Appendix A. Search Strategies

KQ 1-2

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 16, 2021

1 Fatigue Syndrome, Chronic/
2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf.
3 exp Diagnosis/
4 di.fs.
5 diagnos*.ti,ab,kf.
6 (1 or 2) and (3 or 4 or 5)
7 limit 6 to (english language and humans)
8 letter.pt.
9 7 not 8
10 limit 9 to yr="1988 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2021

1 Fatigue Syndrome, Chronic/
2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf.
3 exp Diagnosis/
4 di.fs.
5 diagnos*.ti,ab,kf.
6 (1 or 2) and (3 or 4 or 5)
7 limit 6 to english language

Database: PsycINFO 1806 to February Week 2 2021

1 chronic fatigue syndrome/
2 exp Encephalomyelitis/
3 2 and myalgic.ti,ab,id.
4 ("chronic fatigue syndrome" or "myalgic encephalomyelitis").ti,ab,id.
5 exp diagnosis/
6 diagnos*.ti,ab,id.
7 1 or (2 and 3) or 4
8 (5 or 6) and 7
9 limit 8 to (human and english language)
10 limit 9 to yr="1988 -Current"

Database: Elsevier Embase® February 16, 2021

('chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome':ti,ab,kw OR 'myalgic encephalomyelitis':ti,ab,kw) AND ('diagnosis'/exp OR 'diagnosis':ti,ab,kw OR 'diagnostic':ti,ab,kw) AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'evidence based medicine'/de OR 'human'/de OR 'major clinical study'/de OR 'prospective study'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de OR 'systematic review'/de) AND ('article'/it OR 'article in press'/it OR 'review'/it) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Appendix A. Search Strategies

KQ 3

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to February 16, 2021

1 Fatigue Syndrome, Chronic/
2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf. (
3 (dh or dt or pc or th).fs.
4 exp treatment outcome/
5 exp Complementary Therapies/
6 exp Counseling/
7 exp Psychotherapy/
8 exp Exercise Therapy/
9 exp Drug Therapy/
10 (treatment or therap* or intervention*).ti,ab,kw.
11 (1 or 2) and (or/3-10)
12 limit 11 to (english language and humans)
13 letter.pt.
14 12 not 13
15 limit 14 to yr="1988 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials February 2021

1 Fatigue Syndrome, Chronic/
2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf.
3 (dh or dt or pc or th).fs.
4 exp treatment outcome/
5 exp Complementary Therapies/
6 exp Counseling/
7 exp Psychotherapy/
8 exp Exercise Therapy/
9 exp Drug Therapy/
10 (treatment or therap* or intervention*).ti,ab,kw.
11 (1 or 2) and (or/3-10)
12 limit 11 to english language

Database: PsycINFO 1806 to February Week 2 2021

1 chronic fatigue syndrome/
2 exp Encephalomyelitis/
3 2 and myalgic.ti,ab,id.
4 ("chronic fatigue syndrome" or "myalgic encephalomyelitis").ti,ab,id.
5 2 and 3
6 1 or 4 or 5
7 exp treatment outcomes/
8 exp treatment/
9 exp physical treatment methods/
10 (treatment or therap* or intervention*).ti,ab,id.
11 or/7-10
12 6 and 11

13 limit 12 to (human and english language)
14 limit 13 to yr="1988 -Current"

Database: Elsevier Embase® February 16, 2021
('chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome':ti,ab,kw OR 'myalgic encephalomyelitis':ti,ab,kw) AND ('treatment outcome'/exp OR 'therapy'/exp OR 'treatment':ti,ab,kw OR 'therapy':ti,ab,kw OR 'intervention':ti,ab,kw) AND [english]/lim AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'evidence based medicine'/de OR 'human'/de OR 'major clinical study'/de OR 'outcomes research'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de) AND ('article'/it OR 'review'/it) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

All KQs
Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 16, 2021
1 chronic fatigue syndrome.ti,ab.
2 myalgic encephalomyelitis.ti,ab.
3 1 or 2

Appendix B. ME/CFS PICOTS

	Include	Exclude
Population	KQ 1, 2: Persons presenting for possible ME/CFS KQ 3: Persons diagnosed with ME, CFS, or both using standard criteria	
Interventions	KQ 1: Conditions identified on bases of history, physical examination, or laboratory testing KQ 2: Various diagnostic criteria KQ 3: Forms of counseling and behavior therapy, graded exercise programs, complementary and alternative medicine (acupuncture, relaxation, massage, nutritional supplements, others), pathogenesis-based medications (e.g., immune modulators), and symptom-based medications (beta blockers, antidepressants, anxiolytics, stimulants, mineralcorticoids, ivabradine, others)	KQ 3: Taxiod vaccines
Comparators	KQ 1: N/A KQ 2: Diagnostic accuracy studies and diagnostic concordance studies KQ 3: Placebo, no treatment, usual care, other active interventions (including combination therapies and head-to-head trials)	KQ 2, 3: No comparator
Outcomes	KQ 1: Proportion of patients with diagnosis of other, Non-ME/CFS condition KQ 2: Any potential benefit or harm from diagnosis (such as access to treatment, psychological harms, labeling, risk from diagnostic test, misdiagnosis, other) KQ 3: Overall function (i.e., 36-item Short Form Survey), quality of life, days spent at work/school, proportion working full- or part-time, fatigue (Multidimensional Fatigue Inventory or similar), outcomes related to associated symptoms (psychiatric, gastrointestinal, autonomic dysfunction, orthostatic intolerance, urinary symptoms, multiple chemical sensitivity, and others), adverse effects of interventions, withdrawals and withdrawals due to adverse events, rates of adverse events due to interventions	KQ 1, 2, 3: Not listed as an included outcome
Settings	All KQs: Clinical settings	
Timing	KQ 1, 2: Any duration KQ 3: ≥12 weeks of follow-up	KQ 1: None KQ 3: <12 weeks of follow-up
Study types and designs	All KQ: Studies published in 1988 or after KQ 1, 2, 3: Systematic reviews or meta-analyses of randomized or controlled clinical trials; primary reports of randomized or controlled clinical trials; and large prospective cohort studies for KQ 1, KQ 2, and evaluation of harms, if data are not available from randomized clinical trials	All KQ: Non-systematic reviews, letters to the editor, before and after studies, case-control studies, non-comparative studies; reviews not in English; and studies published before 1988

Appendix C. List of Included Studies

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Appendix C. List of Included Studies

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Brigden A, Beasant L, Gaunt D, et al. Results of the feasibility phase of the managed activity graded exercise in teenagers and pre-adolescents (MAGENTA) randomised controlled trial of treatments for chronic fatigue syndrome/myalgic encephalomyelitis. Pilot Feasibility Stud. 2019;5(151)doi: 10.1186/s40814-019-0525-3. PMID: 31890263. Excluded for not a study (letter, editorial, non-systematic review article, no original data).

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Buchwald D, Pearlman T, Kith P, et al. Screening for psychiatric disorders in chronic fatigue and chronic fatigue syndrome. J Psychosom Res. 1997;42(1):87-94. PMID: 9055216. Excluded for ineligible population.

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Chan JSM, Ho RTH, Chung KF, et al. Qigong exercise alleviates fatigue, anxiety, and depressive symptoms, improves sleep quality, and shortens sleep latency in persons with chronic fatigue syndrome-like illness. Evid Based Complement Alternat Med. 2014 doi: 10.1155/2014/106048. PMID: 25610473 Excluded, used for background.

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Citroner G. Fauci Warns About 'Post-Viral' Syndrome After COVID-19. 2020. https://www.healthline.com/health-news/fauci-warns-about-post-viral-syndrome-after-covid-19. Excluded for not a study (letter, editorial, non-systematic review article, no original data).

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Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non-ME/CFS condition
Brimmer, 2013[1]	CFS Registry USA	N=104 patients referred to CFS registry over the course of 1 year Referral criteria: Include: Medically unexplained, severe fatigue persisting for one month or longer and at least one month's duration of sleep, or problems with memory or concentration, or unexplained joint or muscle pain; BMI <40; Age 12-69 Exclusion (using lab or history): Pregnancy within 12 months Stroke with no full recovery Parkinson's disease COPD or congestive heart failure Insulin-dependent diabetess Uncontrolled diabetes type II Anemia Uncontrolled hypo- or hyper-thyroidism Uncontrolled hypertension Sickle cell anemia Cancer within 5 years Untreated depression Substance abuse within 2 years Anorexia or bulimia within 5 years Schizophrenia, bipolar disorder, dementia Hepatitis B or C	CFS vs. Insufficient fatigue vs. Exclusion condition Age: <18: 3% vs. 16% vs. 2% 18-20: 0% vs. 0% vs. 6% 21-30: 8% vs. 16% vs. 4% 31-40: 24% vs. 16% vs. 11% 41-50: 16% vs. 6% vs. 16% 51-60: 32% vs. 33% vs. 39% 61-70: 16% vs. 11% vs. 22% Female: 89% vs. 72% vs. 96% Race: Black: 8% vs. 0% vs. 14% White: 89% vs. 100% vs. 82% Previous CFS Diagnosis (does not include adolescents): 54% vs. 56% vs. 56%	Using Fukuda, 1994 criteria: CFS: 37/104 (36%) Insufficient fatigue: 18/104 (17%) Exclusionary condition: 49/104 (47%) Active inflammation: 4.1% Alcohol abuse: 8.2358.2% Anemia: 6.1% Anorexia: 2.0% Autoimmune disorder: 2.0% Bipolar: 4.1% Spinal disease: 2.0% Diabetes mellitus: 16.3% Hepatitis C virus: 2.0% High blood urea: 4.1% High C-reactive protein: 20.4% Hypertension: 2.0% Hypothyroidism: 20.4% Depression: 8.2% Mitochondrial myopathy: 2.0% Obesity: 4.1% Obstructive sleep apnea: 4.1% Osteoarthritis: 4.1% Narcolepsy: 2.0% Restless legs syndrome: 6.1% Rheumatoid arthritis: 2.0% Sleep problems: 2.0% Schizophrenia: 2.0% Sickle cell: 2.0% Substance abuse: 6.1% Uncontrolled high blood pressure: 2.0% Urinary tract infection: 8.2%

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non-ME/CFS condition
Devasahayam, 2012[2]	Medical Record Review United Kingdom	N=250 Unclear criteria for referral/diagnosis. Patients referred from general practice to CFS specialty clinic with diagnosis of CFS, confirmed in clinical evaluation at CFS specialty clinic.	Characteristics NR	CFS diagnosis confirmed: 137/250 (54%) Psychiatric diagnoses: 54/250 (22%) Depression: 27/250 (11%) Anxiety: 14/250 (7%) Stress-related disorders (6/250 (2%) Somatoform disorders: 3/250 (1%) Other psychiatric disorders: 4/250 (1.6%) Medical diagnoses: 53/250 (21%) Sleep disorders: 15/250 (6%) Pain disorders: 6/250 (2%) Endocrine disorders: 7/250 (3%) Nutritional disorders: 7/250 (3%) Musculo-skeletal disorders: 3/250 (1%) Gastro-intestinal disorders: 5/250 (2%) Neurological disorders: 3/250 (1%) Others (cardiac disorders and infections): 6/250 (2%) Miscellaneous reasons: 6/250 (2.4%) Fatigue not meeting CFS criteria: 3/250 (1%) Recovered from CFS: 2/250 (1%) No conclusive diagnosis: 1/250 (0.4%)

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non-ME/CFS condition
Mariman, 2013[3]	Prospective cohort Belgium, the Netherlands	N=279 Patients referred for evaluation of unexplained chronic fatigue. Diagnosis based on Fukuda criteria.	Age, mean: 38.8 % Female: 84.9 Race: NR Duration of symptoms: NR Comorbidities: NR	Final Diagnosis: Patients with ≥4 minor Fukuda criteria (n=224): Unequivocal CFS: n=65 CFS with comorbidity: n=59 CFS +psychiatric disorder: n=7 CFS +sleep disorder: n=45 CFS +both: n=7 CFS excluded: n=100 Psychiatric disorder: n=35 Sleep disorder: n=18 Psychiatric + sleep disorder: n=41 Internal disease: n=4 Other conditions: n=2 Patients with <4 minor Fukuda criteria (n=55) Psychiatric disorder: n=18 Sleep disorder: n=9 Psychiatric + sleep disorder: n=17 Internal disease: n=2 Other condition: n=2 No final diagnosis: n=7
Newton, 2010[4]	Retrospective medical record review United Kingdom	N=260 patients referred to CFS specialist service between 2008 and 2009.	NR	Reviewed medical notes of patients referred to CFS specialist service Of those referred, 60% were diagnosed with CFS; 40% had alternative diagnosis including other chronic disease (47%), sleep disorder (20%), psychological (15%), idiopathic fatigue (13%), cardiovascular (4%) and other (1%).

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non-ME/CFS condition
Nijrolder, 2009[5]	Prospective cohort the Netherlands	N=571 patients presenting with fatigue to primary care provider	Age, mean: 43 % Female: 73.9 Race: NR Criteria used for diagnosis: NR Duration of symptoms: <1 month: 8.1% 1 to 3 months: 15.9% 3 to 6 months: 17.9% 6 to 12 months: 18.9% >1 year: 39.2%	Diagnosis during 1-year followup after initial presentation for fatigue: Chronic Fatigue Syndrome: 4/571 (0.7%) Musculoskeletal diagnosis: 111/571 (19.4%) Psychological or social: 94/57 (16.5%) Digestive: 46/571 (8.1%) Neurologic: 38/571 (6.7%) General (includes CFS): 28/571 (4.9%) Infection: 104/571 (18.2%) Respiratory: 28/571 (4.9) Endocrine: 16/571 (2.8%) Cardiovascular: 11/571 (1.9%) Female genital organs: 6/571 (1.1%) Malignant disease: 4/571 (0.7%) Skin: 3/571 (0.5%)
Slomko, 2019[6]	Cross-sectional study Poland	N=1400 patients self-identifying as meeting the Fukuda criteria for ME/CFS	NR, all participants self-completed and met the ME/CFS Fukuda criteria	Other chronic conditions: 1308/1400 (93%) Neurological: 280/1308 (21.4%) Neurodegenerative: 200/1308 (15%) Psychiatric: 654/1308 (50%) Immunologic: 174/1308 (13.5%)
Stadje, 2016[7]	Systematic Review Germany	Systematic review of diagnosis of tiredness, three of the included studies presented estimates of the frequency of CFS	Studies included patients presenting with tiredness	Rates of CFS in three studies: 1.9% (95% CI 0.00 to 10.3%) 0.7% (95% CI 0.2 to 1.8%) 31.2% (95% CI 23.7 to 39.5%)-inclusion criteria for study included 2 of the diagnostic criteria for CFS, and explains the higher prevalence.

Note: Refer to Appendix G for abbreviations and acronyms.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Al-Haggar, 2006[8] High	Egypt Single center 2002 to 2005 Specialty clinic recruited from schools and primary care	Adolescents ≥10 years Fukuda, 1994 criteria No other organic diseases	**CBT + biofeedback (n=50):** 40 to 60 sessions over 18 months, once to twice weekly, then tapered. Patients trained to perform relaxation exercises, to identify circumstances that trigger their symptoms, to avoid or cope well with these stressful events, to change their habits, and even to have the ability of self-control. **Symptomatic treatment (n=46):** not described

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Al-Haggar, 2006[8] High	Age, mean years: 13.1 vs. 11.9 % Female: 39 vs. 35 Race: NR Duration of illness, mean weeks: 27.9 vs. 24.5 Severity of fatigue, checklist score %: 54.8 vs. 51.9 No significant differences	Enrolled: 159 Analyzed: 92 (42 vs. 50)	Lost to follow-up: 63 Switched groups, not included in analysis: 4

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Al-Haggar, 2006[8] High	School attendance, mean (SD) hours per month: 92.8 (18.4) vs. 66.6 (22.8), p=0.004 Fatigue severity, mean (SD) checklist score: 32.2 (3.8) vs. 46.5 (14.2), p=0.02 Patient-reported outcomes, mean (SD) on 4-point Likert scale: Unrefreshing sleep: 2.12 (0.88) vs. 3.32 (1.14), p=0.002 Headache: 2.54 (0.84) vs. 2.86 (0.81), p= 0.03 Myalgia: 2.16 (1.12) vs. 2.96 (0.92), p= 0.005 Joint pains: 2.34 (1.14) vs. 2.34 (1.26), p > 0.05 Tender glands: 1.81 (0.82) vs. 2.22 (0.92), p > 0.05

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Al-Haggar, 2006[8] High	NR	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Arnold, 2015[9] RCT Medium	United States Single center 2006 to 2012 Outpatient research center	"Revised" CDC (Fukuda, 1994) criteria: at least 6 months of persistent fatigue that substantially reduces the person's level of activity; 4 or more of the following symptoms that must occur with fatigue in a 6-month period: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multijoint pain, new headaches, unrefreshing sleep, and postexertional fatigue; other medical conditions that may explain the fatigue; and psychiatric disorders (as diagnosed by the investigator, including eating disorders, psychotic disorders, bipolar disorder, and melancholic depression, are excluded, as well as substance use disorders within 2 years of the onset of fatigue. **Inclusion:** General fatigue score ≥13 on the Multidimensional Fatigue Inventory (MFI) at screening and randomization. **Exclusion:** Current or past melancholic major depressive disorder or previous diagnosis of psychosis, eating disorder, or bipolar disorder; history of substance abuse or dependence within the past year; patients refractory to treatment; unstable medical illness; abnormal thyroid stimulating hormone concentrations; uncontrolled narrow-angle glaucoma; previously treated with duloxetine; use of herbal medications with central nervous system effects or analgesics (except acetaminophen or NSAIDs); alternative therapies.	**Duloxetine (n=30):** 30 mg once daily for 1 week, then 60 mg once daily for 3 weeks, then 90 mg for 4 weeks (as tolerated), then 120 mg (as tolerated) for remaining 4 weeks. Patients received a minimum dose of 60 mg once a day if higher doses were intolerable. At the end of 12 weeks, patients were tapered by a reduction of 30 mg daily until discontinuation. **Placebo (n=30):** Matching placebo **Duration of treatment:** 12 to 13 weeks **Duration of followup:** End of 12 week treatment phase

