National Institute for Health and Care Excellence

Final

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

[l] Multidisciplinary care

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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1. Multidisciplinary care

1.1. Review question

In people with ME/CFS, what is the clinical and cost-effectiveness of different models of multidisciplinary care?

1.1.1. Introduction

People with ME/CFS can require care from a variety of different health and social care professionals because of the problems associated with ME/CFS and its association with a number of co-morbidities. Care may be required from professionals from primary, community, secondary and tertiary care at different stages and severities of the illness. This can include delivery of particular interventions and programmes over shorter timeframes, as well as ongoing monitoring and review. NICE has developed general guidance on principles of organisation of care. The NICE guideline on Patient experience makes recommendations on continuity of care and co-ordination of services based on patient needs and priorities. The NICE guideline on Multimorbidity recognises the potential burden of interactions with multiple services.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults, children and young people who are diagnosed as having ME/CFS.
Interventions	Any MDT strategies evaluated by the eligible literature
Comparisons	Compared to each other, or compared to a suitable comparator (i.e. no MDT care)
Outcomes	CRITICAL OUTCOMES (at longest follow up available) • Quality of life (any validated scales, for example, EQ-5D, SF-36) • Pain (VAS/NRS) • Fatigue/Fatigability (any validated scales) • Physical functioning / exercise tolerance / ADL (any validated scales) • Cognitive functioning (any validated scales) • Sleep quality (any validated scales) • Adverse effects (any reported by the studies) • Psychological outcomes • Patient satisfaction • Benefit status/employment/school attendance/school absences • Update of diagnostic status • Comorbidities • Activity monitoring • Post Exertional Malaise(PEM) / Post exertional symptom exacerbation(PESE) IMPORTANT OUTCOMES (at longest follow up available) • Care needs • Impact on families and carers
Study design	• Systematic reviews • RCTs • Non-randomised studies will be excluded unless there are no randomised studies found. If no randomised studies are found, non-randomised

	comparative trials will be considered (including prospective cohort studies) if they have attempted to detect and, if needed, adjust for, confounders.

1.1.3. 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.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

A search was conducted for randomised trials comparing the effectiveness of treatment strategies delivered by different multidisciplinary teams versus each other or a suitable comparator (i.e. no MDT care) for people with diagnosed ME/CFS.

Very little evidence was identified and the committee discussed if the two studies identified did answer the review question comparing different MDTs. They agreed to include the studies on the basis this was the only evidence and acknowledging that while the studies did not compare different MDTs they did compare different approaches to delivering care for people with ME/CFS.

Two RCTs were included in the review;[13, 22-24] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Both studies were adult populations and the severity of ME/CFS was mixed or unclear. MDT care was compared with primary care, and with care from a psychologist/behavioural therapist.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
O'Dowd 2006[13]	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. 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. Therapists involved in treatment delivery: clinical psychologist x 2, physiotherapist x 1, occupational therapist x1 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	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) Cognitive function (reaction time, total words recalled, correct words) Exercise performance measure (shuttles walked, walking speed, Borg perceived fatigue scale)	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 variability statistics were not reported for all outcomes. Attention control arm compared with primary care for the purpose of this review Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature Other exercise performance measures not extracted: perceived fatigue scale

Study	Intervention and comparison	Population	Outcomes	Comments
Vos-Vromans 2016[23] Vos-Vromans 2012[24] and Vos-Vromans 2017[22] FatiGo trial	Multidisciplinary rehabilitation: thorough assessment by an interdisciplinary team (physical therapist, occupational therapist, psychologist and social worker), 10- week treatment phase (individual sessions, total contact time 33 h), including CBT, elements of body awareness therapy, gradual reactivation, pacing, mindfulness, gradual normalization of sleep/wake rhythm and social reintegration. Interdisciplinary team meetings to discuss progress. Follow up with 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 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.	N=122 people with CFS according to 1994 CDC criteria; consultant confirmed inclusion and exclusion criteria and verified whether an extensive physical examination and 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	Quality of life (SF36) General symptom scales (Sickness Impact profile 8) Fatigue (Checklist individual strength – fatigue severity) Psychological status (Symptom Checklist 90) Activity levels (accelerometer) At 12 months	Conducted in the Netherlands 'Improvement and Satisfaction Questionnaire' – five 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. Serious population indirectness – 1994 CDC criteria used; PEM is not a compulsory feature. 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).

See Appendix D for full evidence tables

1.1.6. Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary 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 Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear (95% CI)
Quality of life (SF36 Pooled 6 and 12 months data) - Mental 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 pooled 6 and 12 months data) – mental in the control groups was 39.07	The mean quality of life (sf36 pooled 6 and 12 months data) - mental in the intervention groups was 1.19 higher (2.26 lower to 4.64 higher)
Quality of life (SF36 Pooled 6 and 12 months data) - Physical 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 pooled 6 and 12 months data) – mental in the control groups was 34.7	The mean quality of life (sf36 pooled 6 and 12 months data) - physical in the intervention groups was 1.23 lower (3.52 lower to 1.06 higher)
Quality of life (Health status (HUI3) Pooled 6 and 12 months 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) pooled 6 and 12 months data) in the control groups was 0.39	The mean quality of life (health status (hui3) pooled 6 and 12 months data) in the intervention groups was 0.01 higher (0.08 lower to 0.09 higher)
Fatigue (Chalder fatigue scale Pooled 6 and 12 months data 0-33) Scale from: 0 to 33.	101 (1 study)	⨁⨁◯◯ LOW1,2 due to risk of	-	The mean fatigue (chalder fatigue scale pooled 6 and 12 months data) in the control groups was	The mean fatigue (chalder fatigue scale pooled 6 and 12 months data) 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 Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear (95% CI)
	6-12 months	bias, indirectness		20.64	0.55 higher (1.56 lower to 2.66 higher)
Cognitive function (total words recalled Pooled 6 and 12 months data)	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean cognitive function (total words recalled pooled 6 and 12 months data) in the control groups was 12.43	The mean cognitive function (total words recalled pooled 6 and 12 months data) in the intervention groups was 0.08 lower (1.2 lower to 1.05 higher)
Cognitive function (correct words Pooled 6 and 12 months data)	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean cognitive function (correct words pooled 6 and 12 months data) in the control groups was 11.76	The mean cognitive function (correct words pooled 6 and 12 months data) in the intervention groups was 0.04 lower (1.14 lower to 1.05 higher)
Cognitive function (reaction time Pooled 6 and 12 months data)	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean cognitive function (reaction time pooled 6 and 12 months data) in the control groups was 618.7	The mean cognitive function (reaction time pooled 6 and 12 months data) in the intervention groups was 0.95 higher (0.87 to 1.03 higher)
Psychological status (HADS Pooled 6 and 12 months data) - Anxiety Scale from: 0 to 21.	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean psychological status (hads pooled 6 and 12 months data) - anxiety in the control groups was 9.83	The mean psychological status (hads pooled 6 and 12 months data) - anxiety in the intervention groups was 0.76 lower (2 lower to 0.48 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 Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear (95% CI)
Psychological status (HADS Pooled 6 and 12 months data) - Depression Scale from: 0 to 21.	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean psychological status (hads pooled 6 and 12 months data) - depression in the control groups was 7.92	The mean psychological status (hads pooled 6 and 12 months data) - depression in the intervention groups was 0.43 lower (0.56 to 0.3 lower)
Psychological status (General health Questionnaire Pooled 6 and 12 months data) Scale from: 0 to 36.	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean psychological status (general health questionnaire pooled 6 and 12 months data) in the control groups was 16.82	The mean psychological status (general health questionnaire pooled 6 and 12 months data) in the intervention groups was 0.41 lower (2.8 lower to 1.98 higher)
Exercise performance measure (Normal walking speed Pooled 6 and 12 months data)	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean exercise performance measure (normal walking speed pooled 6 and 12 months data) in the control groups was 8.76	The mean exercise performance measure (normal walking speed pooled 6 and 12 months data) in the intervention groups was 1.06 higher (0.37 lower to 2.49 higher)
Exercise performance measure (Shuttles walked Pooled 6 and 12 months data)	101 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, indirectness	-	The mean exercise performance measure (shuttles walked pooled 6 and 12 months data) in the intervention groups was 18.3	The mean exercise performance measure (shuttles walked pooled 6 and 12 months data) in the intervention groups was 1.04 higher (0.86 to 1.22 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) or a very indirect population (downgraded by two increments): 1. 1994 CDC criteria used; PEM is not a compulsory feature

Table 4: Clinical evidence summary: Physical therapist + occupational therapist + psychologist + social worker versus psychologist/behavioural therapist; 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 Multidisciplinary rehabilitation versus CBT (95% CI)
Quality of life (SF36) - Mental component Scale from: 0 to 100.	122 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	-	The mean quality of life (sf36) - mental component in the control groups was 49.88	The mean quality of life (sf36) - mental component in the intervention groups was 1.59 higher (1.96 lower to 5.14 higher)
Quality of life (SF36) - Physical component Scale from: 0 to 100.	122 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	-	The mean quality of life (sf36) - physical component in the control groups was 36.67	The mean quality of life (sf36) - physical component in the intervention groups was 2.67 higher (1.45 lower to 6.79 higher)
General impact scale (Sickness impact profile 8) Scale from: 0 to 6160.	122 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness	-	The mean general impact scale (sickness impact profile 8) in the control groups was 791.62	The mean general impact scale (sickness impact profile 8) in the intervention groups was 50.78 higher (186.68 lower to 288.24 higher)
Fatigue (Checklist individual strength - fatigue severity) Scale from: 8 to 56.	122 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	-	The mean fatigue (checklist individual strength - fatigue severity) in the control groups was 40.05	The mean fatigue (checklist individual strength - fatigue severity) in the intervention groups was 5.69 lower (10.62 to 0.76 lower)
Psychological status (Symptom checklist 90) Scale from: 90 to 450.	122 (1 study) 52 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, indirectness	-	The mean psychological status (symptom checklist 90) in the control groups was 139.15	The mean psychological status (symptom checklist 90) in the intervention groups was 7.83 lower (19.84 lower to 4.18 higher)
Activity levels (accelerometer)	122 (1 study) 52 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias,	-	The mean activity levels (accelerometer) in the control groups	The mean activity levels (accelerometer) 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 Multidisciplinary rehabilitation versus CBT (95% CI)
		indirectness, imprecision		was 21526.214	200.96 higher (1914 lower to 2315.92 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) or a very indirect population (downgraded by two increments): 1. 1994 CDC criteria used; PEM is not a compulsory feature
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

See Appendix F for full GRADE tables.

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

1.1.7. Economic evidence

1.1.7.1. Included studies

Two health economic studies with a relevant comparison were included in this review.[13, 22] These are summarised in the health economic evidence profile below (Table 5) and the health economic evidence tables in Appendix H. Both studies are included in the review of clinical studies (above) and in the review of non-pharmacological interventions (Evidence Review G).

1.1.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8. Summary of included economic evidence

Table 5: Health economic evidence profile: Multidisciplinary care vs usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
O'Dowd 2006[13] UK	Partially applicable [(a)]	Potentially serious limitations[(b)]	• RCT (O'Dowd 2006) • Comparators: Education and Support (ES) by specialist team (psychologists, physiotherapist, occupational therapist) vs GP-led care[(c)] • Time horizon: 12 months	£358	0.027 QALYs	£13,259 per QALY gained	Not conducted
Vos-Vromans 2017[22] Netherlands	Partially applicable [(d)]	Potentially serious limitations[(e)]	• RCT (FatiGo) • Comparators: Multidisciplinary rehabilitation (physiotherapist, occupational therapist, psychologist, and social worker) vs psychologist • Time horizon: 12 months	£4,835[(f)]	0.05 QALYs	£105,975 per QALY gained	Probability multidisciplinary rehabilitation is cost effective (£20/£30K threshold): 0%/0%

Abbreviations: ES=Education and support group; GP=general practitioner; QALY= quality-adjusted life year; RCT= randomised controlled trial

(a) Population were diagnosed using the CDC/ Fukuda criteria and therefore might not have post exertional malaise. Used HUI3 rather than EQ-5D. QALYs reported here were estimated by the National Guideline Centre using the HUI3 data and assuming a linear change over time.

(b) 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.

(c) There was also a cognitive behavioural therapy arm, but this was not considered relevant to this review and is not shown in this table.

(d) Population were diagnosed using the Oxford criteria and therefore might not have post exertional malaise. Cost perspective is the Netherlands health service.

(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. Patients were required to report resource use monthly, which resulted in incomplete data. Unclear how QALYs were calculated.

(f) 2012 Euros converted to UK pounds.[14].

1.1.9. Economic model

Original economic modelling was not conducted.

1.1.10. Evidence statements

1.1.10.1. Economic

- One cost–utility analysis found that multidisciplinary rehabilitation (physical therapist, occupational therapist, psychologist and social worker) was not cost effective compared to cognitive behavioural therapy by a psychologist 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 with CBT for adults with ME/CFS (ICER: £7,900 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

1.2. The committee's discussion and interpretation of the evidence

The committee discussed this evidence with the findings from the reviews on access to care (report C), diagnosis (report D), management (reports F and G) and the reports on Children and Young people (Appendix 1) and people with severe ME/CFS (Appendix 2). Where relevant, this is noted.

