines the important considerations for that area of care and is described above in the discussion for that area. However, the committee noted this has the potential to result in disjointed care, in the report on multidisciplinary care (report I) the committee discuss the importance of coordinated care and make relevant recommendations. In addition, the committee agree that there should be an overall care and support plan that is shared with primary care and a copy is held by the patient. This plan can then be referred to in situations such as planning an admission to hospital. In the committee's experience this approach to assessment and planning is common in specialist ME/CFS services.

Assessment and development of the personalised care and support plan

The committee agreed it was important to recommend a holistic assessment after a diagnosis has been confirmed that included a full history, physical functioning, the impact of symptoms on psychosocial wellbeing, current and past experiences of medicines (including tolerance and sensitivities), vitamins and mineral supplements and a dietary assessment. This committee noted this was as a minimum but these were the key areas that would identify the areas of concern and where support is needed. This assessment is then the basis for developing a personalised care and support plan that includes self-management strategies, including energy management, symptom management, managing flare-ups and relapse, support for activities of daily living, mobility, aids and adaptations to increase or maintain independence, information and support needs, education, training or employment support needs and details of the health and social care professionals involved in the person's care, and how to contact them. The care and support plan then provides the basis for the more detailed assessments and plans outlined in the specific interventions.

Flare-ups and relapses

The committee noted that all areas of the care and support plan were supported in the guideline except for information on flare-ups and relapses. The committee agreed was important to give further detail in the recommendations on the management of flare-ups and relapses. In their experience the recognition and management of flare-ups and relapses was key to the successful management of ME/CFS. The committee noted that the energy management and physical activity recommendations provide advice on recognising flare-ups and on what revisions should be made after a flare-up or relapse. The committee considered that it was important to make recommendations giving information what a flare-up is, how to recognise one and how they can lead to a relapse if activity is not monitored and adjusted. The committee advised that flare-ups may occur spontaneously or be triggered by illness, over-exertion beyond the energy limit or stress of any kind and are transient typically resolving spontaneously or in response to temporary changes in energy management. However, the committee noted that if the strategies detailed in the personalised plan or specific intervention plans are not successful then the person should contact their named contact in primary care or the ME/CFS specialist team review. The committee discussed the importance of recognising when a flare-up has moved to a relapse. The person then requires a review of their care and support plan with reduction in activity and increase in rest with the understanding that a relapse may lead to someone moving to a more severe form of ME/CFS. Part of the review of the care and support plan is to consider what the causes of relapse might have been and to consider this when revising the plan.

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