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Arnold, 2015[9] RCT Medium	**Duloxetine vs. placebo** Mean age (years): 43.0 vs. 44.3 % Female: 86.7 (26/30) vs. 86.7 (26/30) Race, % (n/N): 86.7 (26/30) vs. 83.3 (25/30) White, 13.3 (4/30) vs. 13.3 (4/30) African American, 0 vs. 3.3 (1/30) other Duration of illness: NR (all at least 6 months) Severity of symptoms: *CDC Symptom Inventory CFS case definition symptom score (0 to 152 range with lower scores indicating better health):* 39.3 vs. 40.6 *Clinical Global Impression of Severity (CGS-S):* Score of 4 (moderately ill) %: 86.2 (25/29) vs. 90.0 (27/30) Score of 5 (markedly ill): 13.7 (4/29) vs. 10.0 (3/10) Comorbidities: NR	Number randomized: 60 Number analyzed: 57	**Overall:** 5% (3/60) **Duloxetine vs. placebo:** 3.3% (1/30) vs. 6.6% (2/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Arnold, 2015[9] RCT Medium	**Duloxetine vs. placebo** Overall Function: *SF-36 Medical Outcomes Study Short Form-36 Health Survey, range 0 to 100*, mean change (SD): 14.3 (22.6) vs. 7.5 (27.4), between group difference: 6.8 (95% CI, -8.5 to 22.0) p=0.38 SF-36 physical function (0 to 100): NS14.3 (22.6) vs. 7.5 (27.4); difference: 6.8, 95% CI -8.5 to 22.0, p=0.38 Quality of Life: *Clinician Global Impression of Severity*, observed mean change (SD): -1.1 (1.2) vs. -0.4 (1.0), model-based difference between groups: -0.1 (95% CI,-0.3 to 0.0), p=0.02 *Patient Global Impression of Improvement*, observed mean change (SD): -1.1 (1.2) vs. -0.4 (1.0), model based difference between groups: -0.8 (95% CI, -1.7 to 0.0), p=0.06 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Multidimensional Fatigue Inventory (4 to 20, lower scores indicate better health)*: General fatigue, observed mean change (SD): -3.3 (4.2) vs. -1.8 (2.8), model-based difference between groups: -1.0 (95% CI, -2.8 to 0.7), p=0.23 Physical fatigue, observed mean change (SD): -2.4 (4.4) vs. -1.0 (2.7), model-based difference between groups: -0.9 (95% CI, 2.7 to 0.7), p=0.32 Reduced activity, observed mean change (SD): -2.1 (4.4) vs. -1.5 (3.2), model-based difference between groups: 0.0 (95% CI, -1.8 to 1.8), p=0.37 Reduced motivation, observed mean change (SD): -2.6 (4.1) vs. -1.6 (3.8), model-based difference between groups: -0.8 (95% CI, -2.6 to 1.1), p=0.37 Mental fatigue, observed mean change (SD): -3.8 (4.0) vs. -1.4 (3.3), model-based difference between groups: -2.5 (95% CI, -4.4 to -0.6), p=0.01 Outcomes related to associated symptoms: *Brief Pain Inventory, 0 to 10 scales:* Average pain severity, mean (SD): -1.6 (1.5) vs. -0.8 (2.3), model-based differences between groups (log transformation used): 0.73 (95% CI, 0.54 to 1.00), p=0.05 Average pain interference, mean (SD): -1.9 (1.3) vs. -1.1 (2.8), model-based difference between groups (log transformation used): 0.70 (95% CI, 0.51 to 0.96), p=0.03 CDC Symptoms Inventory, CFS Questions, mean change (SD): -9.7 (13.1) vs. -8.2 (14.6), between-group difference at endpoint: -1.5 (95% CI, -9.9 to 6.9), p=0.72 HADS-Depression, change from baseline: -1.6 (2.9) vs. -1.9 (3.0), p=0.67

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Arnold, 2015[9] RCT Medium	**Duloxetine vs. placebo** Adverse Events: Events that differed % (n/N): Nausea: 65.5 (19/29) vs. 20.0 (6/30), p≤0.001 Somnolence: 41.3 (12/29) vs. 10.0 (3/30), p≤0.01 Dizziness: 31.0 (9/29) vs. 6.7 (2/30), p≤0.05 Headache: 10.3 (3/29) vs. 40.0 (12/30), p≤0.05 Dry mouth: 20.7 (6/29) vs. 3.3 (1/30), p≤0.05 Withdrawals due to adverse event: 3, all in treatment group: suicidal ideation (1), somnolence (1), and constipation (1). Serious Adverse Events: 1 suicidal ideation in treatment group	Eli Lilly and Company Investigator-Initiated Trial Program, drug provided by Eli Lilly and Company

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Blacker, 2004[10] RCT Medium	United Kingdom, United States, The Netherlands, Sweden, Belgium 35 centers 1997 to 1999 Specialty clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18 to 65 years, modified CDC criteria, illness duration <7 years. **Exclusion:** Concurrent DSM-IV diagnoses: major depressive disorder, psychotic disorders, panic disorder, substance misuse, somatization disorder, anorexia or bulimia nervosa, obesity, and sleep disorders; received inpatient psychiatric care had previously attempted suicide or both; irritable bowel syndrome; peptic ulcer; severe asthma; endocrine or metabolic disease; HIV; neurological disease; known sensitivity to cholinergic agents; possible exposure to organophosphate compounds; diagnosis of Gulf War syndrome; pregnant or lactating; women with irregular menstrual irregularities associated with fatigue.	**Galantamine 7.5 (n=89):** Galantamine 2.5 mg three times per day **Galantamine 15 (n=86):** Galantamine 5 mg three times per day **Galantamine 22.5 (n=91):** Galantamine 7.5 mg three times per day **Galantamine 30 (n=86):** Galantamine 10 mg three times per day **Placebo (n=82):** Identical placebo three times per day *Note:* For intervention groups doses were titrated over 3 to 8-week period, starting at 2.5 mg/day with weekly increments of 2.5-7.5 mg depending on target dose, which was maintained for another 8 weeks **Duration of treatment:** 16 weeks (8 weeks at full-dose) **Duration of followup:** 4 weeks after final dose
Blockmans, 2003[11] Crossover RCT Medium	Belgium Single Center 1999 to 2001 Specialty clinic: Tertiary care university clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Meet ≥4 CDC minor criteria for CFS. **Exclusion:** History of gastric or duodenal ulcer, arterial hypertension, glaucoma, or diabetes; pregnant; or incomplete or abnormal laboratory screening examination.	**Hydrocortisone (n=50):** Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day **Placebo (n=50):** Placebo Both groups received an injection of 250 µg of adrenocorticotropic hormone three times: once at baseline and before each treatment period. **Duration of treatment:** Two 3-month treatment periods with no washout between **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Blacker, 2004[10] RCT Medium	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo** Mean ages (years): 39 vs. 39 vs. 39 vs. 37 vs. 38 % Female: 72 (64/89) vs. 71 (61/86) vs. 62 (56/91) vs. 62 (53/86) vs. 62 (51/82) % White: 99 (88/89) vs. 92 (79/86) vs. 98 (89/91) vs. 95 (82/86) vs. 94 (77/82) Duration of illness: <7 years, NR by group Severity of symptoms: Fibromyalgia impact questionnaire global well-being score range 356 to 390; NR at baseline by group Comorbidities: NR	Number randomized: 434 Number analyzed: 423	**Overall:** 30% (130/434) **Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:** 20% (18/89) vs. 36% (31/86) vs. 35% (32/91) vs. 31% (27/86) vs. 27% (22/82)
Blockmans, 2003[11] Crossover RCT Medium	For 80 patients who completed the study: Mean age: 38 years % Female: 91 (73/80) Race: NR Duration of illness: mean (range): 30 (16 to 60) months Severity of symptoms: Number of criteria for chronic fatigue syndrome: 6 (SD 2) Comorbidities: NR	Number enrolled: 100 Number analyzed: 80	20% (20/100)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Blacker, 2004[10] RCT Medium	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:** Overall Function: NR Quality of Life: Improved *Clinician Global Impression Scores*, %: 45% (36/80) vs. 35% (22/63) vs. 36% (25/69) vs. 41% (28/68) vs. 30% (20/67); all comparisons are NS between groups *FIQ least square mean change from baseline* Global Well Being (composite): -77.84 vs. -88.65 vs. -29.92 vs. -60.67 vs. -53.89 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Chalder Fatigue Rating Scale least square mean change from baseline (positive changes indicate better health)* Physical: 9.25 vs. 8.77 vs. 11.02 vs. 9.99 vs. 9.86 Mental: 6.46 vs. 5.89 vs. 7.74 vs. 6.60 vs. 6.80 Outcomes related to associated symptoms: *Pittsburgh Sleep Quality Index Total score (0-21, higher score indicates worse sleep):* -1.60 vs. -2.28 vs. -1.43 vs. -1.73 vs. -2.02 all comparisons are NS between groups
Blockmans, 2003[11] Crossover RCT Medium	**Hydrocortisone vs. placebo, results prior to crossover portion of the study** Mean (SD) Overall Function: *SF-36 (0-100 scale, higher scores indicate better health)* Physical functioning: 31.7 (18.2) vs. 30.4 (18.1); p=0.34 Quality of Life: *Visual Analog Scale (0-10)* Degree of well-being: 5.0 (2.4) vs. 4.6 (2.6); p=0.14 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Visual Analog Scale (0-10)* Degree of fatigue: 6.6 (2.0) vs. 6.7 (2.1); p=0.76 *Abbreviated Fatigue Questionnaire score (4-28, higher scores indicate better health)*: 8 (5) vs. 7 (5); p=0.69 Outcomes related to associated symptoms: *Hospital Anxiety and Depression Scale (0-21, lower scores indicate better health)* (n=75) Depression score: 8 (5) vs. 9 (4); p=0.04 (but not significant after Bonferroni correction) Anxiety score: 9 (4) vs. 10 (4); p=0.28

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Blacker, 2004[10] RCT Medium	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo;** Adverse Events: 90% (389) reported adverse events; Depression, nausea and headache most common in both groups Withdrawals due to adverse events: Total: 23% (88/389) By group: 14% (12/89) vs. 23% (20/86) vs.24% (22/91) vs. 26% (22/86) vs.15% (12/82) Serious Adverse Events: 2% (8/389) none attributed to the study drug	Shire Pharmaceutical Development Limited
Blockmans, 2003[11] Crossover RCT Medium	**Hydrocortisone vs. placebo** Adverse Events: 1 acne and weight gain Withdrawals due to Adverse Event: 1 acne and weight gain Serious Adverse Events: None	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Bourke, 2014[12] PACE companion	See White, 2011	See White, 2011	See White, 2011
Burgess, 2012[13] RCT Medium	United Kingdom Single center Study year(s) NR Research center	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria **Inclusion:** Ages 18 to 65 years, met both CDC and Oxford criteria, had CFS for <10 years, able to attend the hospital or have telephone sessions every two weeks. **Exclusion:** Any medical condition that may have accounted for their fatigue, had started or changed medication within 3 months, were pregnant, had psychosis, drug abuse, a somatoform disorder, or melancholic depression.	**Face-to-face (n=35):** Up to 15 sessions of face-to-face CBT, first 2 sessions were 1.5 hours long with additional sessions lasting from 50 to 60 minutes. **Telephone (n=45):** Up to 14 sessions of CBT, first session was face-to-face and lasted up to 3 hours, with additional sessions conducted over the phone. *Note:* Both CBT interventions were aimed at helping patients to change behavioral and cognitive factors, focusing specifically on changing avoidance behavior, unhealthy sleep patterns, and unhelpful beliefs in order to improve levels of fatigue and disability. Individual sessions consisted of socialization with therapist and discussion of approach; agenda setting; homework reviewing; planning of future homework; discussion about how to mange sleep problems; ways to gradually increase activity without overdoing it; identifying and challenging unhelpful cognitions that were standing in the way of behavioral change; social factors if identified as important in perpetuating the symptoms and disability associated with their CFS; management of setbacks; and goals to work toward after treatment during followup. **Duration of treatment:** Varied **Duration of followup:** 12 months after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Bourke, 2014[12] PACE companion	See White, 2011	See White, 2011	See White, 2011
Burgess, 2012[13] RCT Medium	**Face-to-face vs. telephone** Mean age (SD): 38.4 (9.7) vs. 36.7 (10.5) years % Female: 74 (26/35) vs. 82 (37/45) % White: 90 overall (NR per group) % With job to return to: 22 (7/35) vs. 45 (20/45) Duration of illness: Mean (SD): 4.20 (2.21) vs. 3.80 (2.09) years Severity of symptoms: NR Comorbidities: NR	Number enrolled: 80 (35 face-to-face, 45 telephone) Number analyzed at 12 month followup: 43 (23 face-to-face, 20 telephone)	**Face-to-face vs. telephone:** 34% (12/35) vs. 56% (25/45)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Bourke, 2014[12] PACE companion	APT vs. CBT vs. GET vs. control Significantly less muscle pain: CBT vs. control (mean difference=0.38 unit change in frequency, p=0.02) GET vs. control (0.42, p=0.01) GET versus APT (0.37, p=0.01) Significantly less joint pain: CBT versus APT (0.35, p=0.02) GET versus APT (0.36, p=0.02)
Burgess, 2012[13] RCT Medium	**Face-to-face vs. telephone** Overall Function: *Mean (SD) Medical Outcomes Survey Short Form physical functioning scale scores (0-100 scale, higher scores indicate better health)* 3 months: 58.97 (19.38) vs. 62.89 (20.33) 6 months: 65.78 (23.61) vs. 62.96 (20.36) 12 months: 62.32 (24.96) vs. 65.83 (21.73); p=0.043 for change from baseline for both groups, all other p-values NS *Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)* 3 months: 23.35 (8.54) vs. 21.65 (7.42) 6 months: 19.40 (10.77) vs. 23.43 (8.06) 12 months: 20.83 (12.25) vs. 19.40 (8.73); p=0.013 for change from baseline for both groups Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Chalder fatigue scale scores (0-11 scale, lower scores indicate better health, score of ≥4 is cutoff for caseness); all p values are NS* 3 months: 7.08 (3.97) vs. 7.08 (3.56) 6 months: 5.75 (4.49) vs. 7.75 (3.77) 12 months: 6.83 (4.57) vs. 7.89 (3.75) Outcomes related to associated symptoms: *Global improvement scores (% much better or very much better)* 6 months: 60 (15/25) vs. 40 (8/20) 12 months: 57 (13/23) vs. 55 (11/20) Depression: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Bourke, 2014[12] PACE companion	See White, 2011	See White, 2011
Burgess, 2012[13] RCT Medium	**Face-to-face vs. telephone** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Chalder, 2010[14] Lloyd, 2012[15] Medium	United Kingdom Single center 2000 to 2003 Specialty clinic	Adolescents 11 to 18 years Oxford or Fukuda (Sharpe, 1991; Fukuda, 1994) Anti-depressants were acceptable if on a stable dose for 3 months prior to entering the trial Excluded alternative causes for fatigue, major depression, somatization disorder, conversion disorder, history of self-harm, or identifiable disease that could have contributed to their illness	**CBT (n=32):** 13 1-hour sessions of family- focused CBT every 2 weeks **Psycho-education (n=27):** 4 didactic sessions over 6-month period. Involved discussion, information giving, and problem solving but did not include homework assignments and cognitive restructuring. Duration of follow up: 24 months
Chan, 2013[16] Ho, 2012[17] RCT Medium	Hong Kong Special Administrative Region of China Single center 2010 to 2011 Setting NR	Fukuda (Fukuda, 1994) criteria, but diagnosis of CFS-like illness, not CFS, was used **Inclusion:** Ages 18 to 55, unexplained fatigue over 6 months which was of new onset (not lifelong), with ≥4 of 8 following symptoms: impaired memory or concentration, post-exertional malaise, unrefreshing sleep, muscle pain, multijoint pain, new headaches, sore throat, and tender lymph nodes **Exclusion:** Medical condition that may explain the presence of chronic fatigue	**Qigong (n=77):** 2 hour Qigong sessions including 1 hour of exercise training twice a week for 5 weeks, followed by 12 weeks of ≥30 minutes daily home Qigong exercise. **Waitlist (n=77):** Wait list; refrained from qigong exercise. **Duration of treatment:** 4 months (5 weeks training in Qigong exercise and 12 weeks of qigong exercise at home) **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Chalder, 2010[14] Lloyd, 2012[15] Medium	Age, median: 15 vs. 15 % Female: 65.6 vs. 71.0 Race: NR Duration of fatigue, median months: 30 vs. 22 Oxford criteria, %: 100 vs. 93.5 CDC criteria, %: 68.8 vs. 71.0 Comorbid psychiatric diagnosis: 46.9% vs. 22.6%	Enrolled: 63 Analyzed: 59 (32 vs. 27)	Lost to follow up: 0 vs. 4
Chan, 2013[16] Ho, 2012[17] RCT Medium	**Qigong vs. waitlist** Mean age: 42.4 vs. 42.5 years % Female: 72 (52/72) vs. 82 (53/65) Race: NR % Employed full-time: 76 (55/72) vs. 80 (52/65) % Employed part-time: 4.2 (3/72) vs. 1.5 (1/65) % Unemployed: 5.6 (4/72) vs. 1.5 (1/65) % Housewife: 13 (9/72) vs. 15 (10/65) % Regularly exercise: 26 (19/72) vs. 26 (17/65) Mean number of reported fatigue symptoms (SD): 6.3 (1.4) vs. 6.3 (1.4) Duration of illness: ≥6 months	Number enrolled: 154 Number analyzed: 137 (72 qigong, 65 waitlist)	**Overall:** 28% (43/154) **Qigong vs. waitlist:** 31% (24/77) vs. 25% (19/77)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Chalder, 2010[14] Lloyd, 2012[15] Medium	6-month follow up: School attendance: % of expected over 2-week period, mean: 73.4 vs. 64.9; mean difference: 8.5 (-12.3 to 29.3), p=0.42 ≥70% vs. <70%: adjusted OR: 0.87, 95% CI 0.29 to 2.63 Chalder fatigue Likert score (scale 0 to 33), mean (SD): 13.3 (5.9) vs. 14.2 (8.4), mean difference: 0.24, 95% CI -3.61 to 4.10 Child- reported global improvement, % good outcome: 88.9 vs. 89.7; OR 1.08, 95% CI 0.20 to 5.89 Mother-reported global improvement, % good outcome: 89.7 vs. 79.2; OR 2.28, 95% CI 0.48 to 10.73 Independent global improvement, % good outcome: 93.1 vs. 74.1; OR 4.73, 95% CI 0.89 to 25.2 No significant differences: Physical functioning, social adjustment, Strengths and Difficulties Questionnaire scores, treatment satisfaction 24-month follow up (n=24 vs. 20): School attendance, mean % achieving ≥ 70%, 6-months vs. 24-months: CBT groups: 65.6 vs. 90.0; Psycho-education: 66.7 vs. 84.2 Improvement over time: CBT: p=0.06 vs. Psycho-education: p=0.38; OR 1.286, 95% CI 0.183 to 9.021 Maternal-reported Strengths and Difficulties Questionnaire, total score mean at 24-months: 8.16 (5.69) vs. 14.00 (4.94), Group x Time F(df,1) =10.42, p<0.001 Social Adjustment Scale, median impairment at 24 months: 0.60 vs. 1.60, p=0.58 for group differences; CBT over time: p=0.01; Psycho-education over time: p=0.03 No significant effects of group x time (6 and 24 months) in fatigue, SF-36 physical functioning, global functioning, satisfaction, or recovery
Chan, 2013[16] Ho, 2012[17] RCT Medium	**Qigong vs. waitlist** Overall Function: *Mean (SD) QOL SF-12 mental functioning score (6 items scored from 0 to 100, higher scores indicate better health)* From 64 patient subset analysis: 42.7 (7.2) vs. 35.7 (9.5); p=0.001 *Mean (SD) QOL SF-12 physical functioning score (6 items scored from 0 to 100, higher scores indicate better health)* From 64 patient subset analysis: 40.1 (6.9) vs. 37.8 (5.6); p=0.484 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Chalder fatigue scale total fatigue scores (0 to 56 scale, lower score indicates better health)* From entire study: 26.6 (13.6) vs. 33.2 (6.3); p<0.001 *Mean (SD) Chalder fatigue scale physical fatigue scores (0-32 scale, lower score indicates better health)* From entire study: 15.9 (8.0) vs. 20.8 (5.7); p<0.001 *Mean (SD) Chalder fatigue scale mental fatigue scores (0-24 scale, lower score indicates better health)* From entire study: 10.6 (6.1) vs. 12.4 (4.9); p=0.05 Outcomes related to associated symptoms: *Mean (SD) telomerase activity (arbitrary unit)* From 64 patient subset: 0.178 (0.201) vs. 0.104 (0.059), p=0.029, between groups over time