1.2.1. The outcomes that matter most

Quality of life, pain, fatigue/fatigability, physical functioning, cognitive functioning, sleep quality, adverse effects, psychological outcomes, patient satisfaction, benefit status, employment and educational attendance, diagnostic status, co-morbidities, activity monitoring and post exertional malaise (PEM)/ post exertional symptom exacerbation (PESE) were all agreed by the committee to be critical outcomes for decision making.

These outcomes reflect the direct impact ME/CFS symptoms have on a person (specifically levels of pain, fatigue, physical functioning cognitive functioning, sleep quality, psychological outcomes, PEM/PESE, and in turn the impact on quality of life (specifically benefit status, employment and educational attendance).

The impact of the different models of MDTs can be measured by the outcomes listed above, if a particular model is successful symptoms would be managed appropriately and the impact on a person's life would be minimised compared to a strategy (including no review) that did not identify worsening symptoms.

The effectiveness of an MDT is also reflected in these outcomes: diagnostic status, co-morbidity identification, adverse effects and patient satisfaction. Diagnostic status and comorbidity review and identification are key to ensuring that a person is receiving the correct intervention and management for their condition or conditions. If this is not picked up by an MDT this would have a detrimental impact on the person.

Any contact with health and social care services will have an impact on physical and emotional energy levels of people with ME/CFS. It is key that any contact does not make people with ME/CFS worse and their needs are understood so that they can access the service successfully. Adverse effects and patient satisfaction address these concerns.

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.

1.2.2. The quality of the evidence

No evidence was identified for children and young people. No evidence was identified for adults for the outcomes; pain, sleep quality, adverse effects, patient satisfaction, benefit status/employment/school attendance/school absences, update of diagnostic status, comorbidities, PESE/PEM, care needs, and impact on families and carers.

Evidence from 2 randomised trials with follow up over 6 months was identified for this review. The studies compared different approaches for delivering care; one compared an MDT (with a clinical psychologist, physiotherapist and an occupational therapist) to standard care managed in primary care and the other compared a MDT (with a physical therapist, occupational therapist, psychologist and social worker) to a psychologist or behavioural therapist.

The quality of the evidence ranged from low to very low. The main reasons for downgrading were due to risk of bias, indirectness and imprecision. There was a lack of blinding 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.

The committee discussed the CDC 1994 diagnostic criteria used in the studies to recruit eligible participants. The committee have identified PEM 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, the studies did not give further information on the numbers of people with PEM. The committee agreed that a population diagnosed with such criteria may not accurately represent the ME/CFS population and that people experiencing PEM are likely to respond differently to treatment than those who do not experience PEM 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. The studies had small sample sizes increasing the uncertainty around the point estimate.

1.2.3. Benefits and harms

MDT comparisons

The committee acknowledged that the evidence comparing different MDTs was limited and insufficient to base a recommendation for any one type of MDT or a core MDT composition. They noted the only outcomes reported were quality of life, fatigue, cognitive function, psychological and exercise measures. In the study comparing multidisciplinary rehabilitation to CBT delivered by a psychologist/behavioural therapist, fatigue was lower showing clinical benefit in the group receiving multidisciplinary rehabilitation, but the committee noted this was very low quality evidence and were not confident about the effect. No clinically important difference was observed for any other of the outcomes.

The committee noted the evidence came from small studies with indirect populations; both studies recruited participants using the 1994 CDC criteria and one was based in the Netherlands and this limited the relevance of the results to people with ME/CFS and current NHS practice. The committee noted the studies only included adults and did not reflect MDTs caring for children and young people.

Expert testimony

Dr Husain gave an overview of the Persistent Physical Symptoms Research and Treatment Unit at South London and Maudsley (SLAM) NHS Foundation Trust and the units approach

towards the care of people with ME/CFS. Dr Husain noted the service also sees patients with fatigue from other causes such as post-chemotherapy fatigue, MS, fibromyalgia. The criteria for entry to specialist services varies across the country, and some only see people who meet specific diagnostic criteria. The SLAM MDT is composed of psychiatrists, psychologists and a physiotherapist and there is a holistic approach to assessment and management. The service receives referrals from across England with most from Greater London. The initial appointment is a 2-hour assessment, people receive up to 20 sessions with further follow up sessions if required. If other medical conditions are suspected (either as a differential or concomitant diagnosis), investigations are performed and the service has close links with other specialities such as rheumatology, neurology, gastroenterology. Dr Husain commented that it is important when assessing people with ME/CFS that differential and co-existing conditions are considered. It is important to ensure that other causes of fatigue are considered and to assess for mood disorders, such as depression which are common in long term conditions. Dr Husain noted that often people have seen several specialists before they are referred to their service. The care and support plan is developed with the person with ME/CFS and involves families and carers identifying what the person wants to do and to determine limitations. The focus of management is on modifiable current factors that can impact on symptoms and overall wellbeing and not on a cure. The primary management options the service is funded to provide are CBT or GET (as in the NICE guideline ME/CFS published in 2007) and this is reflected in in the composition of the MDT. If input from other HCPs is required such as a dietitian or occupational therapist referral to other services is required. The service manages people with a wide severity of symptoms and disability and has some provision for the home-based management of the people with severe or very severe ME/CFS. Home based management is limited by geographical location, number of staff available, time, and funding. Dr Husain noted that overall non-attendance rates have gone down since virtual consultations have been introduced as a result of COVID; this may reflect the difficulty some people with ME/CFS have in attending appointments in person. Dr Husain noted that with good engagement, assessment, collaboration, taking the patients seriously and making firm diagnoses of conditions such as ME/CFS when appropriate, addresses issues such as stigma. He noted that in his unit, this the hallmark of the service and patients are almost always happy to proceed and the unit has several years of very positive patient feedback all of which is collected anonymously. (see appendix 3: Expert Testimonies for Dr Husain's written testimony).

After Dr Husain had left the meeting the committee discussed the expert testimony presented by Dr Husain and agreed that there are MDT approaches in specialist ME/CFS services but there is variation in how they are run across the NHS. The committee noted services are led by a variety of specialities, including psychiatry, psychology, infectious diseases, immunology, neurology, physiotherapy and occupational therapy. The committee commented that this has led to misunderstanding when people with ME/CFS have been referred to some services feeling there is a mismatch between their illness experience and the speciality. The committee noted this was not a specific comment about SLAM. The committee acknowledged this variety of specialities is largely historical and a result of clinical interests and previous funding allocation.

The committee recognised that although the services for ME/CFS are situated within different specialities they have access to physicians, physiotherapy and psychologists and some have access to occupational therapy and nursing input.

Overall

While the committee were unable to draw conclusions about the specific composition of a multidisciplinary team based on the evidence they agreed that good care for people with ME/CFS results from access to an integrated team of health and social care professionals that are trained and experienced in the management of ME/CFS.

The committee agreed it was important to make consensus recommendations based on their experience about the health and social care support and expertise needed by people with ME/CFS. The committee recommended that care for people with ME/CFS should be provided using a co-ordinated multidisciplinary approach that includes health and social care professionals with expertise in relevant areas. The committee considered that it was important to outline the expertise and skills that people with ME/CFS may need rather than identify a core team of professionals. They agreed that expertise in medical assessment and diagnosis, developing a personalised care and support plan, self-management strategies (including energy management), symptom management including prescribing and medicines management, managing flare ups and relapse, activities of daily living (such as personal care including dental health, housework, food preparation and eating), physical, psychological and emotional and social well-being, diet and nutrition, mobility (including access to aids and rehabilitation services), social care support and support with engagement at work, education and social activities were crucial for the care of people with ME/CFS.

The committee noted that ME/CFS affects each person differently and varies widely in severity. The fluctuating nature of ME/CFS can mean support needs can change and access to different expertise is needed at different times. This is particularly true of people with severe or very severe ME/CFS who have very complex needs that in the committee's opinion are not always sufficiently met (see report on people with severe ME/CFS).

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 programmes

See management reports F & G where the committee outline where it is important that professionals trained in ME/CFS deliver areas of care. The committee agreed that medical assessment and diagnosis would typically require access to a ME/CFS specialist physician or a GP with a special interest in ME/CFS but noted there are highly trained ME/CFS advanced practitioners that can fulfil this role.

Co-ordination of care

They noted that a multidisciplinary approach is required for all long term and complex conditions and this requires good communication and coordination across different services. The committee highlighted the importance of shared care between primary care and specialist teams. In the evidence reports on access to care (evidence report C) and in the commissioned reports on children and young people (appendix 1), and people with severe ME/CFS (appendix 2) the limited time that GPs have to offer in a consultation is highlighted. Some of the committee members working in specialist teams noted they had 1- 2-hour initial appointments with people with suspected ME/CFS and access to professionals who had the time to develop a personalised care and support plan. The committee acknowledged that GPs did not have enough time to carry out the assessments needed to confirm a diagnosis of ME/CFS or to develop a care and support plan in a single standard appointment. The committee recommended that once someone with suspected ME/CFS has had persistent symptoms indicating ME/CFS for 3 months the person should be referred to a specialist team for confirmation of the diagnosis.

Access to ME/CFS specialist teams

ME/CFS specialist teams provide the expertise and skills that are required to provide appropriate care to people with ME/CFS and the committee discussed the availability of

specialist care in the context of recommending MDTs and for referral for the confirmation of diagnosis and development of a care and support plan. Specialist services commonly accept referrals from across England and Wales and is almost always a research centre and shared with the academic side of the NHS Trust they are based in.

Drawing on their experience of the ME/CFS specialist services the committee described the different compositions of ME/CFS specialist teams. A ME/CFS specialist team can have a range of healthcare professionals with expertise in assessing, diagnosing, treating and managing ME/CFS. ME/CFS specialist teams commonly comprise of medically trained clinicians (who have specialist training, specialisms include rheumatology, rehabilitation medicine, endocrinology, infectious disease, neurology, immunology, general practice, paediatrics) and access to health professionals that specialise in ME/CFS, these may include physiotherapists, exercise physiologists, occupational therapists, dieticians, clinical and/or counselling psychologists. The committee agreed it was important that a ME/CFS specialist team has access to a medical clinician to understand when further investigations should be done and the symptoms that may indicate a differential or coexisting condition. The committee noted that many people referred to a ME/CFS specialist service do not end up with a ME/CFS diagnosis. The committee noted that initial appointments to a ME/CFS specialist team could be scheduled for 1-2 hours. The committee were aware that up to a third of ME/CFS services did not have medical input and there are paediatric ME/CFS services that report having no specialist paediatrician dedicated to their service and often rely on a general paediatrician to confirm or refute diagnosis which results in wide variation in pathways and treatment. Children and young people are likely to be cared for under local or regional paediatric teams that have experience working with children and young people with ME/CFS in collaboration with ME/CFS specialist centres.

The committee discussed the importance of specialist teams either employing or having access to allied health professionals that have expertise in managing ME/CFS to support people developing and then supporting personalised care and support plans (for example, physiotherapists, occupational therapists, dieticians, clinical psychologists).

The committee acknowledged that specialist teams are limited in number and in some areas of England and Wales are non-existent. As a result, referral to specialist teams can be difficult; committee members were aware of referrals taking many months and in some cases years.

The committee were aware of different referral processes across England and Wales, with some areas using a tick box criteria that is assessed by an administrator. The committee agreed that referral should be based on the criteria outlined in this guideline but acknowledged that a rigid tick-box criteria can be unhelpful and does not allow for the complexities in symptom assessment that can be present in people with ME/CFS. This approach can result in missed opportunities for early diagnosis and management and referrals should go directly to a specialist team for assessment. Early diagnosis by a specialist team allows early management and follow up that may prevent deterioration in symptoms and wellbeing.

In the committee's experience a shared care approach works well, providing the person with ME/CFS and their GP access to expert advice and education when necessary. Committee members noted that although funding was usually limited to a treatment course people with ME/CFS and their GPs should always have access to specialist information and resources. One example of this was a triage telephone service where people with ME/CFS could contact their specialist team for advice about symptoms or a relapse and facilitate an examination and further investigations if indicated. Committee members working with children and young people noted this continuing contact was particularly important in supporting non specialists caring for people with ME/CFS.

The committee noted that good co-ordination of care and communication across services was particularly important when young people move to adult services and cross referenced to the NICE guideline on transition from children's to adults' services for young people using health or social care services. Some committee members were aware of specific examples of advice in specialist teams for young people with ME/CFS moving to adult services.

As part of the recommendations on specialist care the committee discussed the importance of a named contact in the ME/CFS specialist team. There are the recognised benefits of having one point of contact that can help support someone to navigate access to health and social care and to communicate and co-ordinate care between services. However, the committee noted that access to a specialist team with many professionals can have both favourable and unfavourable consequences for someone with ME/CFS. This can result in a person having contact and appointments with several different people and this can impact negatively on the person's health potentially worsening symptoms. To avoid this unintended consequence of a multidisciplinary care it is important there is one point of contact to co-ordinate care. This was common practice in the committee's experience, and they noted that although during specific treatments one professional is predominantly involved, other team members are easily accessible and can be more involved if the need arises.