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Chalder, 2010[14] Lloyd, 2012[15] Medium	NR	NHS Executive London Region Office
Chan, 2013[16] Ho, 2012[17] RCT Medium	Adverse Events: None reported Withdrawals due to adverse event: None reported Serious Adverse Events: None reported	Centre on Behavioral Health Research Fund, University of Hong Kong

Appendix E2. Evidence Table for Key Question 3

Author, year **Study Design** **Risk of Bias**	**Country** **Number of Centers** **Study Years** **Setting (primary care, specialty clinic or other)**	**Diagnostic criteria** **Inclusion/ Exclusion criteria**	**Interventions (n)** **Duration of treatment** **Duration of followup**
Clark, 2017[18] RCT Medium	United Kingdom 2 centers 2012 to 2015 Secondary care clinics for chronic fatigue	NICE/NHS **Inclusion:** Diagnosed with CFS, meeting NICE criteria, placed on a wait list for therapy, **Exclusion:** <18 years old, current suicidal thoughts or comorbid psychiatric conditions requiring exclusion, had previously read the GES guide or already received GET, or physical contraindications to exercise.	**Graded exercise therapy (n=107):** Given and encouraged to use a self-help booklet with a 6-week program of graded exercise self-management, based off of the PACE trial and on NICE recommendations. Six steps outlined included: stabilizing a daily routine, starting regular stretching, deciding on a physical activity goal and choosing a type of activity with which to start, increasing the duration and then the intensity of physical activity. One 30 minute in-person, Skype, or telephone session with a physiotherapist after randomization to answer questions from the participants was given within 5 days of the randomization, then 3 20 minute appointments were offered over the next 8 weeks via Skype or telephone. These patients also received specialist medical care. **Control (n=104):** Specialist medical care. **Duration of treatment:** ~8 weeks **Duration of followup:** 12 weeks after randomization, ~4 weeks after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Clark, 2017[18] RCT Medium	**Graded exercise therapy vs. control** Mean age: 38.1 vs. 38.7 % female: 82 vs. 76 % White: 88 vs. 90 Duration of illness, mean (range): 46 (23 to 114) vs. 42 (25 to 99) months Severity of symptoms: % meeting CDC criteria: 68 vs. 74 % meeting Oxford criteria: 78 vs. 84 *Mean SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)*: 47.3 vs. 50.1 *Mean Chalder fatigue scale scores (0-56 scale, lower score indicates better health)*: 26.3 vs. 26.0 Comorbidities: % with current major depressive disorder: 9 (10/107) vs. 11 (10/104)	Number enrolled: 211 Number analyzed:199	**Overall:** 6% (12/211) **Graded exercise therapy vs. control:** 9% (10/107) vs. 2% (2/104)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Clark, 2017[18] RCT Medium	**Graded exercise therapy vs. control** Overall Function: *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* : Overall: 55.7 (23.3) vs. 50.8 (25.3), AMD: 6.3 (95% CI, 1.8 to 10.8) p=0.006 Meeting CDC criteria (n=141), mean difference in SF-36: 6.3 (95% CI, 1.1 to 11.6) p=0.019 Meeting Oxford criteria (n=159), mean difference in SF-36: 5.6 (95% CI, 0.8 to 10.4) p=0.024 Work and social adjustment scale mean score at 12 weeks, mean (SD): 23.4 (8.6) vs. 25.4 (8.3) Work and social adjustment scale mean difference at 12 weeks: -1.9 (95% CI, -3.7 to -0.2) p=0.033 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Chalder fatigue scale scores (0 to 33 scale, lower score indicates better health)* : 19.1 (7.6) vs. 22.9 (6.9), AMD: -4.2 (95% CI, -6.1 to -2.3) p<0.0001 Meeting CDC criteria (n=138), mean difference in Chalder fatigue scale score: -4.1 (95% CI, -6.5 to -1.7) p=0.001 Meeting Oxford criteria (n=141), mean difference in Chalder fatigue scale score: -3.5 (95% CI, -5.7 to -1.3) p=0.002 Outcomes related to associated symptoms: International Physical Activity Questionnaire 12 week results % (n/N): Low: 34 (33/97) vs. 47 (46/102) Moderate: 36 (35/97) vs. 33 (33/102) High: 30 (29/97) vs. 20 (20/102) Odds ratio: 3.2 (95% CI, 1.8 to 5.8) p<0.0001 Depression: *Hospital Anxiety and Depression Scale, mean (SD):* 7.4 (4.3) vs. 8.6 (4.7), mean difference: -1.1 (-2.0 to -0.3), p=0.006

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Clark, 2017[18] RCT Medium	**Graded exercise therapy vs. control** Adverse Events: 28% (27/97) vs. 23% (23/101) Withdrawals due to adverse event: None Serious Adverse Events: 1% (1/97) vs. 2% (2/101), not suspected to be reactions: 1 fall on arm, 1 twisted knee, 1 with numbness in leg and arm	United Kingdom National Institute for Health Research Research for Patient Benefit Programme and the Sue Estermann Fund

Appendix E2. Evidence Table for Key Question 3

Author, year **Study Design** **Risk of Bias**	**Country** **Number of Centers** **Study Years** **Setting (primary care, specialty clinic or other)**	**Diagnostic criteria** **Inclusion/ Exclusion criteria**	**Interventions (n)** **Duration of treatment** **Duration of followup**
Crawley, 2019[19] RCT Medium	United Kingdom Single center 2010 to 2013 Tertiary care clinic	NICE (2007) diagnostic criteria **Inclusion:** Aged 12 to 18 years, meeting CFS/ME diagnosis **Exclusion:** Housebound, unable to speak English	**Lightning process (n=51):** Phil Parker Lighting Process; trademarked intervention developed from osteopathy, life coaching, and neuolinguistic programming to train patients to recognize and avoid stimulating or triggering unhelpful psychological responses. 3 group sessions on consecutive days. Included specialist medical care. **Control (n=49):** Specialist medical care; children and their families were offered a variety of treatment options centered around graded activity and sleep improvement **Duration of treatment:** 3 days **Duration of followup:** 12 months for most outcomes, but 6 months for SF-36 (primary outcome)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Crawley, 2019[19] RCT Medium	**Lighting process vs. control:** Mean age (SD): 14.7 (1.4) vs. 14.5 (1.6) % Female: 74.5 (38/51) vs. 77.6 (38/49) Race: NR Duration of illness, median months, IQR: 12 (8.0, 18.0) vs. 12 (7.0, 22.0) Severity of symptoms: Median Chalder fatigue score (0 to 33), (SD): 25.0 (4.2) vs. 25.1 (4.2) Median SF-36 physical function (0 to 100), (SD): 53.0 (18.8) vs. 56.0 (21.5) School attendance in the previous week, n: None: 6 vs. 7 0.5 day: 5 vs. 7 1 day: 3 vs. 3 2 days: 8 vs. 8 3 days: 12 vs. 12 4 days: 12 vs. 9 15 days: 4 vs. 3 Comorbidities: NR	Number enrolled: 100 Number analyzed: 81 (at 6 months)	**Lightning process vs. control at 6 months:** 14% (7/51) vs. 24% (12/49)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Crawley, 2019[19] RCT Medium	**Lightning process vs. control** Overall Function, Mean SF-36 at 6 months: 81.7 vs. 70.2, adjusted (based on age, gender and baseline outcome) difference in means: 12.5 (95% CI, 4.5 to 20.5), p=0.003 Quality of Life: NR, only reported in quality-adjusted life years Mean School Days attended in the previous week: 6 months: 3.2 vs. 2.6, adjusted difference in means: 0.7 (95% CI, 0.0 to 1.4), p=0.064 Mean School Days attended in the previous week: 12 months: 4.1 vs. 3.1, adjusted difference in means: 0.9 (95% CI, 0.2 to 1.6), p=0.018 Proportion full/part-time work: NR Fatigue, Mean Chalder Fatigue Scale (0 to 33) 6 months: 14.4 vs. 19.8, adjusted difference in means: -4.7 (95% CI, -7.9 to 1.6), p=0.003 Fatigue, Mean Chalder Fatigue Scale (0 to 33) 12 months: 12.3 vs, 15.7, adjusted difference in means: -3.2 (95% CI, -6.3 to 0.10), p=0.045 Outcomes related to associated symptoms: Mean Pain VAS 6 months: 23.4 vs. 32.8, adjusted difference in means: -11.3 (95% CI, -23.0 to 0.3), p=0.057 Mean Pain VAS 12 months: 21.8 vs. 32.0, adjusted difference in means: -9.4 (95% CI, -21.5 to 2.7), p=0.125 Depression: HADS-Depression, mean: 6 months: 4.2 vs. 5.9, p=0.141 12 months: 2.8 vs. 4.6, p=0.033

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Crawley, 2019[19] RCT Medium	**Lightning process vs. control** Adverse Events: 3 vs. 2, but one was related to a parent Withdrawals due to adverse event: None reported Serious Adverse Events: None reported	Linbury Trust, Ashden Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Deale, 1997[20] Deale, 2001[21] RCT Medium	United Kingdom Single center Study year(s) NR Hospital clinic specializing in CFS	Oxford (Sharpe, 1991), CDC (Fukuda, 1994) criteria **Inclusion:** Main complaint of medically unexplained, disabling fatigue of ≥6 months; with impairment of physical and mental activities; those taking antidepressants or anxiolytics (dose of ≤10 mg/day of diazepam or equivalent) were included if dose was stable for 3 months before study entry and during the trial. **Exclusion:** Somatization disorder, severe depression, ongoing physical investigations, concurrent new treatment, and inability to attend all treatment sessions.	**CBT (n=30):** 13 individual weekly or biweekly counseling sessions over 4-6 months with the aim of showing patients that activity could be increased steadily and safely without exacerbating symptoms. Graded activity was introduced in session 4, and increased for the duration of the study. Cognitive strategies were introduced in session 8, while the graded activity program continued. **Relaxation (n=30):** 13 individual weekly or biweekly sessions over 4-6 months teaching progressive muscle relaxation, visualization, and rapid relaxation skills. **Duration of treatment:** 4 to 6 months **Duration of followup:** Deale, 1997: 6 months after end of treatment Deale, 2001: 5 years after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Deale, 1997[20] Deale, 2001[21] RCT Medium	**CBT vs. relaxation** Mean age (SD): 31 (9) vs. 38 (11) years % Female: 70 (21/30) vs. 67 (20/30) Race: NR Duration of illness: Mean (SD): 3.4 (2.1) vs. 4.6 (3.3) years Severity of symptoms: "The whole group had near maximum scores on the measures of functional impairment and fatigue" % Unemployed: 63 (19/30) vs. 77 (23/30) % On disability benefits: 53 (16/30) vs. 67 (20/30) Comorbidities: % Current psychiatric diagnosis: 37 (11/30) vs. 40 (12/30) Five patients had additional diagnoses of dysthymia, nine had major depression, three had anxiety disorders, and six had both depression and an anxiety disorder; not listed by group.	Number enrolled: 60 (30 CBT, 30 relaxation) Number analyzed: 60 (30 CBT, 30 relaxation) in Deale, 1997; 53 (25 CBT, 28 relaxation) in Deale, 2001	**CBT vs. relaxation:** 10% (3/30) vs. 13% (4/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Deale, 1997[20] Deale, 2001[21] RCT Medium	**CBT vs. relaxation** Overall Function: *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Posttreatment: 56.2 (26.2) vs. 34.6 (28.3); 6 month followup: 71.6 (28.0) vs. 38.4 (26.9); p<0.03 *% With good outcome on SF-36 physical functioning scale (increase of ≥50 from baseline to 6 months, or end score of ≥83):* 6 months followup: 63 (19/30) vs. 17 (5/30); difference of 46 (95% CI 24 to 68) p<0.001; 5 year followup: 48 (12/25) vs. 32 (9/28); p=0.27 *% With rating by assessor at 3 month followup* Better or much better: 80 (20/25) vs. 26 (6/23); p<0.001; Unchanged or worse: 20 (5/25) vs. 74 (17/23) *Mean (SD) Work and social adjustment scale scores (0-8 scale, lower scores indicate better health)* Posttreatment: 4.1 (1.9) vs. 5.2 (1.8) 6 month followup: 3.3 (2.2) vs. 5.4 (1.8); p<0.001 for between group differences over time Quality of Life: NR Work/School Days: *% With full- or part-time employment at 5 year followup:* 56 (14/25) vs. 39 (11/28); p=0.28 *Mean (SD) hours worked per week (of employed persons, n=14 vs. 11) at 5 year followup:* 35.57 (8.11) vs. 24.00 (4.97); p<0.04 Proportion full/part-time work: NR Fatigue: *Mean (SD) fatigue problem rating scores (0-8 scale, lower scores indicate better health)* Posttreatment: 4.1 (1.9) vs. 5.5 (1.4) 6 month followup: 3.4 (2.2) vs. 5.5 (1.9); p<0.001 for between group differences over time Mean (SD) Chalder fatigue scale scores (0 to 11, scores of ≥4 indicate caseness or excessive fatigue, lower scores indicate better health) Posttreatment: 7.2 (4.0) vs. 7.5 (4.1) 6 month followup: 4.1 (4.0) vs. 7.2 (4.0); p<0.001 for between group differences over time % With fatigue rating by assessor at 3 months followup Better or much better: 72 (18/25) vs. 17 (4/23); p<0.001; Unchanged or worse: 28 (7/25) vs. 83 (19/23) % With score <4 on Chalder fatigue scale 6 month followup: 63 (17/27) vs. 15 (4/26); p=0.001; 5 year followup: 28 (7/25) vs. 25 (7/28); p=1.00 Outcomes related to associated symptoms: Beck Depression Inventory, mean (SD): Posttreatment: 8.9 (5.6) vs. 11.9 (7.4) 6-month follow up: 10.1 (6.9) vs. 12.3 (8.5), p>0.30 % With global improvement rating Better or much better at 6 month followup: 70 (19/27) vs. 31 (8/26); p<0.01; Unchanged or worse at 6 month followup: 30 (8/27) vs. 69 (18/26) Better or much better at 5 year followup: 68 (17/25) vs. 36 (10/28); p=0.05 Other outcomes at 5 year follow % With symptoms "steadily improved" not "consistently absent' or "mild": 68 (17/25) vs. 43 (12/28); p=0.05; % With complete recovery (no longer met CFS criteria, employed full-time, score <4 on Chalder fatigue scale, and score >83 on SF-36): 24 (6/25) vs. 4

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Deale, 1997[20] Deale, 2001[21] RCT Medium	**CBT vs. relaxation** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	South East Thames Regional Health Authority Locally Organized Research Scheme; South Thames Small Project Grant Scheme, Wellcome Trust grant

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Dybwad, 2007[22] RCT Medium	Norway Single center 2005 Hospital clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosis with Fukuda criteria by a medical doctor especially experienced with the condition, duration of condition ≥2 years **Exclusion:** Antidepressive drugs, other conditions that could give fatigue	**Qigong (n=15):** Qigong exercises once a week for 2 hours with a certified instructor, over 15 weeks. Sessions consisted of simple principles of anatomy and physiology (30 minutes), qigong practice (1 hour), and breathing exercises, relaxation and mediation including non-structured conversation among participants (30 minutes) **Control (n=16):** No Qigong training Both groups were encouraged to not start any new treatments during the intervention period. **Duration of treatment:** 6 months **Duration of followup:** End of treatment
Fluge, 2011[23] RCT Medium	Norway Single center 2008 to 2010 Tertiary referral center	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosis of CFS by a neurologist, according to Fukuda 1994 criteria; aged 18 to 65 years; and written informed consent. **Exclusion:** fatigue and not fulfilling CFS criteria; previous malignant disease (except basal cell carcinoma and cervical dysplasia); previous long-term immunosuppressive treatment; previous Rituximab treatment; endogenous depression; lack of ability to adhere to protocol; or evidence of ongoing infection.	**Rituximab 500 mg/m^2, maximum 1,000 mg (15):** diluted in saline to a concentration of 2 mg/mL, given two weeks apart **Placebo (15):** Equal volume of saline given two weeks apart Both groups were given oral cetrizine 10 mg, paracetamol 1 g, and dexamethazone 8 mg prior to infusion. Duration of treatment: two weeks (two treatments) Duration of followup: 12 months

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Dybwad, 2007[22] RCT Medium	**Qigong vs. control** Mean age: 43.2 vs. 45.4 % Female: 80 (12/15) vs. 88 (14/16) Race: NR Duration of illness: 6.5 vs. 9.7 years Severity of symptoms: Mean FSS entire group (n=31): 6.5 Mean SF-36 physical function entire group (n=31): 48 Comorbidities: NR	Enrolled: 31 Analyzed: 28	9.7% (3/31) (1 qigong and 1 control) 1 in qigong group became ill and dropped out before intervention started 1 in control group had a fractured leg and was unable to participate in followup bicycle testing of work capacity 1 had aggravated symptoms from baseline exercise testing
Fluge, 2011[23] RCT Medium	**Rituximab vs. placebo** Mean age (years): 37.3 vs. 31.5 % Female: 80 (12/15) vs. 60 (9/15) Race: NR Duration of illness: mean (range): 5.1 (1.0 to 13.0) vs. 8.1 (0.7 to 18.0) years Severity of symptoms: *SF-36 physical function (percent, lower score denotes increasing symptoms)* , mean (SD): 34 (6) vs. 35 (7) *VAS fatigue score (0 to 10, 10 most severe)* , mean (range): 8.1 (7.3 to 9.8) vs. 7.9 (6.0 to 9.3) Cognitive score, mean (range): 7.7 (5.0 to 9.7) vs. 7.2 (4.0 to 9.3) Pain score, mean (range): 6.5 (4.0 to 9.3) vs. 6.2 (1.3 to 9.0) "Other symptoms" score, mean (range): 7.8 (5.5 to 10.0) vs. 7.9 (5.0 to 10.0) Rnase L genotype 462 Q/Q: 5 vs. 6 Rnase L genotype 462 Q/R: 10 vs. 7 Rnase L genotype 462 R/R: 0 vs. 2 XMRV PCR: 0/15 vs. 0/15 XMRV Coculture: 0/4 vs. 0/5	Number enrolled: 30 Number analyzed: 30	0 (0/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Dybwad, 2007[22] RCT Medium	**Qigong vs. control** Overall Function: Mean SF-36 physical function differences in both groups from baseline to retest (SD), 1.3 (16) vs. 4.7 (13) p=0.34 (adjusted for baseline value) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean change in FSS score (SD): -0.44 (0.60) vs. 0 (0.6), p=0.04, adjusted for baseline values Mean difference: -0.5, 95% CI -0.9 to -0.02; all participants in both groups still clinically fatigued Outcomes related to associated symptoms: Hospital anxiety and depression scale: No significant changes observed after intervention within or between groups, data NR Visual analog scale: Mean change: -1.4 vs. "similar", p=0.05 for between group differences
Fluge, 2011[23] RCT Medium	**Rituximab vs. placebo** Overall function: *SF-36 physical function, (perfect, lower score denotes increasing symptoms)* , max change %, mean (SD): 39 (33) vs. 11 (22) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Major clinical responses: 9 (60%) vs. 7 (7%), p=0.002 Moderate clinical responses: 1 (7%) vs. 1 (7%) Overall, 95% CI: 10 (67%) (95% CI, 41% to 85%) vs. 2 (13%) (95% CI, 4% to 38%), p=0.003 Response duration: weeks, mean (range): 25 (8 to >44), n=10 vs. 41 (34 to >48), n=2 Difference between groups in self reported fatigue score at 40 to 52 weeks: 0.63 (95% CI, -0.09 to 1.34), adjusted p value: 0.25 Difference in physcian-assessed fatigue score at 12 months after intervention: 0.62 (95% CI, -0.09 to 1.34), adjusted p-value: 0.17 Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Dybwad, 2007[22] RCT Medium	**Qigong vs. control** Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	EXTRA funds from the Norwegian Foundation for Health and Rehabilitation and NAFKAM
Fluge, 2011[23] RCT Medium	**Rituximab vs. placebo** Adverse Events: Infusion-related complaints: Palpitations: 1 (7%) vs. 1 (7%) Slight itching: 2 (13%) vs. 0 Nausea: 0 vs. 1 (7%) Discomfort: 2 (13%) vs. 2 (13%) Irregular menstrual bleeding the first two months: 2 (13%) vs. 0 Feeling uneasy and sleepless at 6 to 8 months: 1 (7%) vs. 0 Feeling uneasy and sleepless at 2 to 7 months: 1 (7%) vs. 0 Slight facial acne: 1 (7%) vs. 0 Psoriasis worsening at 2 to 12 months: 2 (13%) vs. 0 Low back pain and balanitis at 5 to 7 months: 1 (7%) vs. 0 Withdrawals due to Adverse Event: None Serious Adverse Events: None	Helse Vest and the legacy of Torstein Hereid.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Fluge, 2019[24] RCT Low	Norway 5 centers 2014 to 2017 4 University hospitals an 1 general hospital	Canadian consensus (Caruthers, 2003) criteria **Inclusion:** ME/CFS according to Canadian consensus criteria; aged 18 to 65 years; had disease for a least 2 years (or ≥5 years if disease was mild), but less than 15 years. **Exclusion:** Patients with very severe disease (completely bedridden and in need of care, WHO class IV).	**Rituximab 500 mg/m^2, maximum 1,000 mg (77)**: diluted in saline to a concentration of 2 mg/mL, given two weeks apart **Placebo (75):** Equal volume of saline with added human albumin (0.4 mg/ML) given two weeks apart In the maintenance phase, pateints recevied a 500 mg fixed dose of rituximab or an equal volume of saline with human albumin at 3, 6, 9 and 12 months. Both groups were given oral cetrizine 10 mg, paracetamol 1 g, and dexamethazone 8mg one hour before infusions. **Duration of treatment:** 12 months **Duration of followup:** 24 months
Friedberg, 2016[25] RCT Medium	United States Recruited from 5 centers nationwide 2011 to 2014 Large tertiary care practices, but intervention took place in participants' homes	CDC (Fukuda, 1994) criteria **Inclusion:** Note from physician confirming CFS diagnosis, aged between 18 and 65 years, considered physically capable of doing the self-management program (e.g. walking assignments), ≥6 months of persistent fatigue, 4 of 8 secondary symptoms (sore throat, muscle pain, joint pain, headaches, sleep difficulties, post-exertional malaise, tender or sore lymph glands, concentration difficulties). **Exclusion:** Pregnancy, fatigue clearly attributable to self-reported medical conditions, self-reported psychosis, substance or alcohol abuse in the 2 years prior to illness onset, concurrent or past depression with melancholic or psychotic features within the 5 years prior to illness onset.	**FSM:ACT (n=45):** Fatigue self management with Web Diaries and Actigraphs; high-tech intervention **FSM:CTR (n=44):** Fatigue self management with paper diaries and step counters; low-tech intervention **Usual care (n=48):** Usual care plus web diaries and actographs. **Duration of treatment:** 12 weeks **Duration of followup:** 12 months All participants in FSM groups received a program to educate patient about diagnosis and casual factors in CFS in addition to stress factors and behaviors that play a role in disturbed sleep patterns, post-exertional symptoms, and push-crash activities was delivered by booklet and audio CDs. No face to face visits or clinical contacts (phone, email, etc.) with an interventionist. Assignments included a daily diary to identify baseline activities, symptoms, and stress levels. The self-management text included behavioral coping strategies. The program encouraged individualized self-scheduling of home-based activities, rest/sleep assignments, and cognitive coping skills.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Fluge, 2019[24] RCT Low	**Rituximab vs. placebo** Mean age (years): 37.8 vs. 35.5 % Female: 83.1 (64/77) vs. 81.1 (60/74) Race: NR Duration of illness: Mean duration (SD): 8.4 (3.1) vs. 7.6 (2.9) years 2 to <5 years: 14.3% (11/77) vs. 24.3% (18/74) 5 to <10 years: 58.4% (45/77) vs. 59.5% (44/74) 10 to 15 years: 27.3% (21/77) vs. 75.7% (56/74) Severity of symptoms: *Baseline SF-36 physical function (scale 0 to 100)* (mean): 35.24 vs. 32.45 Baseline fatigue score (0 to 6 scale): 3.0 vs. 3.0 Comorbidities: Hypothyroidism: 5.2% (4/77) vs. 5.4% (4/74) Allergy: 40.3% (31/77) vs. 41.9 (31/74) Fibromyalgia: 7.8% (6/77) vs. 6.8% (5/74) Depression: 9.1% (7/77) vs. 8.1% 6/74 Anxiety: 11.7% (9/77) vs. 10.8% (8/74) Other (unspecified): 27.3% (21/77) vs. 23.0% (17/74)	Number enrolled: 152 Number analyzed: 151	0 (0/152)
Friedberg, 2016[25] RCT Medium	**FSM: ACT vs. FSM:CTR vs. Usual care** Mean age: 48.01 vs. 46.99 vs. 50.03 years % Female: 84.4 (38/45) vs. 93.2 (41/44) vs. 87.5 (42/48) Race: % Caucasian: 93.3 (42/45) vs. 84.1 (37/44) vs. 97.9 (47/48) % Hispanic/Latino: 2.2 (1/45) vs. 11.4 (5/44) vs. 0 % African American: 2.2 (1/45) vs. 0 vs. 0 % Other: 2.2 (1/45) vs. 4.5 (2/44) vs. 2.1 (1/48) Duration of illness: 12.57 vs. 13.71 vs. 17.26 years Severity of symptoms: Mean SF-36 physical function: 38.22 vs. 36.59 vs. 38.89 % Employment status is disabled: 57 (26/45) vs. 43 (19/44) vs. 63 (30/48) Comorbidities: NR	Number enrolled: 137 Number analyzed: 127 (41 FSM:ACT, 40 FSM:CTR, 46 Usual Care)	Overall: 7.3%

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Fluge, 2019[24] RCT Low	**Rituximab vs. placebo** Overall Function: SF-36 physical function score (0 to 100 range) at 18 months: 45.67 vs. 45.23, mean difference: 0.42 (95% CI, -8.12 to 8.96), p=0.52 Function level, % at 16 to 20 months: 25.25 vs. 25.93, mean difference: -0.68 (95% CI, -5.90 to 4.54), p=0.31 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Fatigue score (range 0 to 6), at 16 to 20 months: 3.12 vs. 3.18, mean difference: -0.06 (95% CI, -0.51 to 0.39), p=0.79 Fatigue Severity Scale Score (range 9 to 63, higher scores indicate worse symptoms), mean at 18 months: 55.98 vs. 56.05, mean difference: -0.07 (95% CI, --3.21 to 3.08), p=0.68 Outcomes related to associated symptoms: Mean steps per 24 hours, 17 to 21 months: 3,777 vs. 3,904, mean difference: -127 (95% CI, -1004 to 749), p=0.58
Friedberg, 2016[25] RCT Medium	**FSM: ACT vs. FSM:CTR vs. Usual care** Overall function: Mean SF-36 physical function (SE): 3 months: 43.25 (3.20) vs. 43.75 (3.32) vs. 37.26 (3.13), all comparisons p>0.05 12 months: 46.50 (3.68) vs. 45.75 (3.68) vs. 44.07 (3.47), all comparisons p>0.05 Quality of life: NR Work/school days: NR Proportion full/part time work: NR Fatigue: Mean fatigue severity scale (SE): 3 months: 6.12 (0.11) vs. 5.92 (0.11) vs. 6.42 (0.10), FSM:ACT vs. FSM:CTR p<0.05, other comparisons p>0.05 12 months: 6.00 (0.13) vs. 6.10 (0.13) vs. 6.42 (0.12), all comparisons p>0.05 Outcomes related to associated symptoms: Mean Beck Depression Inventory (SE): 3 months: 14.40 (1.65) vs. 14.98 (1.65) vs. 19.36 (1.55), all comparisons p>0.05 12 months: 13.08 (1.48) vs. 14.42 (1.48) vs. 18.64 (1.39), Usual care vs. both other arms p<0.05, intervention arms vs. each other p>0.05

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Fluge, 2019[24] RCT Low	**Rituximab vs. placebo** Adverse Events: Any: 81.8% (63/77) vs. 64.9% (48/74) Withdrawals due to Adverse Event: None Serious Adverse Events: 26.0% (20/77) vs. 18.9 (14/74)	Kavli Trust, Norwegian Resarch Council, Norwegian Regional Health Trusts, the MEandYou Foundation, Norwegian ME Association, and the legacy of Torstein Hereid.
Friedberg, 2016[25] RCT Medium	**FSM: ACT vs. FSM:CTR vs. Usual care** Adverse events: NR Withdrawals due to adverse events: NR Serious adverse events: NR	National Institutes of Health, National Institute of Nursing Research

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Fulcher, 1997[26] Crossover RCT Medium	United Kingdom Single center Study year(s) NR Chronic fatigue clinic in a general hospital department of psychology	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients meeting the Oxford criteria **Exclusions:** Patients excluded for current psychiatric disorders, not including simple phobias, using the clinical interview for the DSM-III-R or for co-morbid symptomatic insomnia. Physical screenings and investigations into records were carried out when appropriate to ensure exclusion of other disorders	**Graded exercise (n=33):** Exercise treatment, weekly for 12 weeks of supervised treatment, adapted to the patient's current capacity, with a prescription to exercise at home (mainly by walking, but biking and swimming were also encouraged) 5 days a week starting at 15 minutes per session and increasing to a maximum of 30 minutes per session. Patients were given heart monitors and advised to stay within a maximum of peak oxygen consumption, starting at 40% and increasing to 60% **Flexibility/relaxation (n=33):** 12 weeks of weekly in-person flexibility and relaxation sessions and prescriptions to do sessions at home 5 days a week starting at 10 minutes per session and increasing to 30 minutes per session. Advice to avoid doing any extra physical activities **Duration of treatment:** 12 weeks, then crossover. **Duration of followup:** 1 year survey was done, data from after first 12 week period only

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Fulcher, 1997[26] Crossover RCT Medium	**Graded exercise vs. flexibility/relaxation** Mean age (SD): 37.2 (10.7) years overall, unreported by arm % Female: 74 (49/66) overall, unreported by arm Race: NR Duration of illness: Median (range): 2.7 (0.6 to 19.0) years overall, unreported by arm Severity of symptoms: *Mean Chalder fatigue score (0 to 42) (SD)*: 28.9 (7.1) vs. 30.5 (5.6) *Mean (SD) SF-36 physical function score*: 48.5 (22.1) vs. 47 (18.7) Comorbidities: NR	Number enrolled: 66 Number analyzed: 59 (29 exercise, 30 control)	**Overall:** 12% (7/59) **Graded exercise vs. flexibility/relaxation:** 14% (4/29) vs. 10% (3/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Fulcher, 1997[26] Crossover RCT Medium	**Graded exercise vs. flexibility/relaxation** Overall Function: *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* 12 weeks: 69 (18.5) vs 55 (21.8); p=0.01 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: **Exercise vs. all participants (due to control allowed to crossover to exercise)** Working full- or part-time at 1 year followup: 66% (31/47) vs. 39% (26/66); (95% CI, 9% to 44%); p=NR Fatigue: *Mean (SD) Chalder fatigue scale scores (0-42 scale, lower score indicates better health)* 12 weeks: 20.5 (8.9) vs. 27.4 (7.4); p=0.004 *Mean (SD) Visual analog scale total fatigue score (summed score, 200 noted as 'normal', lower scores indicate better health)* 12 weeks: 253 (48) vs. 286 (67); p=0.04 *Mean (SD) Visual analog scale physical fatigue score (100mm, 100 noted as 'normal', lower scores indicate better health)* 12 weeks: 130 (28) vs. 154 (34); p=0.006 *Mean (SD) Visual analog scale mental fatigue score (100mm, 100 noted as 'normal', lower scores indicate better health)* 12 weeks: 124 (31) vs. 132 (39); p=0.38Outcomes related to associated symptoms: Self-rated CGI score after 12 weeks % Very much better: 31 (9/29) vs. 7 (2/30) % Much better: 24 (7/29) vs. 20 (6/30) % A little better: 38 (11/29) vs. 60 (18/30) % No change: 3 (1/29) vs. 10 (3/30) % A little worse: 3 (1/29) vs.0 (0/30) % Much worse: 0 (0/29) vs. 3 (1/30) % Very much worse: 0 (0/29) vs. 0 (0/30) p=0.05 for between groups comparison Median (IQR) peak O2 consumption (ml/kg/minute) After 12 weeks: 35.8 (30.8-40.7) vs. 29.8 (24.7-34.9); p=0.03 Median increase in peak O2 consumption: 13% vs. 6% Median increase in isometric strength: 26% vs. 15%; p=0.20 Graded exercise group completers only: Rated self as better at 1 year followup: 74% (35/47) Depression: Mean (IQR) *Hospital Anxiety and Depression Scale*: 5.5 (2.9 to 8.1) vs. 4 (0.6 to 7.4), p=0.92 Anxiety: Mean (IQR) *Hospital Anxiety and Depression Scale*: 5.5 (3.0 to 8.0) vs. 7 (3.5 to 1.05), p=0.46 Sleep: Mean (IQR) *Pittsburgh Sleep Quality Index*: 5.0 (3.5 to 6.5) vs. 6 (4.1 to 7.9), p=0.49

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Fulcher, 1997[26] Crossover RCT Medium	**Graded exercise vs. flexibility/relaxation** Adverse Events: NR/unclear ("minimal adverse effects" but no number reported) Withdrawals due to adverse event: NR Serious Adverse Events: NR	Linbury Trust, a Sainsbury charitable trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	**Country Number of Centers Study Years Setting (primary care, specialty clinic or other)**	**Diagnostic criteria Inclusion/ Exclusion criteria**	**Interventions (n) Duration of treatment Duration of followup**
Hobday, 2008[27] RCT High	United Kingdom Single center Study year(s) NR Chronic fatigue clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosis of CFS, no other criteria described. **Exclusion:** Pregnant, taking oral contraceptives, hormone therapy, steroids, NSAID, antibiotics or immunosuppressants; already following significant dietary changes; taking vitamin and mineral supplements above recommended dose; or diagnosed with an eating disorder.	**Low sugar/low yeast (n=25):** Adapted from Beat Candida Cook Book (White, 1999) - omission of all sugar containing foods, refined carbohydrates, and yeast containing foods, alcohol, caffeine; limited fruit, milk; encouraged to have one live yogurt per day. **Healthy eating (n=27):** High fiber, 5 servings of fruit and vegetables per day, reduced fat and refined carbohydrate, fish 2 times a week. **Duration of treatment:** 24 weeks **Duration of followup:** End of treatment
Huanan, 2017[28] RCT Medium	China Single center 2014 to 2015 Hospital clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Aged 18 to 60 years, meeting CDC diagnosis of CFS. **Exclusion:** Cardiovascular, cerebrovascular, liver, kidney, lung, or hematopoietic-system disease; severe hypotension or diabetes mellitus; mental disorders; pregnant or breastfeeding; combined thrombocytopenia and coagulation disorders; severe obesity	**Abdominal tuina (n=40):** Four steps of abdominal tuina, including pressing, kneading, pushing and pulling. Five sessions were given daily each week, with 2 consecutive days of no treatment between weeks. **Acupuncture (n=40):** Acupuncture using chosen acupoints. Five sessions were given daily each week, with 2 consecutive days of no treatment between weeks. **Duration of treatment:** 4 weeks **Duration of followup:** 3 months after treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Hobday, 2008[27] RCT High	**Low sugar/low yeast vs. healthy eating** Mean age: 44 vs. 42 years % Female: 88 (22/25) vs. 78 (21/27) Race: NR Duration of illness: NR Severity of symptoms: *Chalder Fatigue Scale* 23.0 vs. 22.5 Comorbidities: NR	Number enrolled: 52 Number analyzed: 39	**Overall:** 25% (13/52) **Low sugar/low yeast vs. healthy eating:** 24% (6/25) vs. 26% (7/27)
Huanan, 2017[28] RCT Medium	**Abdominal tuina vs. acupuncture** Mean age: 41.8 vs. 42.6 % Female: 44 (17/39) vs. 37 (14/38) Race NR, conducted in China Duration of illness: 10.4 vs. 10.6 months Severity of symptoms: Mean FS-14 score: 8.9 vs. 9.3 Comorbidities: NR	Number enrolled: 80 Number analyzed: 72 (37 abdominal tuina, 35 acupuncture)	**Overall:** 10% (8/80) 2 abdominal tuina patients lost to followup 1 abdominal tuina patients lost to absent contact details. 2 acupuncture patients underwent additional treatments prohibited in the protocol. 2 acupuncture patients lost to a time constraint. 1 acupuncture patient lost to another reason.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Hobday, 2008[27] RCT High	**Low sugar/low yeast vs. healthy eating** Overall Function: *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health:* 42.3 (29.2) vs. 52.2 (24.1); mean difference 9.90, 95% CI -7.43 to 27.23 *social functioning subscale, mean:* 42.0 (29.3) vs. 50.6 (29.4), mean difference 8.60, 95% CI -10.45 to 27.65 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Chalder Fatigue Scale scores (scores of ≥4 indicate caseness for fatigue, lower score indicates better health)* 24 weeks: 16.0 (8.2) vs. 17.7 (10.0); mean difference -1.7, 95% CI -7.5 to 4.1 *Medial Outcomes Survey SF-36 vitality subscale scores (0-100 scale, higher score indicates better health) Mean (SD)* 24 weeks: 29.8 (20.7) vs. 36.2 (26.4); p=0.39 Outcomes related to associated symptoms: *Hospital Anxiety and Depression Score Mean (SD); Anxiety:* 8.5 (5.2) vs. 7.3 (4.1); p=0.43; *Depression:* 6.5 (3.6) vs. 5.4 (3.7); mean difference 1.1, 95% CI -1.2 to 3.5
Huanan, 2017[28] RCT Medium	**Abdominal tuina vs. acupuncture** Overall Function: NR Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean FS-14 (SD): 6.6 (1.8) vs. 7.6 (2.1), mean difference 1.0, 95% CI 0.11 to 1.88 Outcomes related to associated symptoms: Mean self-rating anxiety scale (SD): 47.0 (4) vs. 49 (5), mean difference 2.0, 95% CI -0.05 to 4.05 Mean Hamilton rating scale for depression (SD): 5.6 (1.3) vs. 6.3 (1.2), mean difference 0.70, 95% CI 0.13 to 1.27