One of the themes identified throughout the guideline reviews is a lack of belief from health and social care professionals that ME/CFS exists. The committee were aware of the importance of the therapeutic alliance and the shared beliefs about the cause of ME/CFS. The committee noted this was particularly important for children and young people and they should be involved in the decision making about their key worker.

1.2.4. Cost effectiveness and resource use

Both clinical trials included in the review had conducted an economic analysis. They were each deemed to be partially applicable, for example, they could have included some patients who did not have post exertional malaise. They both had potentially serious limitations: they were all at potentially high risk of bias due to lack of blinding.

In the first 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.

In the second study, an education and support programme provided by a specialist team had higher cost and better quality of life than GP-led usual care. The study sample size was small, and the baseline differences were quite large and drug costs were approximated from limited data, so it was difficult to draw any conclusions about cost effectiveness. However, the trend indicated that education and support would be cost effective at £13,300 per QALY gained.

Overall, the quantitative evidence was limited and the cost effectiveness of an ME/CFS specialist multidisciplinary teams is therefore uncertain. Cost effectiveness of a team is likely to depend on the staff-mix in the team and the therapies offered.

The committee also considered the evidence from the guideline's qualitative evidence reviews, including those on barriers to diagnosis, barriers to care, information for patients and information for health professionals (see Evidence reviews A, B and C); the original qualitative evidence and the expert testimony. Among the themes identified were:

- Many people with ME/CFS have experienced long delays to diagnosis and poor sometimes resulting in worsening of symptoms or even disease progression. Sometimes staff have not believed that the disease or symptoms are real.

- The presence of a specialist team was a facilitator of faster diagnosis and better care for people with ME/CFS.
- Patients and professionals identified the need for a clear clinical management. pathway for ME/CFS and a specialist team would make that pathway more explicit.
- There is a need for a source of information and support for non-specialist health care professionals.

There is evidence that people with ME/CFS have very poor quality of life, worse than most other chronic conditions,[7] and that they require higher levels of health care resource than the general population[4]. So, there is potential for a service that can improve the course of this disease to have a benefit in terms of both health outcome and resource use. The committee recommended that specialist multidisciplinary teams (including a named contact) be used to confirm diagnosis, establish a treatment plan and provide support for primary care services. The exact cost effectiveness of a specialist team is uncertain, but the committee were convinced that their provision would be a good use of NHS resources, leading to faster access to appropriate care and substantially better patient outcomes for people with ME/CFS.

Current provision of specialist teams is very uneven across the country. Implementation of the guideline's recommendations might also require some retraining or possibly a change of skill-mix in some existing services, so that a suitable care pathway can be provided. In 2013, a survey of all 49 ME/CFS services in England showed that most had a physician, occupational therapist, physiotherapist and a clinical psychologist but other professions were less common[10]. The committee did not want to specify a set of professions because skillsets often overlap, so instead they specified the following areas of expertise:

- self-management strategies, including energy management
- symptom management
- managing flares and relapse
- activities of daily living
- emotional wellbeing, including family and sexual relationships
- diet and nutrition
- mobility and avoiding falls and problems from loss of dexterity, including access to aids and rehabilitation services
- social care and support
- support to engage in work, education, social activities and hobbies.

Most people will only require a few elements and only at specific points in time, with emphasis on early assessment and developing a personalised care and support plan. It is intended that appropriate advice and care early will reduce health and care costs downstream by reducing the risk of progression to more severe disease.

1.2.5. Other factors the committee took into account

The committee discussed the need to improve communication between specialist teams. It is not unusual for people with a suspected diagnosis of ME/CFS to be investigated for other conditions and this is an important role of the ME/CFS specialist team. These referrals to other specialities are not necessarily concurrent. Direct consultant to consultant referrals could help provide context for the referrals and avoid further delays with the understanding that people are referred back to ME/CFS specialist teams if their ME/CFS type symptoms persist once treated for any other conditions.

Appendices

Appendix A Review protocols

A.1 Review protocol for multidisciplinary care

ID	Field	Content	Developer comments *(delete before publication)*	QA comments *(delete before publication)*
	Scope	Management of ME/CFS		
	Draft review question	In people with ME/CFS, what is the clinical and cost-effectiveness of different models of multidisciplinary care, including team composition?	NICE GUIDELINES 2007 1.9 Key principles of care for people with severe CFS/ME 1.9.1 General principles of care 1.9.1.1 Management of severe CFS/ME is difficult and complex and healthcare professionals should recognise that specialist expertise is	

			needed when planning and providing care for people with severe CFS/ME. 1.9.1.2 Diagnosis, investigations, management and follow-up care for people with severe CFS/ME should be supervised or supported by a specialist in CFS/ME. 1.9.1.3 People with severe CFS/ME may need to use community services at times. These services may include nursing, occupational therapy, dietetics, respite care, psychology and physiotherapy (see the 'National service framework for long-term conditions'[11]). The input of different professionals should be coordinated by a named professional.	

0.	PROSPERO registration number		Not yet registered	
1.	Review title	In people with ME/CFS, what is the clinical and cost-effectiveness of different models of multidisciplinary care?	Scope: 3.4 In people with ME/CFS, what is the clinical and cost effectiveness of different models of multidisciplinary care, including team composition? Suggest we remove the suffix 'including team composition' because this is intrinsic to different models and therefore tautological.	
2.	Review question	In people with ME/CFS, what is the clinical and cost-effectiveness of different models of multidisciplinary care?		
3.	Objective	To identify the most clinically and cost effective multidisciplinary care model to improve outcomes in adults and children with a diagnosis of ME/CFS	Scope highlights that research has highlighted that many GPs lack the confidence and knowledge to recognise diagnose and manage ME/CFS.	

4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Cinahl Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer.		

		The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.		
5.	Condition or domain being studied	ME / CFS		
6.	Population	Inclusion: Adults, children and young people who are diagnosed as having ME/CFS.		
7.	Intervention/Exposure/Test	Any MDT strategies evaluated by the eligible literature will be compared to each other, or compared to a suitable comparator (i.e. no MDT care)	It would be difficult to define specific MDT strategies as there is wide variation in current practice. It was also anticipated that there would not be many studies in this area. Therefore the committee decided to review the evidence	
8.	Comparator/Reference standard/Confounding factors			

			for any MDT strategies.	
9.	Types of study to be included	• Systematic reviews • RCTs Non-randomised studies will be excluded unless there are no randomised studies found. If no randomised studies are found, non-randomised comparative trials will be considered (including prospective cohort studies) if they have attempted to detect and, if needed, adjust for, confounders.	For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching.	
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.		
11.	Context	N/A		
12.	Primary outcomes (critical outcomes)	Longest follow up available:		

		CRITICAL OUTCOMES: • Quality of life (any validated scales, for example, EQ-5D, SF-36) • Pain (VAS/NRS) • Fatigue (any validated scales) • Physical functioning / exercise tolerance / ADL (any validated scales) • Cognitive functioning (any validated scales) • Sleep quality (any validated scales) • Adverse effects (any reported by the studies) • Psychological outcomes • Patient satisfaction • Benefit status/employment/school attendance/school absences • Update of diagnostic status • Comorbidities • Activity monitoring • Post Exertional Malaise		
13.	Secondary outcomes (important outcomes)	• Care needs • Impact on the carer/family	.	
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion.		

		The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.		
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed:		

		• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.		
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary		

		outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.		

		If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.		
17.	Analysis of sub-groups	Stratification: • Age: children vs young people vs adults • Severity: severe vs not severe Subgroups to investigate if heterogeneity is present: • post infectious onset / no post infectious onset • Duration of illness (<3 months symptoms/3-36 months/>36 months) • Gender • When study was done (pre 2000/post 2000) • Level of care: primary / secondary / tertiary care • Treatment approach used (CBT and rehab/rest/mixed/other)	Stratification of age and severity as they have been identified as needing special consideration in the scope.	
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic		

		☐ Service Delivery ☐ Other (please specify)				
19.	Language	English				
20.	Country	England				
21.	Anticipated or actual start date	01/01/20				
22.	Anticipated completion date	01/01/21				
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**		
		Preliminary searches	☑	☐		
		Piloting of the study selection process	☑	☐		
		Formal screening of search results against eligibility criteria	☐	☐		

		Data extraction	☐	☐		
		Risk of bias (quality) assessment	☐	☐		
		Data analysis	☐	☐		
24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre				
25.	Review team members	From the National Guideline Centre: • Dr Kate Kelley [Guideline lead] • Ms Maria Smyth [Senior systematic reviewer] • Ms Melina Vasileiou [Systematic reviewer] • Dr Richard Clubbe [Systematic reviewer] • Dr Karin van Bart [Systematic reviewer] • Mr David Wonderling [Health economist] • Ms Agnes Cuyas [Information specialist]				

		• Ms Kate Ashmore [Project manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10091	NB this will be left blank in PROSPERO	

29.	Other registration details			
30.	Reference/URL for published protocol			
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.		
32.	Keywords			
33.	Details of existing review of same topic by same authors	N/A		
34.	Current review status	☒ Ongoing		

		☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued		
35..	Additional information	N/A		
36.	Details of final publication	www.nice.org.uk		

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[11] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide

	to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

This literature search strategy was used for the following review question:

- In people with ME/CFS, what is the clinical and cost-effectiveness of different models of multidisciplinary care?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[11]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve.

Searches for patient views were run in Medline (OVID), Embase (OVID), CINAHL, and PsycINFO (ProQuest).

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 June 2020	Exclusions
Embase (OVID)	1974 – 23 June 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 23 June 2020	None
PsycINFO (ProQuest)	Inception – 23 June 2020	Exclusions
Epistemonikos (The Epistemonikos Foundation)	Inception - 23 June 2020	None

Medline (Ovid) search terms

1.	Fatigue Syndrome, Chronic/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.

9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language

Embase (Ovid) search terms

1.	chronic fatigue syndrome/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.

11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	limit 33 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Fatigue Syndrome, Chronic] this term only
#2.	chronic* fatigue*:ti,ab
#3.	(fatigue* near/2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)):ti,ab
#4.	((myalgic or post infection* or postinfection*) near/1 (encephalomyelitis or encephalopathy)):ti,ab
#5.	((ME near/1 CFS) or (CFS near/1 ME) or CFIDS or PVFS):ti,ab
#6.	(Systemic Exertion Intolerance Disease or SEID):ti,ab
#7.	((CFS near/1 SEID) or (SEID near/1 CFS) or (ME near/1 CFS near/1 SEID) or (ME near/1 SEID) or (SEID near/1 ME)):ti,ab
#8.	(Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS)
#9.	((Post-exertional or postexertional) near/2 malaise):ti,ab
#10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia):ti,ab
#11.	((atypical or simulating or resembling) near/1 poliomyelitis):ti,ab
#12.	((chronic epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis):ti,ab
#13.	xenotropic murine leukemia virus-related virus:ti,ab
#14.	effort syndrome*:ti,ab
#15.	((akureyri or iceland or tapanui or "royal free" or "royal free hospital") near/1 disease*):ti,ab

#16.	((yuppie or yuppy or tapanui) near flu):ti,ab
#17.	(or #1-#16)

CINAHL (EBSCO) search terms

S1.	(MH "Fatigue Syndrome, Chronic")
S2.	chronic* fatigue*
S3.	(fatigue* n2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*))
S4.	((myalgic or post infection* or postinfection*) and (encephalomyelitis or encephalopathy))
S5.	((ME and CFS) or (CFS and ME) or CFIDS or PVFS)
S6.	(Systemic Exertion Intolerance Disease or SEID)
S7.	((CFS and SEID) or (SEID and CFS) or (ME and CFS and SEID) or (CFS and ME and SEID) or (ME and SEID) or (SEID and ME))
S8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome) and (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion))
S9.	((Post-exertional or postexertional) n2 malaise)
S10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia)
S11.	((atypical or simulating or resembling) and poliomyelitis)
S12.	(chronic epstein Barr virus or chronic mononucleosis)
S13.	xenotropic murine leukemia virus-related virus
S14.	effort syndrome*
S15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) and disease*) or ((yuppie or yuppy or tapanui) and flu))
S16.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

PsycINFO (ProQuest) search terms

1.	((((chronic* fatigue*) OR (fatigue* NEAR2 (disorder* OR syndrome* OR post viral OR postviral OR immune dysfunction* OR post infection* OR postinfection*)) OR ((myalgic OR post infection* OR postinfection*) NEAR1 (encephalomyelitis OR encephalopathy)) OR ((ME NEAR1 CFS) OR (CFS NEAR1 ME) OR CFIDS OR PVFS) OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS NEAR1 SEID) OR (SEID NEAR1 CFS)) OR ((ME NEAR1 CFS NEAR1 SEID) OR (ME NEAR1 SEID) OR (SEID NEAR1 ME)) OR ((Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) NEAR6 (CFS OR chronic* fatigue* OR ME OR myalgic OR SEID OR systemic exertion)) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR ((atypical OR simulating OR resembling) NEAR1 poliomyelitis)) OR (((chronic NEAR2 epstein Barr virus) OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR ((akureyri OR iceland OR tapanui OR royal free OR royal free hospital) NEAR1 disease*) OR ((yuppie OR yuppy OR tapanui) NEAR1 flu) OR MAINSUBJECT.EXACT.EXPLODE("Chronic Fatigue Syndrome"))) AND (stype.exact("Scholarly Journals") AND la.exact("ENG") AND po.exact("Human") NOT (me.exact("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Clinical Trial" OR "Qualitative Study" OR "Prospective Study" OR "Followup Study" OR "Literature Review" OR "Retrospective Study" OR "Systematic Review" OR "Meta Analysis") AND po.exact("Human"))

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS"

	OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))) OR advanced_abstract_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))))

B.2 Health economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to ME/CFS population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018), with no date restrictions. NHS EED and HTA databases are

hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 June 2020	Exclusions Health economics studies
Embase	2014 –30 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

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Medline (Ovid) search terms

1.	Fatigue Syndrome, Chronic/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.

27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	Economics/
38.	Value of life/
39.	exp "Costs and Cost Analysis"/
40.	exp Economics, Hospital/
41.	exp Economics, Medical/
42.	Economics, Nursing/
43.	Economics, Pharmaceutical/
44.	exp "Fees and Charges"/
45.	exp Budgets/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/37-52
54.	36 and 53

Embase (Ovid) search terms

1.	chronic fatigue syndrome/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.