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Hobday, 2008[27] RCT High	**Low sugar/low yeast vs. healthy eating** Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	Nurses, Midwives and Allied Health Research Fund (Barts and the London NHS Trust), the ME Association and Department Nutrition and Dietetics (Barts and the London NHS Trust).
Huanan, 2017[28] RCT Medium	**Abdominal tuina vs. acupuncture** Adverse Events: Persistent pain for 1 hour during first treatment: 1 vs. 0 Hematoma at needling site: 0 vs. 2 Withdrawals due to AE: None reported Serious Adverse Events: None reported	National Natural Science Foundation

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Janse, 2018[29] RCT Medium	The Netherlands Single center 2013 to 2015 Tertiary care facility in a hospital	CDC (Fukuda, 1994) criteria **Inclusion:** Referred to clinic, including examination to rule out medical explanation for fatigue. At least 18 years of age, score of ≥35 on fatigue subscale of CIS, severely disabled (SIP-8 score ≥700), able to use computer and access to internet. **Exclusion:** Psychiatric comorbidity that could explain the fatigue, involved in legal procedures concerning disability benefit claims, participation in other CFS research.	**iCBT with protocol feedback (n=80):** 7 online modules based on a face-to-face CBT for CFS protocol, tailored to each patients' current activity pattern. Patients were asked by their therapists to report on their progress by email at least fortnightly, according to a prescribed schedule. The therapist provided feedback and sent reminders if needed. **iCBT with feedback on demand (n=80):** Same as above, except patients only received feedback when they asked for advice. Patients received no reminders. **Control (n=80):** Wait list **Duration of treatment:** 6 months **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Janse, 2018[29] RCT Medium	**iCBT with protocol feedback vs. iCBT with feedback on demand vs. control** Mean age: 36.6 vs. 36.4 vs. 39.9 years % Female: 68 (54/80) vs. 58 (46/80) vs. 56 (45/80) Race NR Duration of illness, median (IQR): 4 (7.8) vs. 4.5 (9.5) vs. 6.5 (7.8) years Severity of symptoms: CIS mean: 50.7 vs. 49.9 vs. 49.5 CDC symptoms, median number (IQR): 7 (2) vs. 7 (2) vs. 7 (2) Comorbidities: Any depressive disorder, %: 11 (9/80) vs. 9 (7/80) vs. 10 (8/80) Any anxiety disorder, %: 9 (7/80) vs. 6 (5/80) vs. 10 (8/80) Other psychiatric disorder, %: 1 (1/80) vs. 1 (1/80) vs. 4 (3/80)	Number enrolled: 240 Number analyzed: 240	3% (6/240) lost to followup **iCBT with protocol feedback vs. iCBT with feedback on demand vs. control** 1 vs. 1 vs. 4 4 participants in iCBT with protocol feedback group did not start treatment 6 participants in iCBT with feedback on demand group did not start treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Janse, 2018[29] RCT Medium	**iCBT with protocol feedback vs. iCBT with feedback on demand vs. control** Overall Function: *Mean (SD) SF-36 physical functioning scale scores (0 to 100 scale, higher scores indicate better health):* 73.3 (25.9) vs. 77.0 (21.3) vs. 70.8 (21.0) Difference compared with control: iCBT with protocol feedback: 2.4 (-3.6 to 8.4), p=0.44; iCBT with feedback on demand: 5.8 (0.6 to 11.0), p=0.030 Quality of life: NR Work/school Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) CIS fatigue severity scores (8 to 56 scale, lower scores indicate better health):* 36.3 (14.6) vs. 37.0 (13.1) vs. 43.9 (10.5) Mean difference compared with control (97.5% CI): iCBT with protocol feedback: -8.3 (-12.7 to -3.9), p<0.0001; iCBT with feedback on demand: -7.2 (-11.3 to -3.1), p<0.0001 Outcomes related to associated symptoms: Overall impairment: Mean Sickness Impact Profile 8 (SD): 867.8 (670.4) vs. 885.0 (658.9) vs. 1322.5 (720.8) Mean difference compared with control (95% CI): iCBT with protocol feedback: -338.3 (-514.7 to -161.9), p=0.0002; iCBT with feedback on demand: -356.0 (-530.0 to -182.0), p<0.0001 Psychological distress: Mean Symptom Checklist-90 (SD): 135.0 (36.4) vs. 140.3 (45.0) vs. 154.8 (47.6) Mean difference compared with control (95% CI): iCBT with protocol feedback: -14.2 (-24.7 to -3.8), p=0.0075; iCBT with feedback on demand: -12.6 (-23.6 to -1.6), p=0.0247

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Janse, 2018[29] RCT Medium	**iCBT with protocol feedback vs. iCBT with feedback on demand vs. control** Adverse events: NR Withdrawals due to adverse events: None Serious adverse events: None	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Jason, 2007[30] Jason, 2009[31] Hlavaty, 2011[32] RCT Medium	United States Single site Study year(s) NR Setting not described	CFS Questionnaire based on CDC (Fukuda, 1994) criteria, psychiatric assessment for DSM-IV diagnosis, and medical assessment **Inclusion:** Ages ≥18 years, not pregnant, able to read and speak English, considered to be physically capable of attending the scheduled sessions. **Exclusion:** Persons who used wheelchairs and who were bedridden or housebound; lifelong fatigue; >4 secondary symptoms of CFS; BMI >45; melancholic depression or bipolar depression; alcohol or substance abuse disorder; autoimmune thyroiditis; cancer; lupus; or rheumatoid arthritis.	**CBT (n=29):** 13 sessions of individual CBT, held once every 2 weeks, with graded activity developed in collaboration with the participant; beginning modestly, with activity and rest pre-planned and time-contingent rather than symptom-driven; negative automatic thoughts were reviewed and cognitive strategies were introduced to develop new ways of thinking. **Cognitive therapy (COG) (n=28):** 13 sessions, held once every 2 weeks, of broad-based cognitive approach focused on developing cognitive strategies to better tolerate and reduce stress and symptoms, and to lessen self-criticism. **Anaerobic activity therapy (ACT) (n=29):** 13 sessions, held once every 2 weeks, of anaerobic activity therapy focused on developing individualized, constructive and pleasurable activities with reinforcement. **Relaxation (n=28):** 13 sessions, held once every 2 weeks, focusing on progressive muscle relaxation techniques, breathing, yoga form stretching, and thematic imagery relaxation; participants were shown how to use relaxation techniques in stressful situations. **Duration of treatment:** 6 months **Duration of followup:** 1 year

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Jason, 2007[30] Jason, 2009[31] Hlavaty, 2011[32] RCT Medium	Mean age: 43.8 years % Female: 83 (95/114) % White: 88 (100/114) % Black: 4 (5/114) % Latino: 4 (5/114) % Asian-American: 4 (4/114) CBT vs. COG vs. ACT vs. Relaxation: % Working full or part time: 45 vs. 50 vs. 41 vs. 46 Overall: % On disability: 25 (28/114) % Unemployed: 24 (27/114) % Working part-time: 20 (23/114) % Working full-time: 19 (22/114) % Retired: 6 (7/114) % Part-time student: 4 (5/114) % Full-time student: 1 (1/114) % Working part-time and on disability: 1 (1/114) No statistically significant socio-demographic differences between the groups at baseline Duration of illness: NR, all ≥6 months Severity of symptoms: CBT vs. COG vs. ACT vs. Relaxation Mean (SD) FSS scores (1 to 7, lower score indicates better health): 6.05 (0.60) vs. 6.25 (0.60) vs. 6.23 (0.85) vs. 5.82 (0.74) Comorbidities: % Lifetime axis I diagnosis: 62 (71/114) % Current axis I diagnosis: 39 (44/114)	Number enrolled: 114 (29 CBT, 28 COG, 29 ACT, 28 Relaxation) Number analyzed: 114 (29 CBT, 28 COG, 29 ACT, 28 Relaxation) in Jason, 2007; 81 (49 staying within their energy envelope, 32 going beyond their energy envelope) in Jason, 2009; 82 (22 CBT, 22 COG, 18 ACT, 20 Relaxation) in Hlavaty, 2011	Average drop out rate: 25%, but NR per group

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Jason, 2007[30] Jason, 2009[31] Hlavaty, 2011[32] RCT Medium	**CBT vs. COG vs. ACT vs. Relaxation** Overall Function: *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health)* 12 months: 58.64 (30.44) vs. 61.09 (23.74) vs. 39.72 (27.63) vs. 61.20 (27.70) p<0.01 for CBT and COG over time vs. ACT over time % Achieving clinically significant improvement: 18.2 vs. 30.4 vs. 11.1 vs. 21.7; p=0.49 ***Jason, 2009 data: comparison by energy envelope (data estimated from figure)*** **Stayed within envelope vs. outside envelope** 6 months: 58 vs. 48; p=NR 12 months: 65 vs. 42 Change at 12 months from baseline: 17 vs. 0; p=0.03 ***Hlavaty, 2011 data: comparison by homework compliance level*** **Minimum vs. moderate vs. maximum** Change in SF-36 physical functioning score at 12 months from baseline: 6.99 (19.30) vs. 7.55 (18.85) vs. 17.50 (18.09); p=NR Quality of Life: *Mean (SD) QLS scores (16-112 scale, higher score indicates better health)* 12 months: 69.10 (18.99) vs. 72.52 (10.84) vs. 63.00 (13.86) vs. 72.00 (19.70); p=NR Work/School Days: NR Proportion full/part-time work: % Employed at 12 month followup: 62 vs. 56 vs. 33 vs. 43; p=NS Fatigue: *Mean (SD) FSS scores (1-7 scale, lower score indicates better health)* 12 months: 5.37 (1.19) vs. 5.87 (1.01) vs. 5.77 (1.43) vs. 5.62 (1.06); p=NR ***Jason, 2009 data: comparison by energy envelope (data estimated from figure)*** **Stayed within envelope vs. outside envelope** 6 months: 5.7 vs. 6.1; p=NR 12 months: 5.3 vs. 6.3 Change at 12 months from baseline: -0.9 vs. 0.1; p<0.01 ***Hlavaty, 2011 data: comparison by homework compliance level*** **Minimum vs. moderate vs. maximum** Change in score at 12 months from baseline: -0.17 (0.73) vs. -0.51 (1.00) vs. -0.54 (1.09); p=NR Outcomes related to associated symptoms: Depression outcomes at 12-month followup (*Beck Depression Inventory, 21- item, lower scores indicate better outcome*), mean (SD): 13.95 (13.08) vs. 11.86 (7.36) vs. 16.94 (11.82) vs. 13.50 (9.97), p<0.001

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Jason, 2007[30] Jason, 2009[31] Hlavaty, 2011[32] RCT Medium	**CBT vs. COG vs. ACT vs. Relaxation** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NIAID (Grant Number AI 49720)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Knoop, 2008[33] Tummers, 2010[34] Tummers, 2013[35] Block randomized RCT Medium	The Netherlands Single center 2006 to 2007 Tertiary care facility	CDC (Fukuda, 1994) criteria **Inclusion:** Patients referred for CBT, age ≥18 years, spoke and read Dutch, not engaged in a legal procedure concerning disability-related financial benefits, medically and psychiatrically evaluated to exclude other causes of fatigue; scored ≥35 on the CIS fatigue severity subscale; total score of >700 on SIP-8. **Exclusion:** NR ***Tummers, 2010*** used same population and randomized groups from Knoop 2008 after the end of that trial. ***Tummers, 2013: secondary analysis of Knoop trial and the trial listed under Tummers 2012 (see below)***	**Self-instruction (n=85):** 16 weeks or more program of self-instruction booklet containing information about CFS and weekly assignments. **Wait list (n=86):** Wait list control for 6 to 12 months. **Duration of treatment:** 16 weeks or more **Duration of followup:** 6 to 12 months depending on length of treatment ***Tummers, 2010*** **Stepped care (n=84):** Self-instruction as described above, then up to 14 sessions of individual CBT over 6 months **Care as usual (n=85):** Wait list as described above, then up to 14 sessions of individual CBT over 6 months For both interventions there were 2 treatment protocols, depending on physical activity of the patient (measured by an ankle actometer). Passive patients worked to achieve a base level of activity spread over the day. active patients immediately began graded activity program. **Duration of treatment:** 6 months **Duration of followup:** End of treatment ***Tummers, 2013: secondary analysis of Knoop trial and the trial listed under Tummers 2012 (see below)***

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Knoop, 2008[33] Tummers, 2010[34] Tummers, 2013[35] Block randomized RCT Medium	**Stepped care vs. care as usual** Mean age (SD): 37.6 (10.0) vs. 38.5 (10.6) years % Female: 82 (69/84) vs. 76 (65/85) Race: NR Duration of illness: Median (range): 72 (12 to 420) vs. 96 (12 to 420) months Severity of symptoms: Mean (SD) Number of CDC symptoms: 7.1 (1.6) vs. 7.3 (1.6) Mean (SD) SIP-8 total score: 1,659 (648) vs. 1,515 (545) Mean (SD) CIS Fatigue Severity: 49.1 (5.2) vs. 49.9 (5.6) Comorbidities: NR	Number enrolled: 171 (85 self-instruction, 86 wait list) Number analyzed: 169 (84 self-instruction, 85 wait list)	**Stepped care vs. care as usual** Did not want to continue with CBT: 57% (48/84) vs. 22% (19/85) Excluded because of medical explanation of fatigue: 1 person in each arm of the Knoop study. Diagnoses were constriction of the coronary arteries and Hashimoto's thyroiditis.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Knoop, 2008[33] Tummers, 2010[34] Tummers, 2013[35] Block randomized RCT Medium	**Self-instruction vs. wait list** Overall Function: *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 65.9 (23.2) vs. 60.2 (23.7); p=0.011 *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* Second assessment: 1,079 (690) vs. 1,319 (619); p<0.001 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 38.9 (12.1) vs. 46.4 (8.7); p<0.001 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 27 (23/84; 95% CI, 18 to 37) vs. 7 (6/85; 95% CI, 2 to 13); OR 4.9 (95% CI 1.9 to 12.9); p=0.001 Outcomes related to associated symptoms: NR **Tummers, 2010** **Stepped care vs. care as usual** *Overall Function: Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Posttreatment: 71.6 (23.2) vs. 72.3 (24.3); difference -1.1 (95% CI -7.2 to 5.0); p=0.72 *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* Posttreatment: 826 (655) vs. 819 (653); difference 30.2 (95% CI -178 to 238); p=0.77 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Posttreatment: 35.1 (13.6) vs. 34.9 (13.8); difference 0.2 (95% CI -3.9 to 4.3); p=0.92 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 49 (41/84) vs. 48 (41/85); OR 1.00 (95% CI 0.53 to 1.89); p=1.00 Outcomes related to associated symptoms: Mean (SD) number of CBT sessions: 10.9 (4.4) vs. 14.5 (5.3); p<0.01 Median minutes in sessions (range): 420 (120-1,440) vs. 720 (120-2,040); p=0.01 **Tummers, 2013** Interaction tests for potential moderators from linear regression models (95% CI) Age (years): 0.15 (0.01 to 0.045); p<0.05 Depression: 0.15 (0.04 to 1.95); p=0.04 Self-efficacy: -0.06 (-1.18 to 0.56); p=0.48 Somatic attribution: 0.10 (-0.32 to 1.43); p=0.21 Avoidance of activity: 0.17 (0.03 to 1.78); p=0.04 Focus on bodily symptoms: -0.02 (-0.61 to 0.52); p=0.88 Interaction tests for potential moderators from logistic regression models (95% CI) Age (years): 1.06 (0.99 to 1.13); p=0.10 Depression: 1.40 (1.08 to 1.82); p=0.01 Self-efficacy: 0.81 (0.62 to 1.05); p=0.11 Somatic attribution: 1.13 (0.87 to 1.46); p=0.36 Avoidance of activity: 1.34 (1.03 to 1.74); p=0.03 Focus on bodily symptoms: 1.02 (0.87 to 1.20); p=0.80

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Knoop, 2008[33] Tummers, 2010[34] Tummers, 2013[35] Block randomized RCT Medium	**Self-instruction vs. wait list** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR **Tummers, 2010** **Stepped care vs. care as usual** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Li, 2015[36] Open label pilot RCT High	China 3 centers 2012 to 2014 Hospital clinics	CDC criteria (unspecified), requiring 4 or more of the following 8 symptoms: 1111) Post-exertion malaise lasting more than 24 hours; 2) Unrefreshing sleep; 3) Significant impairment of short-term memory or concentration; 4) Muscle pain; 5) Multi-joint pain without swelling and redness; 6) Headaches of a new type, pattern, or severity; 7) Tender cervical or axillary lymph nodes; 8) Frequent or recurrent sore throat. **Inclusion:** Meeting CDC criteria above and a patient in one of the 3 hospital clinics **Exclusion:** Current or past use of antidepressants for any psychiatric condition; concurrent DSM-IV Axis 1 disorder, vegetarians, nursing or pregnant, use of psychotropic medication in the past month, pervious or current engagement in CFS research, substance dependence or abuse, clinically significant or unstable mental illness.	**Dengzhanshengmai (n=134):** Below therapy SSRI therapy, plus one 1.08 g Dengzhanshengmai capsule containing 4 ingredients: erigeron breviscapus herba, ginseng herba, schisandra herba and ophiopogon japonicus herba once daily. **SSRI (n=134):** Selective serotonin reuptake inhibitor alone: Seroxat 10 to 30 mg per day, Zoloft 25 to 100 mg per day, or Citalopram 10 to 30 mg per day for the first 4 weeks, and then standard doses were given. **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Li, 2015[36] Open label pilot RCT High	**Dengzhanshengmai vs. SSRI** Mean age: 35.1 vs. 36.8 years % Female: 56 (75/134) vs. 63 (84/134) Race: NR, conducted in China Duration of illness, Mean: 15.7 vs. 14.5 months Severity of symptoms: *Multidimensional fatigue inventory subscales (4 to 20, higher scores indicating worse symptoms), mean:* General fatigue: 10.7 vs. 10.2 Physical fatigue: 9.6 vs. 9.4 Mental fatigue: 7.6 vs. 7.4 Reduced activity: 8.9 vs. 8.6 Reduced motivation: 7.3 vs. 7.2 Comorbidities: Current psychiatric comorbidities excluded, otherwise NR.	Number enrolled: 268 Number analyzed: 223 possibly, but unclear whether an intention to treat approach was used for efficacy analysis 45 patients (24 vs. 21) didn't complete the study due to drug unavailability in the pharmacy	Unclear Loss to followup and other reasons for dropout: 3.0% vs. 2.2%

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Li, 2015[36] Open label pilot RCT High	**Dengzhanshengmai vs. SSRI** Overall Function: NR Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Multidimensional fatigue inventory subscales (4 to 20, higher scores indicating worse symptoms)*, mean improvement: Improvement from week 2 to end of treatment General Fatigue: 1.3 (0.7) vs. 0.8 (0.6), p<0.01 Physical Fatigue: 1.0 (0.4) vs. 0.6 (0.3), p<0.01 Reduced Activity: 1.3 (0.6) vs. 1.0 (0.5), p<0.01 Improvement from week 8 to end of treatment Reduced Motivation: 2.4 (1.0) vs. 2.1 (0.8), p<0.01 No improvement Mental Fatigue: data not shown, p>0.05 Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Li, 2015[36] Open label pilot RCT High	**Dengzhanshengmai vs. SSRI** Adverse Events: 55 vs. 56; Hypertension: 8 vs. 2, p=0.05 All others NS between groups Withdrawals due to adverse events: 13 vs. 10 Serious adverse events: None	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Lopez, 2011[37] Pilot RCT High	United States Single center Study year(s) NR Setting not described	CDC (Fukuda, 1994) criteria **Inclusion:** 18 to 60 years of age, ≥8th grade education, fluent in English. **Exclusion:** Active or previous medical condition that would explain the presence of chronic fatigue, positive for Lyme disease, had an infection that was treated with antibiotics within 3 weeks of the study, had surgery requiring general anesthesia within the past month of the study, were on any immunomodulator, had a history of major psychiatric illness, were undergoing psychotherapy, had a history of substance or drug use within 2 years of the onset of CFS, or a history of major psychiatric illness.	**Group CBT (n=44)**: 12 weekly 2-hour group sessions of cognitive behavioral stress management consisting of 2 parts: 1) relaxation component and 2) didactic and discussion component; main technique used was cognitive restructuring targeting cognitive appraisals of ongoing stressors. **Control (n=25):** 1 half-day session of psychoeducation summarizing strategies from the 12 week intervention, given during the 6th week of the CBT intervention. **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment
Malaguarnera, 2007[38] RCT Medium	Italy Single center 2000 to 2001 University hospital clinic	CDC (Holmes,1988) and (Fukuda, 1994) criteria **Inclusion:** >70 years of age recruited from clinic or residing in a nursing home with ≥4 of the Holmes major criteria or ≥6 of the Fukuda minor criteria **Exclusion:** Infections, anemia, electrolyte imbalances, metabolic or endocrine disorders, or malignancies	**ALC (n=48):** 2g acetyl L-carnitine twice per day **Placebo (n=48):** Matching placebo Patients in both groups received a special diet for 2 weeks prior to randomization, and had clinical visits once a week during the study. A diet diary was given thrice per week **Duration of treatment:** 180 days **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Lopez, 2011[37] Pilot RCT High	Mean age (SD): 45.9 (9.3) years % Female: 88 (61/69) % White: 77 (53/69) % Latino: 17 (12/69) % Caribbean Islander: 1 (1/69) % Biracial: 1 (1/69) % Another ethnic group: 3 (2/69) % Working full-time: 13 (9/69) % Working part-time: 19 (13/69) % Unemployed: 16 (11/69) % Retired: 4 (3/69) % Student: 3 (2/69) % On disability: 45 (31/69) Duration of illness: NR Severity of symptoms: Number of CFS symptoms, Mean (SD): 12.14 (2.89) Comorbidities: NR	Number enrolled: 69 (44 group CBT, 25 control) Number analyzed: 58 (38 group CBT, 20 control)	**Overall:** 15.9% (11/69) **Group CBT vs. control:** 13.6% (6/44) vs. 20% (5/25)
Malaguarnera, 2007[38] RCT Medium	**ALC vs. placebo** Mean age: 76.2 vs. 78.4 % Female: 52 (25/48) vs. 50 (24/48) Race: NR Duration of illness: NR Severity of symptoms: Mean Physical fatigue: 13.4 vs. 13.1 Fatigue severity scale: 50.4 vs. 50.1 Comorbidities: % Sleep disorders: 90 vs. 88	Enrolled: 96 Analyzed: 96	Unclear

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Lopez, 2011[37] Pilot RCT High	**Group CBT vs. control** Overall Function: NR Quality of Life: *Mean (SD) QOLI scores* *Category score (range 1-4, lower scores indicate better health)* After treatment: 2.81 (1.15) vs. 3.26 (0.87); p=0.02 Raw score after treatment: 1.17 (1.83) vs. 0.82 (1.37); p=0.05 T score after treatment: 39.28 (14.17) vs. 36.42 (10.56); p=0.05 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) POMS-Fatigue subscale (0-28 scale, lower scores indicate better health)* After treatment: 17.85 (7.34) vs. 20.09 (6.99); p=0.06 Outcomes related to associated symptoms: *Mean (SD) Total CDC Symptom Severity scores* After treatment: 2.01 (0.33) vs. 2.08 (0.39); p=0.04 Depression: NR
Malaguarnera, 2007[38] RCT Medium	**ALC vs. placebo** Overall Function: Mean functional limitation PF score (SD): 86.9 (17.40 vs. 70.8 (19.1), mean difference: 16.1, 95% CI 8.70 to 23.50 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean physical fatigue (SD), Wessely and Powell Scale: 6.4 (2.2) vs. 12.6 (2.4), mean difference: -6.2, 95% CI -7.1 to 5.3 Mean mental fatigue (SD), Wessely and Powell Scale: 4.4 (1.6) vs. 7.2 (1.9), mean difference -2.8, 95% CI -3.5 to -2.1 Mean Fatigue severity scale (SD): 27.9 (9.7) vs. 48.9 (6.9), mean difference: -21.00, 95% CI -24.41 to 17.59 Likelihood of prolonged post-exercise fatigue: 48% vs. 96%, RR 0.50, 95% CI 0.37 to 0.68 Likelihood of activity reduction >50%: 56% vs. 75%, RR 0.75 (0.56 to 1.01) Outcomes related to associated symptoms: Painful throat: 77% vs. 77%, RR 1.00 (0.80 to 1.24) Painful lymph nodes: 16% vs. 12%, RR 1.33 (0.50 to 3.55) Muscle pain: 67% vs. 90%, RR 0.74 (0.60 to 0.93) Neuropsychiatric complaints: 52% vs. 71%, RR 0.74 (0.53 to 1.02) Spreading arthralgias: 80% vs. 83%, RR 0.95 (0.78 to 1.15) Headaches: 61% vs. 61%, RR 1.00 (0.72 to 1.38) Sleep disorders: 62% vs. 84%, RR 0.75 (0.58 to 0.97)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Lopez, 2011[37] Pilot RCT High	**Group CBT vs. control** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NIH
Malaguarnera, 2007[38] RCT Medium	**ALC vs. placebo** Adverse Events: None reported Withdrawals due to AE: None reported Serious Adverse Events: None reported	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
McKenzie, 1998[39] RCT McKenzie, 2000[40] Medium	United States Single center 1992 to 1996 Specialty clinic	CDC (Holmes, 1988) and CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-55 years, illness began over a period 6 weeks or less. **Exclusion:** Contraindication to systemic steroids, medical or psychiatric condition that required medication, severe active depression	**Hydrocortisone (n=35):** Oral hydrocortisone 20-30 mg every morning and 5 mg every afternoon (for total dose of 16 mg/m^2 daily) **Placebo (n=35):** Placebo **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
McKenzie, 1998[39] RCT McKenzie, 2000[40] Medium	**Hydrocortisone vs. placebo** Mean age: 37 vs. 38 years % Female: 83 (29/35) vs. 77 (27/35) % White: 97 (34/35) vs. 94 (33/35) Duration of illness: Mean: 47 vs. 60 months; p=0.07 Severity of symptoms: *Self-rating Wellness score (0 to 100, 0 most severe):* 38.8 vs. 37.6; p=0.50 Comorbidities: Depression: 1 vs. 3; p=0.36 Somatoform pain disorder: 20 vs. 20; p>0.99 Somatization disorder: 3 vs. 6; p=0.31 Major depressive episode: 1 vs. 1; p>0.99 Generalized anxiety disorder: 1 vs. 0; p=0.50 Phobic disorder: 2 vs. 3; p=0.68 Posttraumatic stress disorder: 1 vs. 2; p=0.62 Obsessive-compulsive disorder: 1 vs. 0; p=0.50	Number enrolled: 70 Number analyzed: 70 Number enrolled in bone mineral density assessment published in 2000: 30 Number analyzed: 23 (11 hydrocortisone and 12 placebo)	10% (7/70)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
McKenzie, 1998[39] RCT McKenzie, 2000[40] Medium	**Hydrocortisone vs. placebo** Overall Function: *Mean change (SD) in Activity Scale (10 point scale):* 0.3 (1.1) vs. 0.7 (1.4); p=0.32 Quality of Life: *Global Wellness scale (0-100, lower score most severe)* Improvement: 20/30 (67%) vs. 19/35 (54%); p=0.31 Mean change: 6.3 (11.7) vs. 1.7 (8.8); p=0.06 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean Change in POMS subscales* Fatigue (negative changes indicate better health): -3.6 (5.3) vs. -1.8 (4.5); p=0.21 Vigor (positive changes indicate better health): 1.2 (3.3) vs. 0.7 (3.3); p=0.45 Outcomes related to associated symptoms: *Beck Depression Inventory (0-63, higher most severe)* change: -2.1 (5.1) vs. -0.4 (4.1); p=0.17 Symptom Checklist-90-R general severity index (0-360, improvement is reflected by a negative change) mean change: -0.1 (0.2) vs. -0.1 (0.2); p=0.20

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
McKenzie, 1998[39] RCT McKenzie, 2000[40] Medium	**Hydrocortisone vs. placebo** Adverse Events: Increased appetite: 17 vs. 8; p=0.02 Weight gain: 19 vs. 8; p=0.006 Difficulty sleeping: 17 vs. 8; p=0.02 Suppression of adrenal glucocorticoid responsiveness: 12 vs. 0; p<0.001 Any reaction: 31/35 vs. 27/35; p=0.17 Withdrawals due to adverse event: 1 rash with placebo Serious Adverse Events: None Bone mineral density assessments after 12 weeks in a subset of patients: Hydrocortisone (n=11) Lateral spine mean percentage change: -2.0% (95% CI, -3.5 to -0.6), p=0.03 AP spine mean percentage change: -0.8% (95% CI, -1.5 to -0.1), p=0.06 Lateral spine median percentage change: -1.1% (range -5.7 to 1.30%) AP spine median percentage change: -0.6% (range -3.0 to 0.8%) Placebo (n=12) Lateral spine mean percentage change: +1.0% (95% CI, -1.0 to 3.0), p=0.34 AP spine mean percentage change: +0.2% (95% CI, -1.4 to 1.5), p=0.76 Lateral spine median percentage change: 1.5% (range -5.0 to 7.2) AP spine median percentage change: 1.0% (range -2.96 to 4.3) Hydrocortisone vs. placebo: Percentage change in lateral spine: p=0.03 Percentage change in AP: p=0.22	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Montoya, 2013[41] RCT Medium	United States Single center 2007 to 2008 Specialty clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Age18 and older; suspected viral onset of CFS; elevated antibody titer meeting additional criteria. **Exclusion:** low antibody titers on repeat testing, hypothyroidism, uncontrolled major depression, hepatitis C, conflicting medication	**Valganciclovir (n=20):** Oral valganciclovir 900 mg twice a day for 21 days, then 900 mg once daily for total of 6 months **Placebo (n=10):** Placebo **Duration of treatment:** 6 months **Duration of followup:** 6 months followup after treatment discontinuation (unblinding and outcomes measured at 9 months)
Montoya, 2018[42] RCT Medium	United States 4 centers 2013 to 2014 ME/CFS research sites	CDC (Fukuda, 1994) criteria **Inclusion:** Between 18 and 59 years of age, meeting CDC criteria for ME/CFS, complaining of alertness and/or concentration deficits, in otherwise good health based on medical history and screening evaluation, willing to abstain from nutritional, herbal, or caffeine-containing products during the trail. **Exclusion:** Major depression defined by Zung Depression Score >60, daily use of anxiety medications, daily concurrent use of more than 1 antidepressant, use of medications such as monoamine oxidase inhibitors, other CNS stimulants, and narcotic opioids.	**Methylphenidate hydrochloride (n=67):** 5 mg methylphenidate hydrochloride with a mitochondrial modulator (containing vitamins, minerals, amino acids, and antioxidants) twice daily for week 1 and 10 mg twice daily for weeks 2 through 12. Subjects were allowed to decrease dosage to 5 mg for tolerability issues **Placebo (n=68):** Matched placebo twice daily **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Montoya, 2013[41] RCT Medium	**Valganciclovir vs. placebo** Mean age: 50 vs. 48 years % Female: 75 (15/20) vs. 50 (5/10) Race: NR Duration of illness: Mean: 12.7 vs. 13.5 years; p=0.820 Severity of symptoms: *Multidimensional Fatigue Inventory total score (20-100, 100 is most severe)* : 81.25 vs. 76.00; p=0.447 Comorbidities: NR	Number enrolled: 30 Number analyzed: 30 (20 valganciclovir, 10 placebo)	1 from each group
Montoya, 2018[42] RCT Medium	**Methylphenidate hydrochloride vs. placebo** Mean age: 42.8 vs. 42.3 % Female: 78 (49/63) vs. 66 (43/65) % Race: 90 (57/63) vs. 91 (59/65) White, 3 (2/63) vs. 0 Asian, 5 (3/63) vs. 8 (5/65) African American, 5 (3/63) vs. 2 (1/65) other Duration of illness %: 52 (33/63) vs. 54 (35/65) <10 years, 48 (30/63) vs. 46 (30/65) ≥10 years Severity of symptoms: *Mean CIS total score (ranges from 20 to 140, higher scores indicate worse health):* 112.2 vs. 112.4 Comorbidities: NR	Number enrolled: 135 Number analyzed: 128	**Overall:** 27% (37/135) **Methylphenidate hydrochloride vs. placebo** 34% (23/67) vs. 21% (14/68)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Montoya, 2013[41] RCT Medium	**Valganciclovir vs. placebo** Overall Function: *Change in self-reported physical function (positive change indicates better health)* 1.02 vs. 0.46; p=0.217 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Change in MFI-20 (negative changes indicate better health)* Baseline to 9 months: -6.15 vs. -1.10; p=0.224 Change in FSS (negative changes indicate better health) -0.06 vs. 0.02; p=0.006 Outcomes related to associated symptoms: *CDC Symptom inventory:* NS
Montoya, 2018[42] RCT Medium	**Methylphenidate hydrochloride vs. placebo** Overall Function: NR Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean CIS total score (ranges from 20 to 140, higher scores indicate worse health):* 95.3 vs 98.6, mean change from baseline: -16.9 (±23.52) vs. -13.8 (±22.15), (95% CI, -11.1 to 4.0), p=0.359 Mean VAS fatigue change from baseline: -18.2 mm (±25.05) vs. -11.1 mm (±22.08), (95% CI, -11.5 to 2.3), p=0.189 Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Montoya, 2013[41] RCT Medium	**Valganciclovir vs. placebo** Adverse Events: 0 Withdrawals due to adverse event: 0 Serious Adverse Events: 1 patient with cancer in each group considered not related to intervention	Hoffman-La Roche
Montoya, 2018[42] RCT Medium	**Methylphenidate hydrochloride vs. placebo** Adverse Events: Headache: 5 vs. 5 Anxiety: 4 vs. 5 Fatigue: 9 vs. 4 Dizziness: 4 vs. 1 Nausea: 3 vs. 3 All differences p=NS Withdrawals due to adverse event: 8 vs. 3 Serious Adverse Events: Pyelonephritis (thought to be unrelated, resolved after 3 days of onset with appropriate treatment): 1 vs. 0	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Moss-Morris, 2005[43] RCT Medium	New Zealand Single center Study year(s) NR CFS private general practice	CDC (Fukuda, 1994) criteria **Inclusion:** Interested in a graded exercise study, ages 18 to 65 years and meeting Fukuda criteria. **Exclusion:** Patients unable to exercise for medical reasons including obesity or patients already performing regular exercise.	**Graded exercise (n=25):** Graded exercise therapy, increasing from 10 to 15 minutes 4 to 5 times a week to 30 minutes per day 5 days per week. Intensity was measured using heart rate and was increased through the duration of the intervention. Exercise participants also received standard medical care. **Usual care (n=24):** Standard medical care alone. **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment
Nijhof, 2012[44] Nijhof, 2013[45] Crawley, 2012[46] RCT Medium	The Netherlands Two center Study year(s) NR Pediatric hospital and treatment coordinating center	CDC (Fukuda, 1994) criteria **Inclusion:** Adolescents aged 12 to 18 years, access to a computer with internet connection, meeting CDC CFS criteria. **Exclusion:** Primary depression, anxiety disorder or suicidal risk assessed with computerized self-report questionnaires.	**FITNET (n=68):** 21 interactive CBT modules and support from a trained cognitive behavioral psychotherapist, solely through e-consults every other week or immediately in the case of emergencies. Parents followed a parallel program, with the same frequency of email contacts, and access to the module's content, psychoeducation, and e-consult application. Patients and parents had separate accounts and could not see each others' responses. The parents of patients younger than 15 were asked to coach the patients, but the parents of older patients were asked to encourage their children to take responsibility of their treatment. The aim of treatment was return to full-time education. FITNET participants agreed not to undergo any other treatments. **Usual care (n=67):** Individual or group-based rehabilitation programs, cognitive behavioral therapy face-to-face, or graded exercise programs, or both. Records were kept of the care that was given. This group was given the opportunity to use FITNET after 6 months. **Duration of treatment:** 6 months **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Moss-Morris, 2005[43] RCT Medium	**Graded exercise vs. usual care** Mean age (SD): 36.7 (11.8) vs. 45.5 (10.4) years; p=0.009 % Female: 60 (15/25) vs. 79 (19/24) Race: NR Duration of illness: Median (range): 2.7 (0.60 to 20) vs. 5.0 (0.5 to 45) years Severity of symptoms, Mean (SD): Physical fatigue: 14.55 (5.40) vs. 14.61 (4.86) Mental fatigue: 9.90 (3.74) vs. 10.74 (3.90) Total fatigue score: 24.45 (8.79) vs. 25.35 (8.05) SF-36 Physical functioning: 53.10 (18.39) vs. 45.65 (21.07) 22.4% of patients overall were unemployed and unable to work due to disability Comorbidities: Diagnosed cases NR	Number enrolled: 49 Number analyzed: 43 (22 exercise, 21 control)	**Overall:** 12% (6/49) **Graded exercise vs. usual care:** 12% (3/25) vs. 13% (3/24)
Nijhof, 2012[44] Nijhof, 2013[45] Crawley, 2012[46] RCT Medium	**FITNET vs. usual care** Mean age (SD): 15.9 (1.3) vs. 15.8 (1.3) % Female: 79 (54/68) vs. 85 (57/67) Race NR Mean duration of illness (range): 16.0 (6 to 84) vs. 19.0 (6 to 108) months Severity of symptoms: Fatigue severity: Mean CIS-20, range 8 to 56, (SD): 51.2 (4.4) vs. 51.6 (4.6) Comorbidities: NR	Number enrolled: 135 Number analyzed at 6 months: 131 (67 FITNET, 64 usual care) Number analyzed at 12 months: 127 (64 FITNET, 63 usual care)	**Overall:** 6 months: 3.0% (4/135) **FITNET vs. usual care:** 1.5% (1/68) vs. 4.5% (3/67) **Overall:** 12 months: 5.9% (8/135) **FITNET vs. usual care:** 5.9% (4/68) vs. 6.0% (4/67)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Moss-Morris, 2005[43] RCT Medium	**Graded exercise vs. usual care** Overall Function: *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* 12 weeks: 69.05 (21.94) vs. 55.00 (22.94); p=0.49 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Chalder fatigue scale total fatigue scores (0 to 42 scale, lower scores indicate better health)* 12 weeks: 13.91 (10.88) vs. 24.41 (9.69); p=0.02 *Mean (SD) Chalder fatigue scale physical fatigue subscale scores (0 to 32 scale, lower score indicates better health)* 12 weeks: 7.91 (7.06) vs. 14.27 (5.75); p=0.02 *Mean (SD) Chalder fatigue scale mental fatigue subscale scores (0 to 24 scale, lower score indicates better health)* 12 weeks: 6.00 (4.06) vs. 10.14 (4.27); p=0.03 Outcomes related to associated symptoms: *Self-rated CGI at 6 months* % Much or very much improved: 54 (12/22) vs. 24 (5/21); p=0.04; NNT=3.2
Nijhof, 2012[44] Nijhof, 2013[45] Crawley, 2012[46] RCT Medium	**FITNET vs. usual care** Overall Function: Physical functioning (CHQ-CF87 cutoff score of 85% or more) at 6 months: 78% (52/67) vs. 20% (13/64), RR 3.8 (95% CI, 2.3 to 6.3), NNT 1.8, p<0.0001 Quality of Life: NR Work/School Days: Full school attendance at 6 months (10% absence or less): 75% (50/67) vs. 16% (10/64), RR 4.8 (95% CI, 2.7 to 8.9), NNT 1.7, p<0.0001 Proportion full/part-time work: NR Fatigue: Fatigue severity at 6 months, CIS-20, cutoff score <40: 85% (57/67) vs. 27% (17/64), RR 3.2 (95%CI, 2.1 to 4.9), NNT 1.7, p<0.0001 Outcomes related to associated symptoms: Self-rated improvement at 6 months (answer "yes" to statement "I have completely recovered" or "I feel much better but still experience some symptoms"): 78% (52/67) vs. 27% (17/64), RR 2.9 (95% CI, 1.9 to 4.5), NNT 2.0, p<0.0001 Recover at 12 months (some patients in usual care group crossed over to FITNET group at the 6 month point): 64% (41/64) vs. 8% (5/63)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Moss-Morris, 2005[43] RCT Medium	**Graded exercise vs. usual care** Adverse Events: 2% (1/49) 10 of 25 patients refused to repeat fitness test as felt initial test harmful Withdrawals due to adverse event: 1 patient withdrew due to injured calf Serious Adverse Events: NR	University of Auckland Staff Grants
Nijhof, 2012[44] Nijhof, 2013[45] Crawley, 2012[46] RCT Medium	**FITNET vs. usual care** Adverse Events: None reported Withdrawals due to adverse event: None reported Serious Adverse Events: None reported	Netherlands Organisation for Health Research and Development