11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.
43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.
45.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	34 and 48

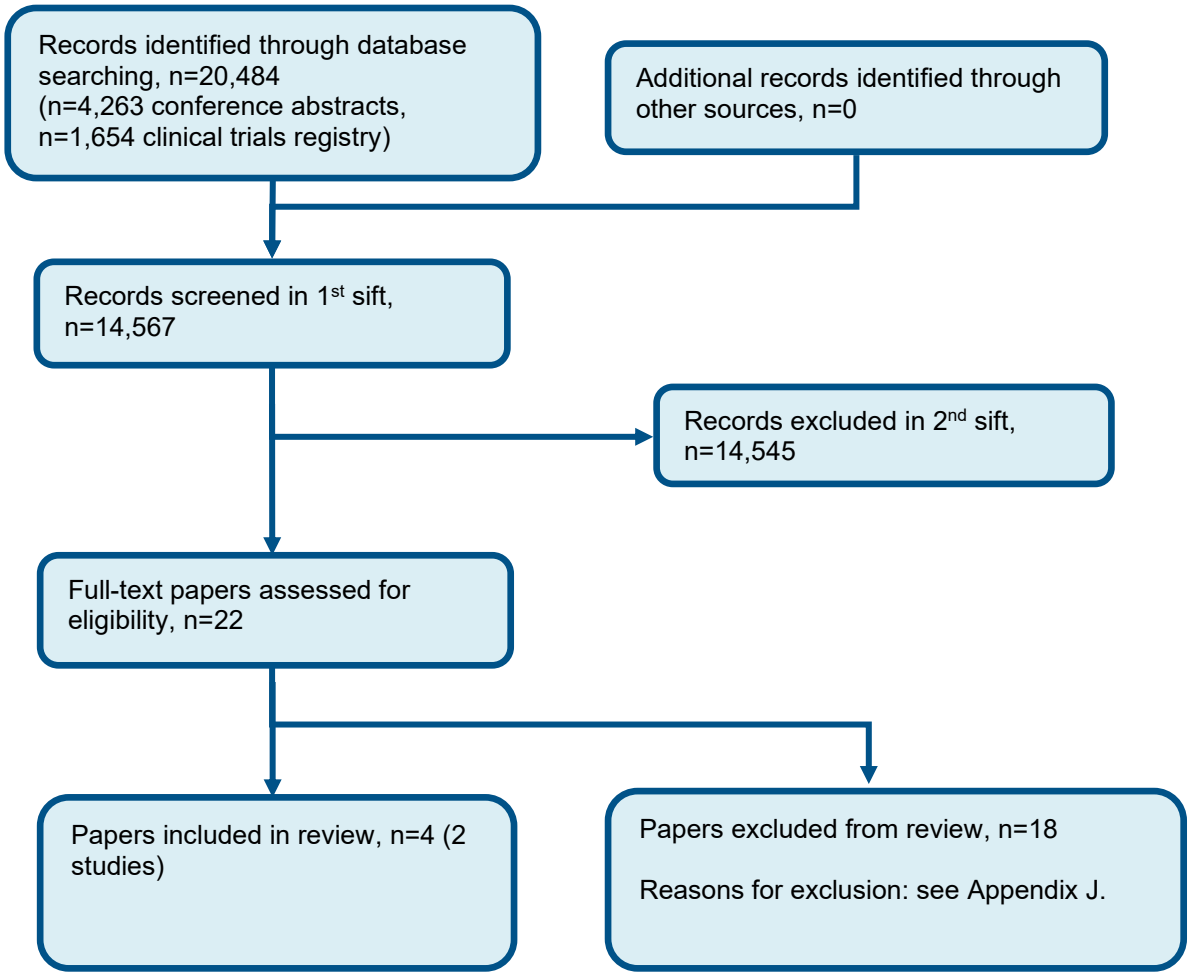
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Fatigue Syndrome, Chronic
#2.	(chronic fatigue or fatigue syndrome*)

#3.	((myalgic adj (encephalomyelitis or encephalopathy)))
#4.	(((ME adj CFS) or (CFS adj ME)))
#5.	(post viral fatigue or post viral syndrome* or viral fatigue syndrome* or PVFS)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(neurasthenic neuroses or epidemic neuromyasthenia or post infectious encephalomyelitis or neurataxia or neuroasthenia)
#8.	(((atypical or simulating or resembling) adj poliomyelitis))
#9.	(chronic epstein Barr virus or chronic mononucleosis)
#10.	(xenotropic murine leukemia virus-related virus)
#11.	(((chronic fatigue and immune dysfunction syndrome*) or cfids or chronic fatigue-fibromyalgia syndrome* or chronic fatigue disorder* or Systemic Exertion Intolerance Disease or SEID or effort syndrome or post infectious fatigue))
#12.	((((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)))
#13.	#7 OR #8 OR #9 OR #10 OR #11 OR #12
#14.	#6 or #13

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of multidisciplinary care



Appendix D Effectiveness evidence

Study	O'Dowd 2006[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=153)
Countries and setting	Conducted in United Kingdom; Setting: Pain management centre in UK hospital.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: According to Fukuda criteria (CDC)
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Presentation consistent with CDC criteria; patient given informed consent
Exclusion criteria	Concurrent severe mental illness (i.e. psychosis and allied conditions); planned or concurrent rehabilitation; inability to attend all treatment sessions; ongoing physical investigations
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: CBT/EAS/SMC: 41.6/38.8/42.9. Gender (M:F): 51:102. Ethnicity: unclear
Further population details	
Extra comments	CBT/EAS/SMC: lives alone 14%/12%/22%; total number of symptoms 7/9/9; time since diagnosis >36 months 22%/34%/40%; psychological or psychiatric treatment for CFS previously 17%/13%/18%; current antidepressants 44%/46%/30%; required help because of CFS 68%/73%/66%;
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=52) Intervention 1: Psychological and behavioural interventions - CBT. The CBT used in this trial was designed to do two things: first to attempt to modify thoughts and beliefs about symptoms and illness, and second to attempt to modify behavioural responses to symptoms and illness, such as rest, sleep and activity. The ultimate goal of the treatment was to increase adaptive coping strategies and therefore reduce the distress and disability. The content of the programme included: ● Elucidation of core beliefs regarding their illness and its management. ● Monitoring of activity levels and introduction of appropriate timetable. ● Introduction to exercises designed to increase general level of fitness, balance and confidence in

Study	O'Dowd 2006[13]
	exercise. A range of aerobic, strength, balance and stretching exercises were taught. ● Behavioural modification of sleep patterns. ● Mood management advice. ● Goal setting. The CBT groups were introduced to a structured incremental exercise programme following a group discussion about the unhelpful nature of activity cycling, following CBT principles. The calculation of a deliberately low 'baseline' for exercise as a means of counteracting activity cycling was taught, and instructions were given about pacing up by small increments once the exercise level had been achieved successfully for several days (flexibility was allowed for patients to choose their own frequency of increments). Advice was given to patients to reduce the level of exercise considerably should a significant increase in symptoms be experienced at some stage in the future, and the balance between the risks and the benefits of prolonged rest during such a setback was explored. The management of setbacks was a specific subject included in the CBT group syllabus. Duration 14 weeks (8 fortnightly meetings, each lasting 2 hours). Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: CBT CFS-specific and delivered by 4 therapists with experience in chronic illness management (one with considerable experience with ME/CFS) (n=50) Intervention 2: Advice - occupational or school. Education and Support group (EAS). The same therapists met with these groups, in the same setting, at the same time and for the same duration and frequency as the CBT groups. The focus of these groups was on the sharing of experiences and the learning of basic relaxation skills. Each week, a different relaxation exercise was taught. These groups served as a control for the non-specific effects of therapy and controlled for the effects of therapist time and attention. In order to validate the role of the physiotherapist within the EAS condition, a stretch programme was introduced. This included 16 stretches for major muscle groups in the body, and patients were advised to perform each stretch twice, in a relaxed manner. The purpose of the stretches was explained as loosening the muscles so that a state of relaxation in the muscles could be achieved. If further questions regarding exercise were asked in these groups, the group was informed that there was controversy regarding the value of aerobic exercise, and therefore we did not wish to introduce exercise if it were to be unhelpful for some patients. The physiotherapist also participated in the teaching of relaxation techniques, including in particular those that involved movement such as progressive muscle relaxation and slow diaphragmatic breathing. . Duration 14 weeks. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: unclear whether relaxation intervention was CFS-specific; delivered by 4 therapists with experience in chronic illness management (one with considerable experience with ME/CFS) (n=51) Intervention 3: usual care - standard medical care. This group did not attend the hospital other than to

Study	O'Dowd 2006[13]
	complete the assessment material at baseline and 6 and 12 months. They continued to be managed in primary care . Duration 14 weeks. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus ADVICE - OCCUPATIONAL OR SCHOOL

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical at Pooled 6 and 12 months data; MD; -0.4 (95%CI -2.86 to 2.06, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF36 mental at Pooled 6 and 12 months data; MD; 3.16 (95%CI -0.05 to 6.38, Units: 0-100, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Health status (HUI3) at Pooled 6 and 12 months data; MD; 0.023 (95%CI -0.0065 to 0.11, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue score at Pooled 6 and 12 months data; MD; -3.16 (95%CI -5.59 to -0.74, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Study	O'Dowd 2006[13]
Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear Protocol outcome 3: Cognitive function at longest follow up available - Actual outcome for adults; severity mixed or unclear: total words recalled at Pooled 6 and 12 months data; MD; 0.77 (95%CI -0.32 to 1.86, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 5, Reason: unclear - Actual outcome for adults; severity mixed or unclear: correct words at Pooled 6 and 12 months data; MD; 0.84 (95%CI -0.26 to 1.94, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 5, Reason: unclear - Actual outcome for adults; severity mixed or unclear: reaction time at Pooled 6 and 12 months data; MD; 0.99 (95%CI 0.9 to 1.08, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 5, Reason: unclear Protocol outcome 4: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: HADS anxiety at Pooled 6 and 12 months data; MD; -0.51 (95%CI -1.7 to 0.68, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear - Actual outcome for adults; severity mixed or unclear: HADS depression at Pooled 6 and 12 months data; MD; -0.13 (95%CI -1.13 to 0.87, Comments:	

Study	O'Dowd 2006[13]
ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear - Actual outcome for adults; severity mixed or unclear: General health Questionnaire at Pooled 6 and 12 months data; MD; -1.8 (95%CI -4.17 to 0.57, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear Protocol outcome 5: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Normal walking speed at Pooled 6 and 12 months data; MD; 1.77 (95%CI 0.025 to 3.51, Units: shuttles, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear - Actual outcome for adults; severity mixed or unclear: Shuttles walked at Pooled 6 and 12 months data; MD; 1.16 (95%CI 0.94 to 1.43, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus STANDARD MEDICAL CARE Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: SF36 physical at Pooled 6 and 12 months data; MD; -1.63 (95%CI -4.05 to 0.78, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);	