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	**Country Number of Centers Study Years Setting (primary care, specialty clinic or other)**	**Diagnostic criteria Inclusion/ Exclusion criteria**	**Interventions (n) Duration of treatment Duration of followup**
Öckerman, 2000[47] Crossover RCT High	Sweden Number of centers: NR Study year(s): NR Setting: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18 to 70 years, symptom score ≥49 for 13 symptoms and ≥5 for total well being. **Exclusion:** smokers, active dental treatment, electrical hypersensitivity, pollen allergy, use of drugs or antioxidants and other medial diseases and/or treatment.	**Pollen (n=22):** Antioxidant extract of pollen (Polbax), 7 tablets taken at one time per day. **Placebo (n=22)**: Placebo *Note:* All patients given pollen or placebo for 3 months followed by a 2-week wash-out period with no treatment followed by 3-month of pollen or placebo. **Duration of treatment:** 3 months **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Öckerman, 2000[47] Crossover RCT High	Mean age: 50 years % Female: 86 (19/22) Race: NR Duration of illness: NR	Number enrolled: 22 Number analyzed: 22	**Overall:** 4.5% (1/22)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Öckerman, 2000[47] Crossover RCT High	**Pollen vs. placebo, results both pre- and post-crossover with each participant represented in both groups** Overall Function: NR Quality of Life: *Mean total well-being score (0-10 Likert type scale, lower scores indicate better health; Likert scale 0=no problem to 10=extremely serious symptom)* 5.48 vs. 6.45; p=NR Change from baseline: -1.66 vs. -0.21; p<0.01 *Change in total well-being after treatment*; p value NR Worse: 9.5% (2/21) vs. 18% (4/22) No change: 29% (6/21) vs. 59% (13/22) Better: 62% (13/21) vs. 23% (5/22) Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean fatigue score (Likert scale 0=no problem to 10=extremely serious symptom)* 7.52 vs. 7.14; p=NR Change from baseline: -0.43 vs. -0.18; p<0.05 Outcomes related to associated symptoms: *Mean depression score (Likert scale 0=no problem to 10=extremely serious symptom)* 5.16 vs. 6.60; p=NR Change from baseline: -0.74 vs. -0.10; p<0.001

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Öckerman, 2000[47] Crossover RCT High	**Pollen vs. placebo** Adverse Events: Gastrointestinal - 1 or 2 patients Withdrawals due to AE: None Serious Adverse Events: None	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
O'Dowd, 2006[48] RCT Medium	United Kingdom Single Center 2000 to 2002 Health psychology department of a general hospital	CDC (Fukuda, 1994) criteria **Inclusion:** Presentation consistent with ME/CFS described by Fukuda; NHS patients; able to read and understand patient information leaflet. **Exclusion:** Concurrent severe mental illness (i.e. psychosis and allied conditions); planned or concurrent rehabilitation; inability to attend all treatment sessions; or ongoing physical investigation.	**Group CBT (n=52):** 8 2-hour group CBT sessions every other week over a 16 week period aimed at modifying thoughts and beliefs about symptoms and illness; and modifying behavioral responses to symptoms and illness, such as rest, sleep, and activity; with goal to increase adaptive coping strategies and reduce the distress and disability of CFS. Physical structured incremental group exercise sessions were included before a break midway through the session. **Group Support (n=50):** 8 2-hour group education and support sessions every other week over a 16 week period focusing on sharing of experiences and learning of basic relaxation skills. **Usual care (n=51):** Managed in primary care and received no other intervention. **Duration of treatment:** 16 weeks **Duration of followup:** 12 months

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
O'Dowd, 2006[48] RCT Medium	**Group CBT vs. group support vs. usual care** Mean age (SD): 41.6 (12.0) vs. 38.8 (11.8) vs. 42.9 (11.6) years % Female: 54 (28/52) vs. 76 (38/50) vs. 71 (36/51) Race: NR % Discontinued main occupation due to CFS: 77 (36/52) vs. 63 (29/50) vs. 70 (35/51) Duration of illness: % With symptoms for >60 months: 42 (21/50) vs. 50 (25/50) vs. 54 (27/50) % Diagnosed >12 months before study: 57% (28/49) vs. 45% (20/44) vs. 62% (29/47) Severity of symptoms: Mean number of symptoms (IQR): 7 (6.5-9) vs. 9 (8-10) vs. 9 (7-10) Comorbidities: NR	Number enrolled: 153 (52 CBT, 50 support, 51 usual care) Number analyzed: 153 (52 CBT, 50 support, 51 usual care)	**Group CBT vs. group support vs. usual care:** 25% (13/52) vs. 8% (4/50) vs. 14% (7/51)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
O'Dowd, 2006[48] RCT Medium	**Group CBT vs. group support vs. usual care** Overall Function: Group CBT vs. group support vs. usual care *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health); all p values are NS* 6 months: 33.4 (9.04) vs. 32.3 (9.30) vs. 34.5 (9.95) 12 months: 35.2 (8.15) vs. 32.5 (7.91) vs. 35.0 (9.93) *% Reporting SF-36 score in normal range (score was on or above the 5th centile for the distribution, estimated as the mean -1.645 × SD for the gender-specific age group)* 6 months: 40 (17/43) vs. 24 (11/45) vs. 44 (20/46) 12 months: 46 (18/39) vs. 26 (12/46) vs. 44 (19/44); OR 1.03 (95% CI 0.38 to 2.73) for support vs. CBT; OR 1.51 (95% CI 0.58 to 3.91) for usual care vs. CBT; OR 1.47 (0.56 to 3.81) for support vs. usual care *% Reporting ≥15% increase from baseline* 6 months: 24 (11/43) vs. 33 (15/45) vs. 28 (13/46) 12 months: 26 (10/39) vs. 26 (12/46) vs. 43 (19/44) 6 and/or 12 months: 32 (15/NR) vs. 40 (19/NR) vs. 49 (23/NR); OR 1.29 (95% CI 0.58 to 2.86) for group support vs. CBT; OR 1.68 (95% CI 0.76 to 3.69) for usual care vs. CBT; OR 1.30 (95% CI 0.61 to 2.76) for usual care vs. group support *Mean incremental shuttle walking test; shuttles walked (number of complete 10 meter shuttles)* 6 months: 28.5 vs. 25.6 vs. 23.6 12 months: 28.9 vs. 24.1 vs. 24.2 *Difference between groups from baseline to 12 months* CBT vs. group support: 1.16 (95% CI 0.94 to 1.43); CBT vs. usual care: 1.20 (95% CI 0.99 to 1.45) Group support vs. usual care: 1.04 (95% CI 0.86 to 1.24) Mean incremental shuttle walking test; normal walking speed (number of shuttles per level per minute) 6 months: 12.1 vs. 8.76 vs. 9.39 12 months: 12.2 vs. 10.0 vs. 9.46 5 and/or 12 months: 11.58 (0.71) vs. 9.82 (0.53) vs.8.76 (0.47); p=0.006 Continued below

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
O'Dowd, 2006[48] RCT Continued	Difference between groups from baseline to 12 months CBT vs. group support: 1.77 (95% CI 0.025 to 3.51); p=0.0055 CBT vs. usual care: 2.83 (95% CI 1.12 to 5.53); p=0.0055 Group support vs. usual care: 1.06 (-0.37 to 2.49); p=0.15 Quality of Life: Mean (SD) health related quality of life utility scores (higher scores indicate better health); all p values are NS 6 months: 0.43 (0.28) vs. 0.34 (0.32) vs. 0.41 (0.25) 12 months: 0.45 (0.34) vs. 0.34 (0.35) vs. 0.46 (0.30) Difference between groups from baseline at 12 months CBT vs. group support: 0.023 (95% CI -0.065 to 0.11); CBT vs. usual care: 0.029 (95% CI -0.052 to 0.11) Group support vs. usual care: 0.006 (95% CI -0.082 to 0.095) Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean (SD) Chalder fatigue scale (0 to 33 scale, lower scores indicate better health) 6 months: 17.9 (8.41) vs. 21.4 (7.55) vs. 21.8 (6.90); p=0.19 12 months: 17.4 (7.32) vs. 21.4 (7.79) vs. 18.8 (7.19); p=0.19 Difference between groups from baseline at 6 and 12 months pooled CBT vs. group support: -3.16 (95% CI -5.59 to -0.74); p=0.011 CBT vs. usual care: -2.61 (95% CI -4.92 to -0.30); p=0.027* Support vs. usual care: 0.55 (95% CI -1.56 to 2.66); p=NR *Note: this number is -2.16 in the text and -2.61 in the table Outcomes related to associated symptoms: HADS-Depression: 6 months: 6.84 (3.46) vs. 8.20 (3.81) vs. 7.78 (3.76) 12 months: 6.82 (3.80) vs. 7.74 (4.02) vs. 7.44 (4.42) Mean difference, adjusted for baseline: -0.13 (-1.13 to 0.87) vs. -0.56 (-1.69 to 0.58) vs. -0.43 (-1.56 to 0.70), p=0.52

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
O'Dowd, 2006[48] RCT Medium	**Group CBT vs. group support vs. usual care** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	National Health Service Health Technology Assessment Program

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Oka, 2014[49] RCT Medium	Japan Single center Study year(s) NR Hospital department of psychosomatic medicine	CDC (Fukuda, 1994) criteria **Inclusion:** Outpatients with CFS; fatigue did not improve sufficiently with ordinary treatment including pharmacotherapy, psychotherapy, and GET for at least 6 months; aged 20 to 70 years; level of fatigue serious enough to cause an absence from school or workplace at least several days a month but not serious enough to require assistance with the activities of daily living; able to fill out questionnaire without assistance; able to sit for at least 30 minutes; able to visit hospital regularly every 2 to 3 weeks. **Exclusion:** Fatigue due to a physical disease, had previously practiced yoga, or having idiopathic chronic fatigue.	**Yoga (n=15):** 1-on-1 sitting isometric yoga with an instructor for 20 minutes, once every 2 to 3 weeks, along with pharmacotherapy. Yoga program was designed to avoid exacerbation of symptoms and post-exertion malaise, while providing some reconditioning exercise therapy. It included abdominal breathing practice. Participants were asked to practice the program on non-class days if they could, and were given a videodisc and a booklet. All patients received at least 4 sessions with the instructor, mean=5.6. **Control (n=15):** Conventional pharmacotherapy alone, and wait-list for yoga. **Duration of treatment:** Approximately 2 months (9.2±2.5 weeks) **Duration of followup:** 2 months after end of treatment
Ostojic, 2016[50] Crossover RCT High	Serbia Single center 2014 to 2015 Setting NR	CDC (Fukuda, 1994) criteria **Inclusion:** Fulfilling CDC CFS criteria and aged >18 years. **Exclusion:** Psychiatric comorbidity, use of any dietary supplement within 4 weeks prior to study commencing, unwillingness to return for followup, or pregnancy.	**Guanidinoacetic acid (n=NR):** 2.4 grams daily orally **Placebo (n=NR):** Cellulose daily orally Patients in both groups were asked not to use any dietary supplements during the study. **Duration of treatment:** 3 months, then washout before crossover (NR here) **Duration of followup:** End of first treatment period; 3 months after randomization

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Oka, 2014[49] RCT Medium	**Yoga vs. control** Mean age: 38.0 vs. 39.1 % Female: 80 (12/15) vs. 80 (12/15) Race NR, conducted in Japan Duration of illness: NR Severity of symptoms: Chalder's fatigue scale: Mean physical fatigue: 16.4 vs. 16.5 Mean mental fatigue: 9.5 vs. 9.7 Mean total score: 25.9 vs. 26.1 Comorbidities: at least 2 patients in yoga group had fibromyalgia, NR overall	Number enrolled: 30 Number analyzed: 30	None
Ostojic, 2016[50] Crossover RCT High	**Overall:** Mean age: 39.3 years % Female: 100 (21/21) Race NR, conducted in Serbia Duration of illness: NR Severity of symptoms: Mean MFI Physical fatigue: 11.2 Comorbidities: NR	Enrolled: 21 Analyzed: 14	7 participants lost during the intervention period due to reasons not connected to the study

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Oka, 2014[49] RCT Medium	**Yoga vs. control** Overall Function: SF-8 Physical functioning: Only reported as pre-post change in yoga group: 39.6 vs. 42.5, p=NS Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Chalder's fatigue scale: Mean physical fatigue (SD): 12.3 (3.8) vs. 16.1 (3.6), p=0.009; mean difference 3.80, 95% CI 1.03 to 6.57 Mean mental fatigue (SD): 6.9 (4.4) vs. 9.7 (3.1), p=0.007; mean difference 2.80, 95% CI -2.83 to 8.43 Mean total score (SD): 19.2 (7.5) vs. 25.8 (5.9), p=0.003; mean difference 6.6, 95% CI 1.55 to 11.65 Outcomes related to associated symptoms: NR
Ostojic, 2016[50] Crossover RCT High	**Guanininoacetic acid vs. placebo** Overall Function: NR Quality of Life: Health-related quality of life, mean score (SD), p is for ANOVA treatment vs. time interaction: Physical common score: 55.2 (2.8) vs. 52.8 (4.2), mean difference 2.4, p=0.04 Mental common score: 51.1 (5.5) vs. 45.8 (6.5), mean difference 5.3, p<0.005 Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean *MFI, higher scores indicate worse fatigue* (SD), p is for ANOVA treatment vs. time interaction: General fatigue: 11.6 (1.3) vs. 11.8 (1.5) , mean difference -0.2, p=0.44 Physical fatigue: 11.7 (1.2) vs. 11.6 (1.4), mean difference 0.1, p=0.99 Reduced activity: 13.9 (1.2) vs. 11.7 (1.8), mean difference -2.2, p<0.005 Reduced motivation: 13.1 (1.9) 15.0 (1.8), mean difference -1.9, p=0.03 Mental fatigue: 12.2 (1.7) vs. 14.0 (0.9), mean difference -1.8, p=0.01 Outcomes related to associated symptoms: Musculoskeletal soreness at rest, mean score (SD), p is for ANOVA treatment vs. time interaction: 1.2 (1.0) vs. 1.4 (1.3), p=0.31