Study	O'Dowd 2006[13]
	Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: SF36 mental at Pooled 6 and 12 months data; MD; 4.35 (95%CI 0.72 to 7.97, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: Health status (HUI3) at Pooled 6 and 12 months data; MD; 0.029 (95%CI -0.052 to 0.11, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear Protocol outcome 2: Fatigue at longest follow up available - Actual outcome for adults; severity mixed or unclear: Chalder fatigue score at Pooled 6 and 12 months data; MD; -2.61 (95%CI -4.92 to -0.3, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear Protocol outcome 3: Cognitive function at longest follow up available - Actual outcome for adults; severity mixed or unclear: total words recalled at Pooled 6 and 12 months data; MD; 0.69 (95%CI -0.47 to 1.86, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Study	O'Dowd 2006[13]

- Actual outcome for adults; severity mixed or unclear: correct words at Pooled 6 and 12 months data; MD; 0.80 (95%CI -0.3 to 1.89, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: reaction time at Pooled 6 and 12 months data; MD; 0.93 (95%CI 0.86 to 1.02, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS anxiety at Pooled 6 and 12 months data; MD; -1.27 (95%CI -2.52 to -0.02, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: HADS depression at Pooled 6 and 12 months data; MD; -0.56 (95%CI -1.69 to 0.58, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: General health Questionnaire at Pooled 6 and 12 months data; MD; -2.21 (95%CI -4.52 to 0.1, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but

Study	O'Dowd 2006[13]
small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear Protocol outcome 5: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Normal walking speed at Pooled 6 and 12 months data; MD; 2.83 (95%CI 1.12 to 5.53, Units: shuttles, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: Shuttles walked at Pooled 6 and 12 months data; MD; 1.2 (95%CI 0.99 to 1.45, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADVICE - OCCUPATIONAL OR SCHOOL versus STANDARD MEDICAL CARE Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: SF36 physical at Pooled 6 and 12 months data; MD; -1.23 (95%CI -3.52 to 1.05, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: SF36 mental at Pooled 6 and 12 months data; MD; 1.19 (95%CI -2.26 to 4.63, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear	

Study	O'Dowd 2006[13]

- Actual outcome for adults; severity mixed or unclear: Health status (HUI3) at Pooled 6 and 12 months data; MD; 0.006 (95%CI -0.082 to 0.095, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue score at Pooled 6 and 12 months data; MD; 0.55 (95%CI -1.56 to 2.66, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: total words recalled at Pooled 6 and 12 months data; MD; -0.076 (95%CI -1.2 to 1.05, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: correct words at Pooled 6 and 12 months data; MD; -0.044 (95%CI -1.14 to 1.05, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: reaction time at Pooled 6 and 12 months data; MD; 0.95 (95%CI 0.87 to 1.03, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	O'Dowd 2006[13]
Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear Protocol outcome 4: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: HADS anxiety at Pooled 6 and 12 months data; MD; -0.76 (95%CI -2 to 0.47, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: HADS depression at Pooled 6 and 12 months data; MD; -0.43 (95%CI -0.56 to 0.7, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: General health Questionnaire at Pooled 6 and 12 months data; MD; -0.41 (95%CI -2.8 to 1.98, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear Protocol outcome 5: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Normal walking speed at Pooled 6 and 12 months data; MD; 1.06 (95%CI -0.37 to 2.49, Units: shuttles, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear	

Study	O'Dowd 2006[13]
- Actual outcome for adults; severity mixed or unclear: Shuttles walked at Pooled 6 and 12 months data; MD; 1.04 (95%CI 0.86 to 1.24, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available

Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[23] (Vos-Vromans 2017[22], Vos-Vromans 2012[24])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=122)
Countries and setting	Conducted in Netherlands; Setting: Four rehabilitation centres
Line of therapy	Unclear
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: consultant confirmed the inclusion and exclusion criteria and verified whether an extensive physical examination and 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.
Stratum	adults; severity mixed or unclear: age between 18 and 60 years; meeting CDC criteria, Checklist Individual Strength fatigue subscale score of 40 or more - no further detail on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	met the US Centers for Disease Control and Prevention (CDC-94) criteria for CFS; a Checklist Individual Strength fatigue subscale score of 40 or more; willingness to participate in a treatment aimed at changing behaviour; age between 18 and 60 years and comprehension of written and verbal Dutch

Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[23] (Vos-Vromans 2017[22], Vos-Vromans 2012[24])
Exclusion criteria	medical condition explaining the presence of chronic fatigue; psychotic, major or bipolar depressive disorder, dementia, anorexia, bulimia nervosa or a body mass index ≥45 kg m 2; alcohol and/or drug abuse; pregnancy; already received CBT or MRT for CFS in the past; had to travel for more than 1 h to the nearest participating rehabilitation centre
Recruitment/selection of patients	patients referred to 4 rehabilitation centres meeting eligibility criteria during the recruitment period
Age, gender and ethnicity	Age - Mean (SD): multidisciplinary rehabilitation 40 (10.2), CBT 40.6 (12) years. Gender (M:F): 25/97. Ethnicity: country of birth The Netherlands n=110, other European country n=6, country outside Europe n=4
Further population details	NA
Extra comments	In some regions in the Netherlands, the incidence of Q fever increased during the trial. As Q fever can cause similar symptoms to those of CFS, patients from high-risk regions were additionally tested for Q fever and excluded from the study in case of a positive diagnosis.
Indirectness of population	No indirectness: NA
Interventions	(n=62) Intervention 1: Psychological and behavioural interventions - pragmatic rehabilitation. Patient-centred and based on addressing modifiable components that are related with the precipitation, predisposition and perpetuation of CFS. Observational phase: thorough assessment (interview, physical examination, baseline assessment and goal setting) by an interdisciplinary team (physical therapist, occupational therapist, psychologist and social worker) over 2 weeks (total contact time 8.5 h). Followed by 2 weeks without treatment in which the therapists and the consultant in rehabilitation medicine discussed findings, defined the treatable components and proposed treatment. 10-week treatment phase: individual sessions (total contact time 33 h), weekly visits to the PT and OT and biweekly visits to the psychologist and social worker. Included CBT and, depending on the individual analysis, elements of body awareness therapy, gradual reactivation, pacing, mindfulness, gradual normalization of sleep/wake rhythm and social reintegration. PT and OT focused on the gradual reactivation of the patient by increasing activities under supervision. PT focused on body awareness therapy, aiming to establish increased awareness and consciousness of the body and its relation to psychological well-being. PT and OT taught patient to pace activities and avoid bursts of extreme activity followed by extreme fatigue. Patient coached to reintegrate into society by making a plan to return to work or school and increase

Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[23] (Vos-Vromans 2017[22], Vos-Vromans 2012[24])
	social activities. Psychologist and OT addressed the gradual normalization of a patient's sleep/wake rhythm. According to CBT principles, the psychologist focused on modification of dysfunctional beliefs regarding illness symptoms, activity, self-expectations and self-esteem and the development of more effective coping strategies. Every therapist followed the principles of CBT and incorporated them with mindfulness principles. Interdisciplinary team meetings scheduled to discuss progress. Follow-up phase (12weeks): patients returned for 2 days to meet with the social worker and 2 therapists of their choice. Issues of social reintegration and participation discussed and patients encouraged to continue using the principles learned. Most therapists had experience in treating patients with chronic pain and/or chronic fatigue and familiar with CBT. They received training for each discipline (3–5 day) and attended 2 team meetings and 2 supervision meetings for each discipline during the trial. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (Most therapists had experience in treating patients with chronic pain and/or chronic fatigue; MRT tailored to CFS). (n=60) Intervention 2: Psychological and behavioural interventions - 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, over 6 months. Weekly contact with the psychologist or behavioural therapist for 6 weeks, followed by biweekly contact for next 20 weeks. Protocol specifically tailored for either relatively active or passive patients. Relatively active patients started by practising at an activity level in which an increase of symptoms is avoided. For passive patients, physical activities were gradually increased from the beginning of therapy. 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. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or

Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[23] (Vos-Vromans 2017[22], Vos-Vromans 2012[24])
	specialist CFS practitioners specifically designed for ME/CFS (Therapists were experienced in treating patients with complaints of chronic pain and/or chronic fatigue, CBT tailored to CFS).
Funding	Other (Netherlands Organisation for Health Research and Development, Rehabilitation Fund, Foundation Nutsohra and ME/CVS Stichting Nederland)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIDISCIPLINARY REHABILITATION versus CBT

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical component summary at 52 weeks; MD; 2.67 (95%CI -1.45 to 6.79) (p value : 0.2)
SF36 physical component summary 0-100 Top=High is good outcome, Comments: Baseline values: MRT 30.59 (7.93), CBT 32.6 (7.78)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance) n=112 (55 CBT, 57 MRT)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment ; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

- Actual outcome for adults; severity mixed or unclear: SF36 mental component summary at 52 weeks ; MD; 1.59 (95%CI -1.96 to 5.13) (p value : 0.38)
SF36 mental component summary 0-100 Top=High is good outcome, Comments: Baseline values: MRT 46.57 (9.23), CBT 44.38 (9.02)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance) n=112 (55 CBT, 57 MRT)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment ; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile 8 at 52 weeks; MD; 50.78 (95%CI -186.68 to 288.24) (p value : 0.67)
Sickness Impact Profile 8 0-6160 Top=High is poor outcome, Comments: Baseline values: MRT (1418.27 (614.24), CBT 1222.17 (633.53)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance) n=112 (55 CBT, 57 MRT)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[23] (Vos-Vromans 2017[22], Vos-Vromans 2012[24])

Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment ; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual Strength - fatigue severity at 52 weeks ; MD; -5.69 (95%CI -10.62 to -0.76) (p value : 0.02) Checklist Individual Strength 8-56 Top=High is poor outcome, Comments: Baseline values: MRT 51.47 (5.08), CBT 51.05 (5.09)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance) n=112 (55 CBT, 57 MRT)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment ; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Symptom Checklist 90 at 52 weeks ; MD; -7.83 (95%CI -19.84 to 4.19) (p value : 0.2) Symptom Checklist 90 90-450 Top=High is poor outcome, Comments: Baseline values: MRT 158.73 (39.86), CBT 163.87 (34.4)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance) n=112 (55 CBT, 57 MRT)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment ; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 5: activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Accelerometer at 52 weeks ; MD; 2009.58 (p value : 0.85), Comments: Reported CIs: -19140.04 - 23159.19 Baseline values: MRT 206233.65 (40264.16), CBT 202033.66 (43379.41)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance) accelerometer registers the peak acceleration (in counts) every minute in two directions (longitudinal and transverse axis). A count is a measure of frequency and intensity of acceleration and deceleration (with higher counts indicating a higher degree of physical activity). n=80. Skin rash and unwillingness to either wear the monitor or travel to the rehabilitation centre to collect the monitor were the main reasons for not providing activity monitor data

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic

Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[23] (Vos-Vromans 2017[22], Vos-Vromans 2012[24])
and clinical characteristics at referral; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

Appendix E Forest plots

E.1 Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear

Figure 2: Quality of life (SF36); 0-100; high is good outcome

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 Mental				
O'Dowd 2006	1.19	1.7602	100.0%	1.19 [-2.26, 4.64]
Subtotal (95% CI)			**100.0%**	**1.19 [-2.26, 4.64]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.68 (P = 0.50)				
4.1.2 Physical				
O'Dowd 2006	-1.23	1.1684	100.0%	-1.23 [-3.52, 1.06]
Subtotal (95% CI)			**100.0%**	**-1.23 [-3.52, 1.06]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.05 (P = 0.29)				

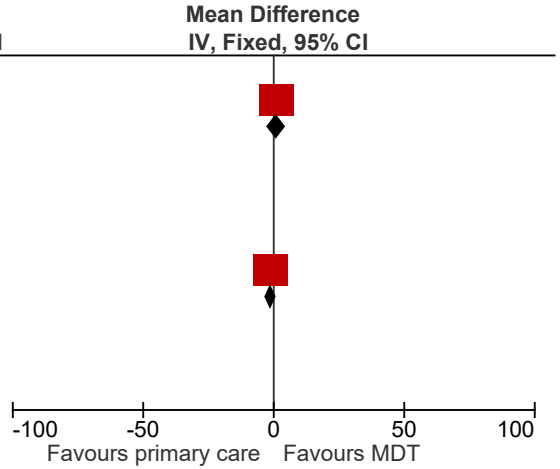


Figure 3: Quality of life (Health status (HUI3)); scale not reported; high is good outcome

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	0.006	0.0449	100.0%	0.01 [-0.08, 0.09]
Total (95% CI)			**100.0%**	**0.01 [-0.08, 0.09]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.13 (P = 0.89)				

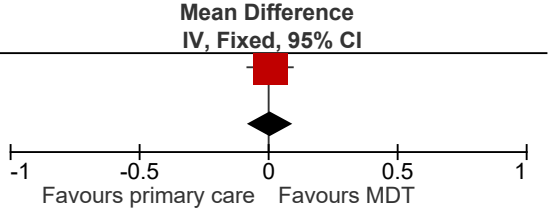


Figure 4: Fatigue/fatigability (Chalder fatigue questionnaire); 0-33; high is poor outcome

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	0.55	1.0766	100.0%	0.55 [-1.56, 2.66]
Total (95% CI)			**100.0%**	**0.55 [-1.56, 2.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)

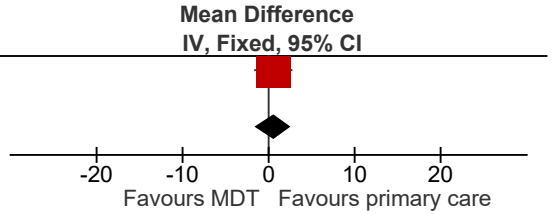


Figure 5: Cognitive function (total words recalled)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	-0.076	0.5735	100.0%	-0.08 [-1.20, 1.05]
Total (95% CI)			**100.0%**	**-0.08 [-1.20, 1.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)

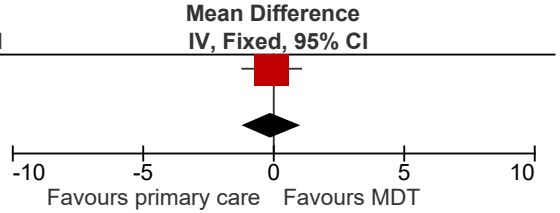


Figure 6: Cognitive function (correct words)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	-0.044	0.5592	100.0%	-0.04 [-1.14, 1.05]
Total (95% CI)			**100.0%**	**-0.04 [-1.14, 1.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)

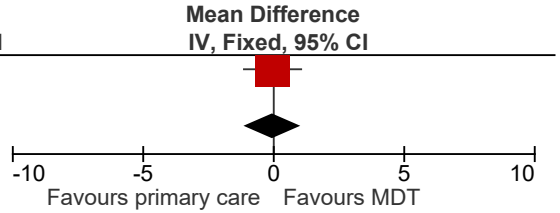


Figure 7: Cognitive function (reaction time)

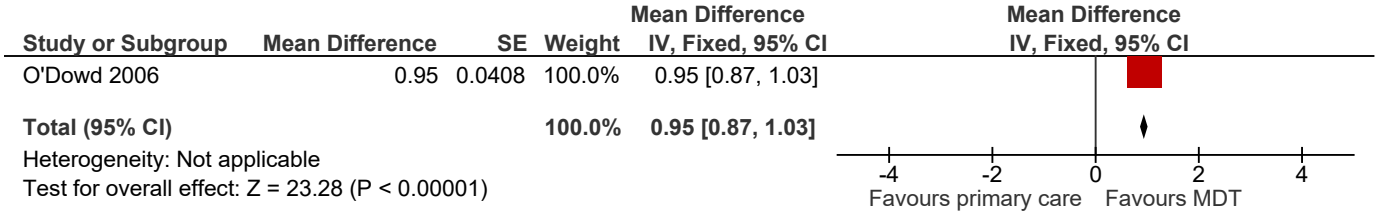


Figure 8: Psychological status (Hospital Anxiety and Depression Scale); 0-21; high is poor outcome

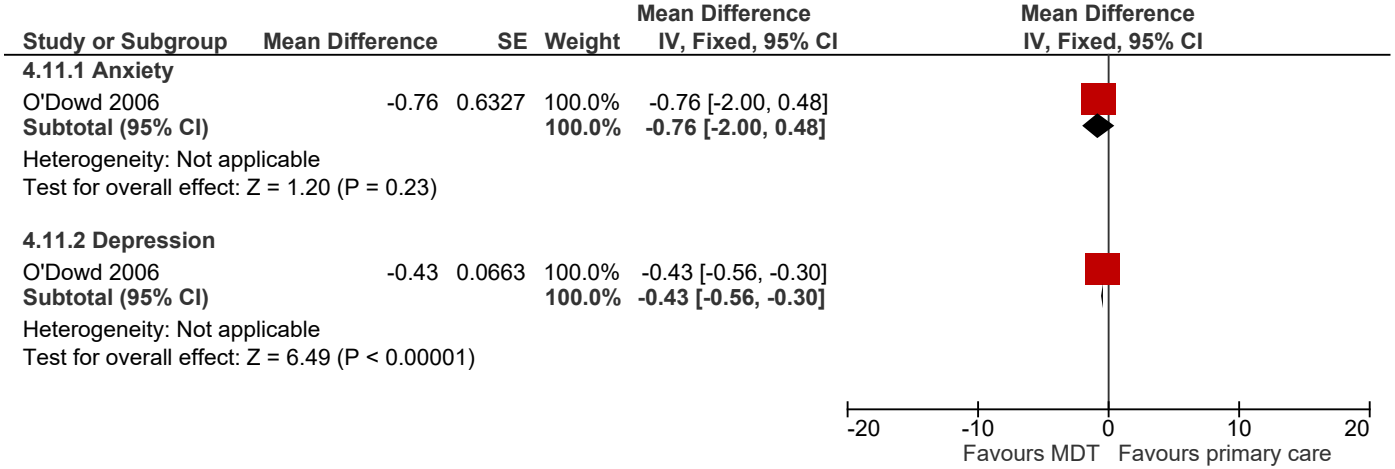


Figure 9: Psychological status (General health questionnaire); 0-36; high is poor outcome

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	-0.41	1.2194	100.0%	-0.41 [-2.80, 1.98]
Total (95% CI)			**100.0%**	**-0.41 [-2.80, 1.98]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)

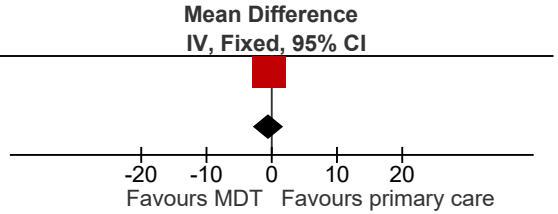


Figure 10: Exercise performance measure (Normal walking speed)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	1.06	0.7296	100.0%	1.06 [-0.37, 2.49]
Total (95% CI)			**100.0%**	**1.06 [-0.37, 2.49]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

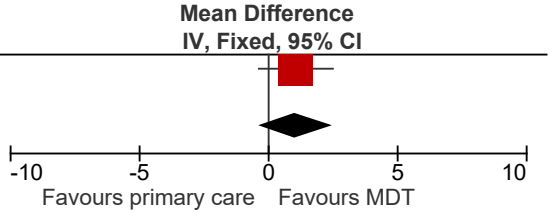


Figure 11: Exercise performance measure (Shuttles walked)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	1.04	0.0918	100.0%	1.04 [0.86, 1.22]
Total (95% CI)			**100.0%**	**1.04 [0.86, 1.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 11.33 (P < 0.00001)

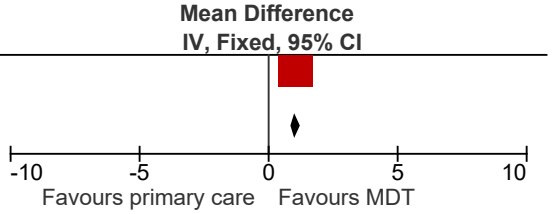
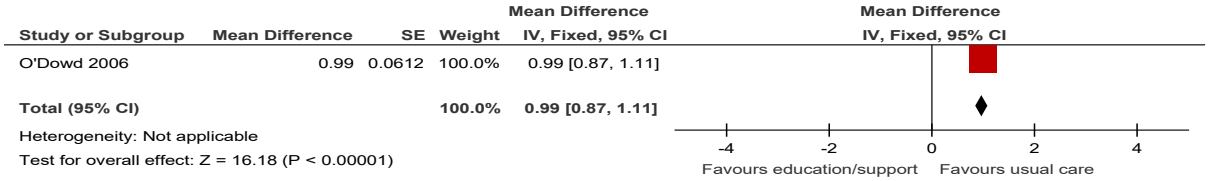


Figure 12: Exercise performance measure (perceived fatigue- modified Borg scale)



E.2 Physical therapist + occupational therapist + psychologist + social worker versus psychologist/behavioural therapist; adults, severity mixed or unclear

Figure 13: Quality of life (SF36); 0-100; high is good outcome

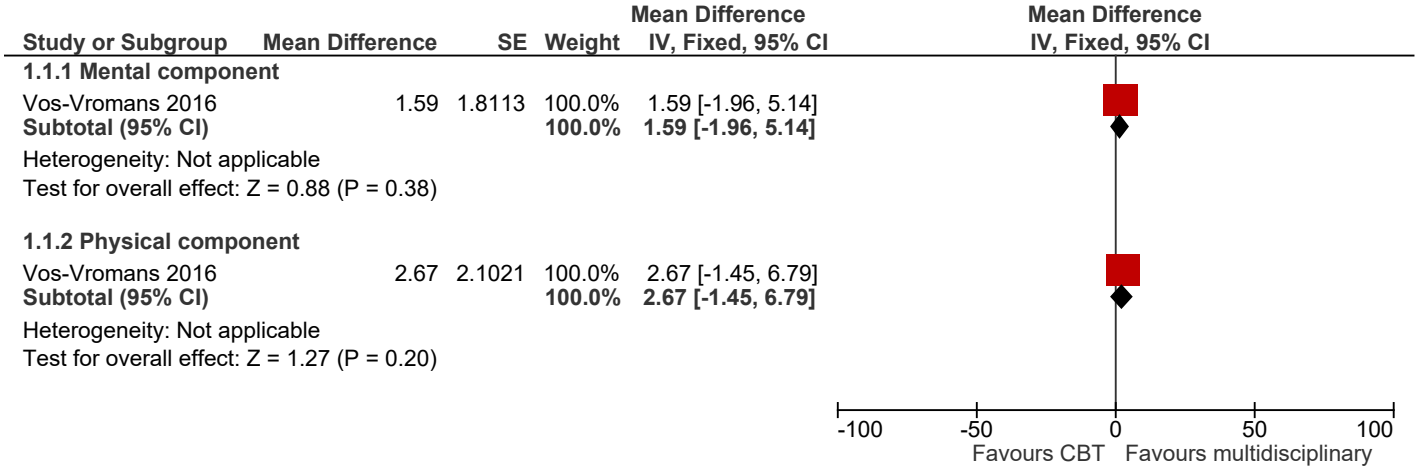


Figure 14: General symptom scales (Sickness impact profile 8); 0-6160; high is poor outcome

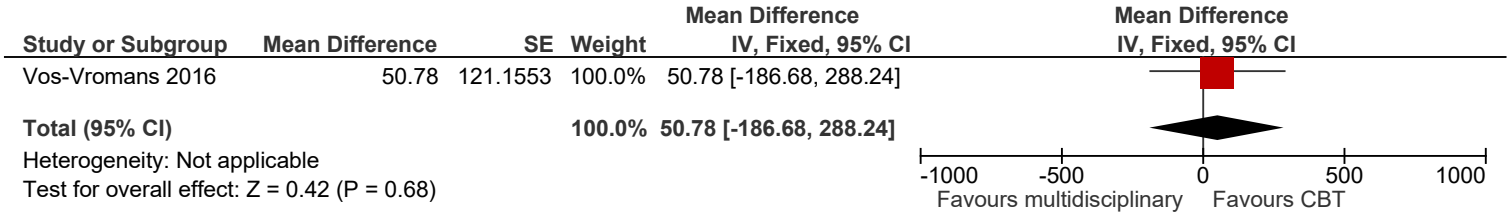


Figure 15: Fatigue (Checklist individual strength – fatigue severity); 8-56; high is poor outcome

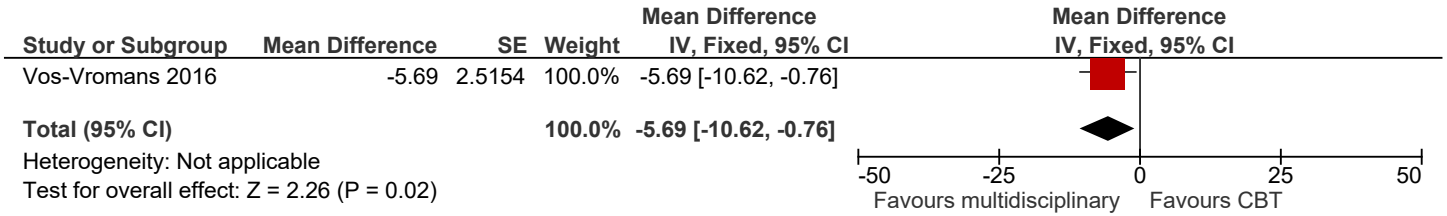


Figure 16: Psychological status (Symptom checklist 90); 90-450; high is poor outcome

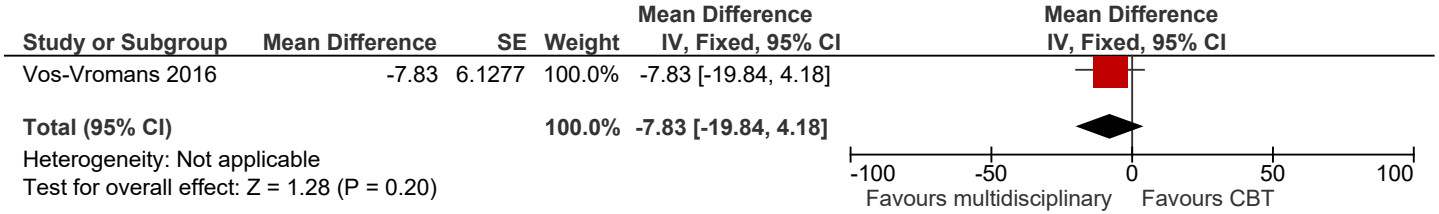
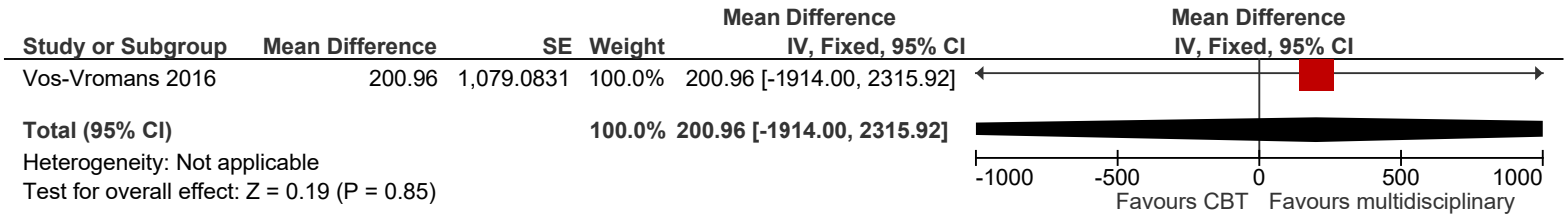


Figure 17: Activity levels (accelerometer); high is good outcome



Source/Note: Values have been divided by one decimal place in order to display the effect estimate

Appendix F GRADE tables

Table 9: Clinical evidence profile: Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear	Control	Relative (95% CI)	Absolute		
Quality of life (SF36 Pooled 6 and 12 months data) - Mental (follow-up 6-12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.19 higher (2.26 lower to 4.64 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (SF36 Pooled 6 and 12 months data) - Physical (follow-up 6-12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.23 lower (3.52 lower to 1.06 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Health status (HUI3) Pooled 6 and 12 months data) (follow-up 6-12 months; range of scores: -0.36-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.01 higher (0.08 lower to 0.09 higher)	⊕⊕OO LOW	CRITICAL
Fatigue (Chalder fatigue scale Pooled 6 and 12 months data 0-33) (follow-up 6-12 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.55 higher (1.56 lower to 2.66 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (total words recalled Pooled 6 and 12 months data) (follow-up 6-12 months; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.08 lower (1.2 lower to 1.05 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (correct words Pooled 6 and 12 months data) (follow-up 6-12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.04 lower (1.14 lower to 1.05 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (reaction time Pooled 6 and 12 months data) (follow-up 6-12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.95 higher (0.87 to 1.03 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS Pooled 6 and 12 months data) - Anxiety (follow-up 6-12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.76 lower (2 lower to 0.48 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS Pooled 6 and 12 months data) - Depression (follow-up 6-12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.43 lower (0.56 to 0.3 lower)	⊕⊕OO LOW	CRITICAL
Psychological status (General health Questionnaire Pooled 6 and 12 months data) (follow-up 6-12 months; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.41 lower (2.8 lower to 1.98 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Normal walking speed Pooled 6 and 12 months data) (follow-up 6-12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.06 higher (0.37 lower to 2.49 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Shuttles walked Pooled 6 and 12 months data) (follow-up 6-12 months; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.04 higher (0.86 to 1.22 higher)	⊕⊕OO LOW	CRITICAL

[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) or a very indirect population (downgraded by two increments): 1. 1994 CDC criteria used; PEM is not a compulsory feature

Table 10: Clinical evidence profile: Physical therapist + occupational therapist + psychologist + social worker versus psychologist/behavioural therapist; adults, severity mixed or unclear

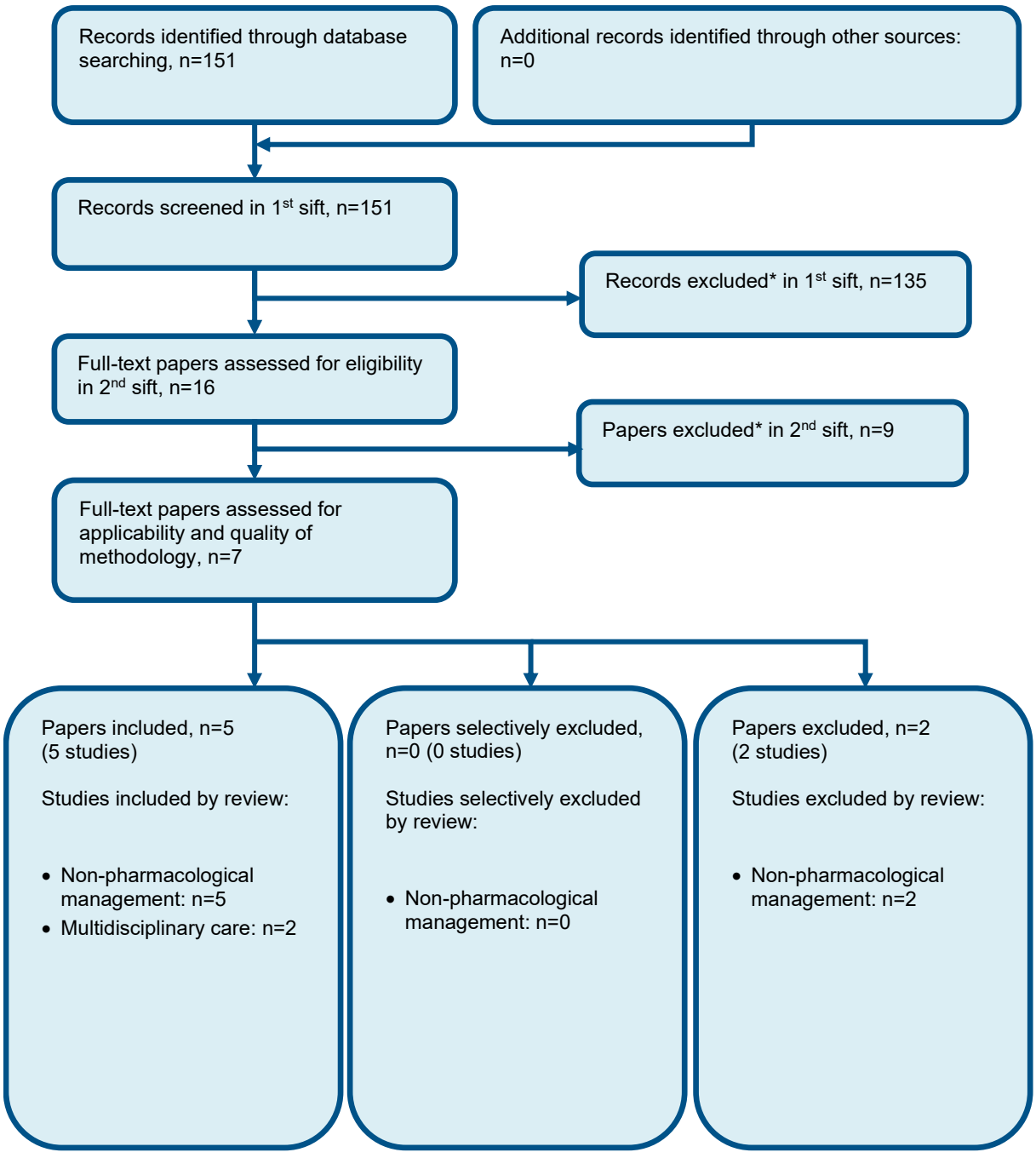
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multidisciplinary rehabilitation versus CBT**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF36) - Mental component (follow-up 52 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	62	60	-	MD 1.59 higher (1.96 lower to 5.14 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36) - Physical component (follow-up 52 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	62	60	-	MD 2.67 higher (1.45 lower to 6.79 higher)	⊕OOO VERY LOW	CRITICAL
General impact scale (Sickness impact profile 8) (follow-up 52 weeks; range of scores: 0-6160; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	62	60	-	MD 50.78 higher (186.68 lower to 288.24 higher)	⊕⊕OO LOW	CRITICAL
Fatigue (Checklist individual strength - fatigue severity) (follow-up 52 weeks; range of scores: 8-56; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	62	60	-	MD 5.69 lower (10.62 to 0.76 lower)	⊕OOO VERY LOW	CRITICAL

Psychological status (Symptom checklist 90) (follow-up 52 weeks; range of scores: 90-450; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	62	60	-	MD 7.83 lower (19.84 lower to 4.18 higher)	⊕⊕OO LOW	CRITICAL
Activity levels (accelerometer) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	62	60	-	MD 200.96 higher (1914 lower to 2315.92 higher)	⊕OOO VERY LOW	CRITICAL

[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) or a very indirect population (downgraded by two increments): 1. 1994 CDC or Oxford criteria used; PEM is not a compulsory feature.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G Economic evidence study selection

Figure 18: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

NB. Two papers were included in both the non-pharma and the multidisciplinary care reviews, in parallel with the review of clinical effectiveness.

Appendix H Economic evidence tables

Study	O'Dowd 2006[13]			
Study details	**Population & interventions**	**Costs (mean per patient)**	**Health outcomes (mean per patient)**	**Cost effectiveness**
Economic analysis: CEA (health outcome: HUI3). CUA [(a)] **Study design:** RCT **Approach to analysis:** Within-trial analysis **Perspective:** UK NHS **Time horizon/Follow-up**: 12 months **Discounting:** Costs: NA; Outcomes: NA	**Population:** The participants were NHS patients, currently managed in primary care. Presentation consistent with ME/CFS as described by Fukuda and colleagues, from the Centers for Disease Control and prevention N: 153 (followed up for 12 months) **Mean age:** 41.1 (SD 11.9) **Intervention 1:** **Standard Medical Care (SMC).** Patients continued to be managed in primary care **Intervention 2:** **Cognitive behavioural therapy (CBT).** 8 group sessions.The CBT used in this trial was designed to do two things: first to attempt to modify thoughts and beliefs about symptoms and illness, and second to attempt to modify behavioural responses to symptoms and illness, such as rest, sleep and activity. The ultimate goal of the treatment was to increase adaptive coping strategies and therefore reduce the distress and disability. The content of the programme included: ● Elucidation of core beliefs regarding their illness and its management. ● Monitoring of activity levels and introduction of appropriate timetable. ● Introduction to exercises designed to increase general level of fitness, balance and confidence in	**Intervention costs** Intervention 1: £0 Intervention 2: £344 Intervention 3: £344 **Health care costs:** Intervention 1: £391 Intervention 2: £285 Intervention 3: £376 **Drug costs** Intervention 1: £64 Intervention 2: £71 Intervention 3: £90 **Total NHS costs:** Intervention 1: £452 Intervention 2: £699 Intervention 3: £810 Incremental (2−1): +£248 Incremental (2−3): -£110 (95% CI: NR; p=NR) **Currency & cost year:** 2003 £UK	**HUI3 - difference between 12 months and baseline:** Intervention1: 0.021 Intervention 2: 0.047 Intervention 3: 0.075 **QALYs gained** [(a)] 2 vs 1: 0.013 3 vs 2: 0.014	2 vs 1 CBT cost £19,000 per QALY gained vs SMC 3 vs 2 EAS cost £7,929 per QALY gained vs CBT 3 vs 1 EAS cost £13,259 per QALY gained vs SMC CBT is subject to extended dominance **Analysis of uncertainty:** Standard deviations were reported. No sensitivity or statistical analysis was conducted.

	exercise. A range of aerobic, strength, balance and stretching exercises were taught. ● Behavioural modification of sleep patterns. ● Mood management advice. ● Goal setting. The CBT groups were introduced to a structured incremental exercise programme following a group discussion about the unhelpful nature of activity cycling, following CBT principles. The calculation of a deliberately low 'baseline' for exercise as a means of counteracting activity cycling was taught, and instructions were given about pacing up by small increments once the exercise level had been achieved successfully for several days (flexibility was allowed for patients to choose their own frequency of increments). Advice was given to patients to reduce the level of exercise considerably should a significant increase in symptoms be experienced at some stage in the future, and the balance between the risks and the benefits of prolonged rest during such a setback was explored. The management of setbacks was a specific subject included in the CBT group syllabus. **Intervention 3:** **Education and support (EAS).** 8 group sessions. The same therapists met with these groups, in the same setting, at the same time and for the same duration and frequency as the CBT groups. The focus of these groups was on the sharing of experiences and the learning of basic relaxation skills. Each week, a different relaxation exercise was taught. These groups served as a control for the non-specific effects of therapy and controlled for the effects of therapist time and attention.	**Cost components incorporated:** Intervention-therapist and administrator time Health care - GP visits, outpatient appointments, inpatient stays Drugs - SSRIs, tricyclics, hypnotics, analgesics, anti-inflammatories, benzodiazapines, other		

	In order to validate the role of the physiotherapist within the EAS condition, a stretch programme was introduced. This included 16 stretches for major muscle groups in the body, and patients were advised to perform each stretch twice, in a relaxed manner. The purpose of the stretches was explained as loosening the muscles so that a state of relaxation in the muscles could be achieved. If further questions regarding exercise were asked in these groups, the group was informed that there was controversy regarding the value of aerobic exercise, and therefore we did not wish to introduce exercise if it were to be unhelpful for some patients. The physiotherapist also participated in the teaching of relaxation techniques, including in particular those that involved movement such as progressive muscle relaxation and slow diaphragmatic breathing.			

Data sources
Health outcomes: HUI3 and resource use were for trial participants. **Quality-of-life weights:** HUI3. **Cost sources:** Intervention costs were clinician and administrator time. Healthcare contacts were extracted from GP records. Prescribed medication was elicited sing patient questionnaires, Unit costs were from the PSSRU, NHS reference costs and prescription cost analysis.
Comments
Source of funding: NHS Health Technology Assessment programme **Limitations:** Population were selected using the CDC/ Fukuda criteria and therefore some might not have post exertional malaise. Treatment effects were from a single trial rather than a systematic review. Outcomes are very imprecise. There is a very high risk of bias for the effectiveness outcome due to lack of blinding and selection. HUI3 instead of EQ-5D. Costing of drugs was approximate because only broad categories were recorded with no information about quantities. The relatively short time horizon could be be a limitation. There were differences at baseline including male/female ratio (CBT=46%male, EAS=24%, SMC=29%). **Other:**
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CEA= cost–effectiveness analysis; CUA=cost-utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); NR= not reported; QALYs= quality-adjusted life years; RCT: randomised controlled trial.
(a) QALYs were calculated by the National Guideline Centre health economist by assuming a linear transition between baseline and 12 months.
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Vos-Vromans, 2017[22]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Within trial analysis (RCT) **Approach to analysis:** Mean costs and mean QALYs compared over the duration of the study period (12 months). **Perspective:** Dutch provider perspective [(a)] **Follow-up:** 12 months **Treatment effect duration:** 12 months **Discounting:** Costs = NR Outcomes = NR	**Population:** Patients aged between 18-60 who meet the US centres for disease control and prevention (CDC-94) criteria and have a CIS fatigue subscale score of ≥40 **Cohort settings:** Mean age: Intervention 1 = 40.4, Intervention 2 = 41.6 N = 109 **Intervention 1:** Individual cognitive behavioural therapy (CBT) is a psychotherapeutic approach where a model of perpetuating cognitions and behaviours of CFS is used to explain the persistence of CFS. These perpetuating factors include: 'high physical attributions' which will decrease physical activity and increase fatigue and functional impairment; low sense of control over symptoms and focussing on physical sensations have a direct causal effect on fatigue severity and functional impairment; a perceived lack of social support also increases the fatigue severity and functional impairment. The CBT programme occurs over 16 therapy sessions, spread over 6 months, the first 6 weeks the patient has weekly sessions followed by a single session every 2 weeks for the remaining 20 weeks. The CBT intervention has three key phases: intake, gradual reactivation and finally prevention of relapse phase. 1) Intake – Four sessions occur in four weeks, patient is asked about: cause and course of the complaints, the present complaints, illness beliefs and illness behaviour, coping, social interactions/participation, and the expectations and personal goals of the patient. Therapist tries to determine patient's activity level and categorises patient as relatively active or low activity patient. Therapist explains the model of perpetuating cognitions and behaviours of CFS and how to overcome CFS by changing patterns of thinking and changing behaviour.	**Health care costs (mean per patient):** Intervention 1: £2816 Intervention 2: £7650 Incremental (2−1): £4835 (95% CI: £3942 to £5781; p=NR) **Patient & family costs (mean per patient):** Intervention 1: £1392 Intervention 2: £2571 Incremental (2−1): -£1240 (95% CI: -£2953 to £124; p=NR) **Currency & cost year:** 2012 euros (presented here as 2012 UK pounds[(b)]) **Cost components incorporated:** General practitioner care, mental healthcare specialist, paramedical care, medical specialist	**QALYs (mean per patient):** Intervention 1: 0.60 Intervention 2: 0.65 Incremental (2−1): 0.05 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £105,975 **Analysis of uncertainty:** A probabilistic sensitivity analysis (PSA) was conducted which reported that the estimated probability MRT was cost-effective when compared to CBT at the £20K/30K threshold: 0%/0%[(c)]

	2) Gradual reactivation - Graded exercise therapy is used to gradually increase physical activity at home (walking and bicycling). The schedule is provided by the therapist according to patient's personal goals. Patient receives feedback at the following therapy session about the changes to their activity and importance is also placed on the balance between different activities with emphasis placed on patient's personal responsibility to see to the schedule. Increases to social/mental activities can also be scheduled if needed. During dialogue between patient and increasing exercise at home, patient is taught to change negative believes regarding symptoms of fatigue self-expectations and self-esteem. Lifestyle advice is provided if deemed appropriate. Sleep/wake rhythm is encouraged immediately at start of the treatment and sleeping during the day is not allowed. A plan to return to work is also organised. 3) Prevention of relapse – Patients are encouraged to cope with disturbances which may arise from sleep/wake rhythm normalisation and activity increase by using techniques learned during therapy. In the relatively active patient group, they are taught to spread out activities during the day and to be active within physical and mental boundaries. For patients with low activity level, activities will be increased from beginning of therapy. **Intervention 2:** Individual multidisciplinary rehabilitation treatment (MRT) uses a biopsychosocial model of CFS including biological, physical and psychosocial aspects. In the biopsychosocial model of CFS various precipitating, predisposing and perpetuating factors are merged, suggesting that multiple pathways may lead to the causation and persistence of CFS. The protocol of the MRT varies between patients based on treatable components (precipitating, predisposing and perpetuating factors), present complaints and personal needs of a patient. The MRT intervention has three phases including observation, treatment and prevention of relapse.	care, hospital care, medication and over the counter medication, alternative healers, company physician and cost of intervention.		

	1) Observation – 2 week period where therapists (psychologist, social worker, physical therapist and occupational therapist) get acquainted with patient. Patients are asked the cause and course of the complaints, the present complaints, illness beliefs and illness behaviour, coping, the social environment the patient lives in, expectations and personal goals. Psychologist (two 1hr sessions) elaborates on psychological history, present psychological wellbeing, use of medical care including medication, stress factors, cognitions, attitudes and mood (state of mind). The social worker (two 1hr sessions) assesses the social context in which the patient lives (relationships, family and role in a family), work situation and communication. The physical therapist (five 30minute sessions) makes an estimation of the physical condition and the patient's body awareness. The occupational therapist (four 30minute sessions) aims at ergonomics, lifestyle, day/week schedule and the variety of activities during the day/week. The therapists and rehabilitation physician discuss the components and methods that will be used ruing the treatment phase. The results of this meeting will be discussed with patient who will sign a contract committing to the proposed therapy. 2) Treatment – Two weeks after observation phase, the treatment phase starts which lasts 10 weeks. The type of method use depends on patient goals/need this includes: body awareness therapy (increased awareness and consciousness of the body and relation to psychological wellbeing); cognitive behaviour therapy; gradual reactivation initially under close supervision of physical therapist and occupational therapist; pacing where patient is taught to pace their activities during the day/week this will occur in the second phase of treatment where patient is given greater autonomy and responsibility to manage activities based on their experience; principles of mindfulness; normalising of sleep/wake rhythm with sleeping during the day being stopped immediately; social reintegration under supervision of the occupational therapist and social worker.			

	3) Prevention of relapse - Six weeks after end of treatment patient visits the social worker and then 13 weeks after end of treatment patient will visit two therapists of their choice.			

Data sources

Health outcomes: Health-related quality of life (EQ-5D-3L) reported directly from patients. **Quality-of-life weights:** The EQ-5D UK was used in the base case and Dutch tariff in a sensitivity analysis. **Cost sources:** Resource use from within RCT; costs reported as the mean costs incurred per patient for the trial duration (2008 – 2011). Medication costs were based on the tariffs from Dutch College of Health Insurance, costs for CBT or MRT treatment hours calculated using the Dutch diagnosis-dependent treatment combination also known as DBC.

Comments

Source of funding: Netherlands Organisations for Health Research and Development, Rehabilitation Fund, Foundation Nutsohra **Limitations**: Population were selected using the CDC/ Fukuda criteria and therefore some might not have post exertional malaise. 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. Another limitation of this study is that it has used the DBC to calculate the cost of each intervention. The DBC payment is where hospitals are reimbursed a fixed fee for a combination of diagnosis and treatment for example in this study a participant who required 49-129 hours of rehabilitation treatment would incur a cost of £3027 however, given that the duration is so broad, resource uptake of an individual requiring 49 hours versus 129 hours would be substantially different. Therefore, there is uncertainty around the true costs of CBT and MRT. Unclear how QALYs calculated. Difference in QALYs at baseline but controlled for using regression analysis.

Overall applicability: Partially Applicable [(d)] **Overall quality:** Minor limitations [(e)]

Abbreviations: CUA= cost–utility analysis; da= deterministic analysis; DBC= Diagnosis Treatment Combination (DBC) case-mix System; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) All costs and ICERs were recalculated by the National Guideline Centre to report a provider perspective, in keeping with the NICE reference case.

(b) Converted using [2014] purchasing power parities[14]

(c) It is unclear which QALY estimate has been used to determine the probability that MRT was cost-effective when compared to CBT at different thresholds.

Directly applicable / Partially applicable / Not applicable

Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I Health economic model

No original economic modelling was undertaken.

Appendix J Excluded studies

J.1 Clinical studies

Table 11: Studies excluded from the clinical review

Study	Exclusion reason
Bourke 2014[1]	Inappropriate comparison – intervention vs. no intervention
Clark 2016[2]	Inappropriate comparison – intervention vs. no intervention
Clark 2017[3]	Inappropriate comparison – intervention vs. no intervention
Crawley 2018[5]	Inappropriate comparison – same MDT in both arms, intervention differed (Lightning process)
Dougall 2014[6]	Inappropriate comparison – intervention vs. no intervention
Gibson 1999[8]	Incorrect study design – non-randomised
Lloyd 1993[9]	Data not extractable
Núñez 2011[12]	Inappropriate comparison – intervention vs. no intervention
Pinxsterhuis 2017[15]	Unclear comparator – usual care not standardised and unclear whether MDT was involved
Sabes-Figuera 2012[16]	Not review population – no diagnosis of ME/CFS
Taylor 2004[17]	Incorrect intervention – not MDT care
Taylor 2006[18]	Systematic review is not relevant to review question or unclear PICO
Toussaint 2012[19]	Not review population – fibromyalgia, chronic fatigue and/or CFS
Viner 2004[20]	Incorrect study design – non-randomised
Vos-Vromans 2009[21]	Citation only
Walwyn 2013[25]	Inappropriate comparison – intervention vs. no intervention
White 2007[27]	Inappropriate comparison – intervention vs. no intervention
White 2011[26]	Inappropriate comparison – intervention vs. no intervention

J.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Appendix K MIDs for continuous outcomes

K.1 Clinical psychologist + physiotherapist + occupational therapist (attention control) versus primary care; adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 physical) Pooled 6 and 12 month data. Scale from: 0 to 100.	3.68
Quality of life (SF36 mental) Pooled 6 and 12 month data. Scale from: 0 to 100.	5.65
Quality of life (Health status (HUI3)) Pooled 6 and 12 month data. Scale from: -0.36 to 1.	0.15
Fatigue (Chalder fatigue score) Pooled 6 and 12 month data. Scale from: 0 to 33.	3.16
Cognitive function (total words recalled) Pooled 6 and 12 month data.	1.92
Cognitive function (correct words) Pooled 6 and 12 month data.	1.83
Cognitive function (reaction time) Pooled 6 and 12 month data.	54.48
Psychological status (HADS anxiety) Pooled 6 and 12 month data. Scale from: 0 to 21.	2.18
Psychological status (HADS depression) Pooled 6 and 12 month data. Scale from: 0 to 21.	1.64
Psychological status (General health Questionnaire) Pooled 6 and 12 month data. Scale from: 0 to 36.	3.58
Exercise performance measure (Normal walking speed) Pooled 6 and 12 month data.	3.36
Exercise performance measure (Shuttles walked) Pooled 6 and 12 month data.	11.46

K.2 Physical therapist + occupational therapist + psychologist + social worker versus psychologist/behavioural therapist; adults, severity mixed or unclear

Outcomes	MID
Quality of life: SF-36 mental component summary SF36 mental component summary. Scale from: 0 to 100.	4.56
Quality of life: SF-36 physical component summary SF36 physical component summary. Scale from: 0 to 100.	3.93
General symptom scales Sickness Impact Profile 8. Scale from: 0 to 6160.	311.94

Outcomes	MID
Fatigue (Checklist Individual Strength - fatigue severity) Scale from: 8 to 56.	2.54
Psychological status (Symptom Checklist) SCL-90. Scale from: 90 to 450.	18.57
Activity levels (Accelerometer) (Values divided by one decimal place)	2091.09

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