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Oka, 2014[49] RCT Medium	**Yoga vs. control** Adverse Events: Dizziness: 1 vs. 0 Tiredness: 2 vs. 0 Lightheadedness: 2 vs. 0 Withdrawals due to AE: None reported Serious Adverse Events: None reported	Health and Labour Sciences Research Grant for integrative medicine
Ostojic, 2016[50] Crossover RCT High	**Guanininoacetic acid vs. placebo** Adverse Events: None reported Withdrawals due to AE: None reported Serious Adverse Events: None reported	Serbian Ministry of Science, National Strength and Conditioning Association International, Faculty of Sport and Physical Education

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Peterson, 1990[51] RCT Medium	United States Single center 1988 Specialty clinic	CDC (Holmes, 1988) criteria **Inclusion:** Diagnosis of CFS **Exclusion:** No evidence of underlying psychopathology as an explanation of chronic fatigue found during interview by psychiatric co-investigator	**IgG (n=15):** IV IgG (1 g/kg) every 30 days for 6 months (6 infusions) **Placebo (n=15):** IV placebo (1% albumen solution) every 30 days for 6 months (6 infusions) **Duration of treatment:** 6 months **Duration of followup:** End of treatment
Pinxsterhuis, 2017[52] RCT Medium	Norway 6 centers 2011 to 2012 Hospitals, specific settings NR	CDC (Fukuda, 1994) and Canadian (Carruthers, 2003) criteria **Inclusion:** Ages ≥18, CFs diagnosis by medical specialist, meeting CDC and Canadian diagnostic criteria, physically able to attend the program. **Exclusion:** Pregnancy.	**Self-management (n=73):** 8 2.5 hour group meetings held every other week conducted by a peer counselor (experienced individual with chronic fatigue syndrome) and occupational therapist, after participating in a 3 day program. Participants were taught how to take greater initiative in coping with their illness and for dealing with healthcare professionals and significant others, through educational presentations, the exchange of experiences among participants, modeling of self-management skills, guided mastery practice, and informative feedback. There was one meeting for relatives consisting of a presentation about chronic fatigue, the content of the self-management program, and an exchange of experiences among relatives. **Control (n=73):** Treatment as usual, not standardized in Norway. **Duration of treatment:** 16 weeks **Duration of followup:** 1 year after randomization

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Peterson, 1990[51] RCT Medium	**IgG vs. placebo** Mean age: 45 vs. 36 % Female: 73 (22/30); NR by group Race: NR Duration of illness: Mean: 3.8 years; NR by group Severity of symptoms: Number of CFS symptoms 8.8; NR by group Comorbidities: NR	Number enrolled: 30 Number analyzed: 28	7% (2/30)
Pinxsterhuis, 2017[52] RCT Medium	**Self-management vs. control** Mean age: 44.0 vs. 43.8 % Female: 94.4 (67/71) vs. 81.1 (54/66), p=0.022 Race: NR Duration of illness: Median time diagnosed (range): 3 (1 to 21) vs. 3 (0 to 17) years Severity of symptoms: M*ean (SD) SF-36 physical functioning (0 to 100 scale with lower score indicating greater disability):* 45.8 (18.2) vs. 46.2 (20.2) *Mean (SD) Fatigue Severity Scale Score (9 to 63 scale with higher scores indicating greater disability):* 56.6 (5.6) vs. 58.0 (4.5) Comorbidities: NR	Number enrolled: 146 Number analyzed at 6 months: 125 (63 self-management, 62 usual care) Number analyzed at 12 months: 118 (59 self-management, 59 usual care)	**Self-management vs. control** 13.9% overall Did not receive treatment: 2/73 vs. 7/73 Did not complete 6 month followup: 10/73 vs. 11/73 Did not complete 12 month followup: 14/73 vs. 14/73

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Peterson, 1990[51] RCT Medium	**IgG vs. placebo** Overall Function: *Medical Outcome Study Short Form (0-100 scale, higher scores indicate better health)* Mean (SD) Physical: 56.0 (23.2) vs. 51.8 (22.2); p=NS Social: 5.2 (5.5) vs. 9.4 (7.9); p<0.05 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR
Pinxsterhuis, 2017[52] RCT Medium	**Self-management vs. control** Overall Function: *Mean (SD) SF-36 physical functioning (0 to 100 scale with lower score indicating greater disability):* 6 months: 47.5 (21.2) vs. 50.5 (23.7); p=NS; Mean change from baseline (95% CI): 0.6 (-2.9, 4.0) vs. 4.3 (-0.4, 8.9) 12 months: 48.9 (17.7) vs. 46.3 (22.3); p=NS; Mean change from baseline (95% CI): 0.8 (-4.2, 5.7) vs. -0.3 (-5.4, 4.9) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Fatigue Severity Scale Score (9 to 63 scale with higher scores indicating greater disability):* 6 months: 56.0 (6.8) vs. 55.5 (8.2); p=0.039; Mean change from baseline (95% CI): -0.2 (-1.7, 1.3) vs. -2.7 (-4.7, -0.7) 12 months: 56.4 (6.9) vs. 57.1 (6.7); p=NS; Mean change from baseline (95% CI): 0.4 (-1.4, 2.2) vs. -1.4 (-3.0, 0.1) Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Peterson, 1990[51] RCT Medium	**IgG vs. placebo** Adverse Events: 20% overall Headaches: 93% vs. 60%; p=0.03 Withdrawals due to adverse event: 2 (1 in each group) Serious Adverse Events: 2 IgG and 3 placebo	Baxter Healthcare Corporation.
Pinxsterhuis, 2017[52] RCT Medium	**Self-management vs. control** Adverse Events: NR Withdrawals due to adverse event: 1 vs. 1 lost due to ill health after starting allocated treatment 1 vs. 1 lost due to ill-health Serious Adverse Events: NR	The Norwegian Foundation for Health and Rehabilitation and The National Advisory Unit for CFS/ME

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Powell, 2001[53] Bentall, 2002[54] Powell, 2004[55] RCT Medium	United Kingdom Single center Study year(s) NR Outpatient clinic	Oxford (Sharpe, 1991) criteria **Inclusion:** Referred to a chronic fatigue or infectious diseases clinic; aged 15 to 55 years; CFS diagnosis using Oxford criteria confirmed; scoring <25 on the physical functioning subscale of the SF-36. **Exclusion:** Undergoing further investigations or taking other treatments, including antidepressants (unless the same dose had been taken for ≥3 months without improvement); psychotic illness; somatization disorder; eating disorder; history of substance misuse; confinement to a wheelchair or bed.	**Graded Exercise (Minimum) (n=37):** Medical assessment followed by 2 face-to-face evidence-based explanations of symptoms that encouraged graded activity. A graded exercise program was designed in collaboration with each patient and tailored to current functional abilities. The role of psychosocial factors was discussed. **Graded Exercise (Telephone) (n=39):** Medical assessment followed by 2 face-to-face evidence-based explanations of symptoms that encouraged graded activity. A graded exercise program was designed in collaboration with each patient and tailored to current functional abilities. The role of psychosocial factors was discussed. These were followed up by 7 planned 30-minute telephone contacts over 3 months. **Graded Exercise (Maximum) (n=38):** Medical assessment followed by 2 face-to-face evidence-based explanations of symptoms that encouraged graded activity. A graded exercise program was designed in collaboration with each patient and tailored to current functional abilities. The role of psychosocial factors was discussed. These were followed up by 7 1-hour face-to-face treatment sessions over 3 months. **Standard medical care (Control) (n=34):** Standard medical care: a medical assessment, advice, and a booklet that encouraged graded activity and positive thinking, but gave no explanation for the symptoms. These patients were offered the intervention at 1 year, and 30 completed the intervention. Duration of treatment: Up to 3 months **Duration of followup:** 1 year (Powell 2001), 2 years for treatment groups, but one year after treatment for original control group (Powell 2004)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Powell, 2001[53] Bentall, 2002[54] Powell, 2004[55] RCT Medium	**Minimum vs. telephone vs. maximum vs. control** Mean age: 34 vs. 32 vs. 33 vs. 34 % Female: 76% (28/37) vs. 85% (33/39) vs. 82% (31/38) vs. 71% (24/34) Race: NR Mean duration of illness: 51.2 vs. 51.5 vs. 55.0 vs 48.6 months Severity of symptoms: Mean SF-36 physical functioning (95% CI): 16.0 (15.0 to 17.0) vs. 15.8 (14.6 to 17.0) vs. 16.0 (14.8 to 17.0) vs. 16.3 (12.2 to 17.5) Fatigue scale (range 0 to 11, with higher scores indicating worse fatigue), mean scores (95% CI): 19.4 (10.0 to 10.7) vs. 9.9 99.2 to 10.6) vs. 10.2 (9.9 to 10.6) vs. 10.6 (10.4 to 10.9) Comorbidities: NR	Enrolled: 148 Analyzed: 148 Powell 2004 analyzed: 144	Powell 2001 14% dropped out (21/148), 19 were in intervention groups 2 participants did not complete the questionnaire at 3 months and 1 did not complete the questionnaire at 1 year, but last obtained values were carried forward Powell 2004 5 more lost at 2 years: 2 lost to followup, 2 developed other medical conditions, 1 died by suicide.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Powell, 2001[53] Bentall, 2002[54] Powell, 2004[55] RCT Medium	**Minimum vs. telephone vs. maximum vs. control** Overall Function: *Mean (95% CI) SF-36 physical functioning (score range 10 to 30, where 30 is best physical functioning):* 3 months: 22.8 (21.1 to 24.4) vs. 22.3 (20.6 to 24.0) vs. 22.8 (21.2 to 24.3) vs. 16.3 (14.9 to 17.7) 6 months: 24.0 (22.4 to 25.6) vs. 23.0 (21.2 to 24.7) vs. 24.1 (22.6 to 25.6) vs. 17.2 (15.6 to 18.7) 1 year: 24.1 (23.3 to 26.8) vs. 24.3 (22.5 to 26.0) vs. 24.9 (23.4 to 26.4) vs. 16.9 (15.4 to 18.4), p<0.001 (initial scores and depression scores used as covariates) 2 year (Powell 2004) Mean score, (SD): 24.11 (5.94) vs. 23.64 (6.39) vs. 25.45 (4.72) vs. 22.47 (7.02) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (95% CI) Fatigue scale (score range 0 to 11 with higher scores indicating worse fatigue):* 3 months: 5.0 (3.4 to 6.6) vs. 3.7 (2.3 to 5.2) vs. 4.3 (2.9 to 5.8) vs. 10.4 (10.1 to 10.8) 6 months: 3.8 (2.5 to 5.2) vs. 4.0 (2.5 to 5.5) vs. 3.4 (2.2 to 4.6) vs. 9.9 (9.1 to 10.8) 1 year: 3.2 (1.8 to 4.7) vs. 3.5 (2.1 to 4.9) vs. 3.1 (1.8 to 4.4) vs. 10.1 (9.3 to 10.8), p<0.001 (initial scores and depression scores used as covariates) 2 year (Powell 2004) Mean score, (SD): 4.46 (4.78) vs. 3.59 (4.69) vs. 2.84 (3.67) vs. 6.07 (4.60) Outcomes related to associated symptoms: Depression: *Mean hospital anxiety and depression scale depression score (95% CI) (score range to 21 with higher scores indicating worse depression)* 3 months: 6.1 (4.7 to 7.4) vs. 5.9 (4.5 to 7.3) vs. 5.8 (4.8 to 6.9) vs. 11.2 (9.6 to 12.9) 6 months: 5.4 (3.9 to 6.9) vs. 5.6 (4.3 to 6.9) vs. 5.0 (3.8 to 6.2) vs. 11.0 (9.2 to 12.9) 12 months: 4.2 (3.0 to 5.5) vs. 4.6 (3.2 to 6.0) vs. 4.2 (2.9 to 5.5) vs. 10.1 (8.4 to 11.7), p<0.001 (initial scores used as a covariate) 2 year (Powell 2004) Mean score, (SD): 5.11 (5.12) vs. 4.77 (4.67) vs. 4.08 (4.33) vs. 8.37 (5.75) Anxiety: *Mean hospital anxiety and depression scale anxiety score (95% CI) (score range to 21 with higher scores indicating worse anxiety)* 3 months: 9.2 (7.3 to 10.7) vs.7.7 (6.1 to 9.2) vs. 8.7 (7.2 to 10.1) vs. 11.4 (9.8 to 13.1) 6 months: 8.7 (7.1 to 10.2) vs. 7.5 (6.0 to 9.0) vs. 7.7 (6.2 to 9.2) vs. 10.6 (8.8 to 12.4) 12 months: 7.1 (5.8 to 8.5) vs. 6.5 (5.1 to 7.9) vs. 7.7 (6.1 to 9.3), p<0.01 (initial scores and depression scores used as covariates) 2 year (Powell 2004) Mean score, (SD): 7.65 (4.78) vs. 7.03 (5.07) vs. 7.13 (4.47) vs. 9.17 (4.80) *Sleep problem questionnaire: Mean score (95% CI) (score range 0 to 20 with higher scores indicating worse sleep problems):* 3 months: 9.0 (7.4 to 10.5) vs. 10.1 (8.2 to 11.9) vs. 8.7 (7.2 to10.3) vs. 11.6 (9.8 to 13.5) 6 months: 7.4 (5.7 to 9.1) vs. 9.1 (7.2 to 11.0) vs. 8.2 (6.6 to 9.9) vs. 12.1 (10.1 to 14.1) 12 months: 6.7 (5.0 to 8.4) vs. 8.6 (6.8 to 10.3) vs. 7.1 (5.6 to 10.3) vs. 11.5 (9.7 to 13.4), p<0.001 (initial scores and depression scores used as covariates) 2 year (Powell 2004) Mean score, (SD): 7.62 (5.30) vs. 8.15 (5.59) vs. 7.92 (5.50) vs. 10.07 (6.06)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Powell, 2001[53] Bentall, 2002[54] Powell, 2004[55] RCT Medium	**Minimum vs. telephone vs. maximum vs. control** Adverse Events: NR Withdrawals due to AE: 1 dropped out due to dissatisfaction with treatment Serious Adverse Events: NR	Linbury Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Rimes, 2013[56] Pilot RCT High	United Kingdom Single center Study year(s) NR, recruitment process was conducted on 2 separate occasions, 1 year apart Tertiary care facility	CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) criteria **Inclusion:** Adults with CFS who had completed CBT in the previous year at a National Health Service CFS Unit and who had been diagnosed as still having CFS according to CDC or Oxford criteria. **Exclusion:** Therapist determined interpersonal difficulties which would make group participation unsuitable for patient or other participants, current major depression, not interested, not able to attend regularly.	**MBCT (n=18):** Introductory session of mindfulness-based cognitive therapy, followed by 8 weekly sessions, lasting 2.25 hours. Conducted in 2 groups, the first had 11 participants and the second had 7 participants. Mindfulness meditation practices also undertaken at home using compact discs. Each class included group discussion including problem solving and awareness. Participants were also offered a 2 month followup mindfulness course. **Control (n=19):** Wait list group was informed that their MBCT intervention would begin in 4 months. **Duration of treatment:** 8 weeks **Duration of followup:** 2 months after end of 8 week treatment
Roerink, 2017[57] RCT Low	The Netherlands Single center 2014 to 2016 Specialty clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Women aged 18 to 59 years with CFS and severe fatigue leading to functional impairment (CIS-fatigue ≥40 and SIP ≥700). **Exclusion:** Use of medication (except oral contraceptives and acetaminophen), use of psychotropic medication in the past month, psychiatric comorbidity (major depression, psychosis, eating disorders, anxiety disorders, bipolar disease, and posttraumatic stress disorder), evident somatic comorbidity that explains fatigue, fatigue lasting >10 years without recent progression, substance abuse within the past 3 months, current engagement in legal procedure with respect to disability claims	**Anakinra (n=25):** 100 mg subcutaneously daily for 28 days **Placebo (n=25):** subcutaneously daily for 28 days **Duration of treatment:** 4 weeks **Duration of followup:** 20 weeks after treatment ended

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Rimes, 2013[56] Pilot RCT High	**MBCT vs. control** Mean age: 41.4 vs. 45.2 % Female: 25 (4/16) vs. 11 (2/19) % White UK: 94 (15/16) vs. 63 (12/19) % Other White: 6 (1/16) vs. 26 (5/19) % Black African: 0 vs. 5 (1/19) % Other (not specified): 0 vs. 5 (1/19) Duration of illness: Mean (SD): 8.5 (4.4) vs. 6.1 (4.8) years Severity of symptoms: NR Comorbidities: NR	Randomized: 37 Analyzed: 35 (16 MBCT, 19 control)	**MBCT vs. control** 5% (2/37) overall Did not receive treatment: 1/18 vs. 0/19 Discontinued treatment after 1 session: 1/18 vs. 0/19
Roerink, 2017[57] RCT Low	**Anakinra vs. placebo** Mean age: 30 vs. 32 100% female Race: NR Duration of illness: Median (range): 44 (7 to 109) vs. 38 (9 to 108) months Severity of symptoms: Mean fatigue severity *CIS-fatigue score (ranges from 8 to 56, higher scores indicate worse fatigue)* : 52 vs. 51 Mean functional impairment *SIP (ranges from 0 to 5799, higher scores indicate worse health)* : 1647 vs. 1706 Comorbidities: NR	Number enrolled: 50 Number analyzed: 50	0% (0/50)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Rimes, 2013[56] Pilot RCT High	**MBCT vs. control** Overall Function: 2 months Mean Physical Functioning PF-10, higher scores indicate better functioning (SD): 65.6 (26.3) vs. 55.9 (23.3) 2 months Mean Work and Social Adjustment Scale, 0 to 40 scale with lower scores indicating better health (SD): 20.0 (10.4) vs. 25.8 (6.7) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: 2 months Mean Modified Chalder Fatigue Scale, 0 to 33 with lower scores indicating better health (SD): 21.3 (6.2) vs. 25.0 (6.1) Outcomes related to associated symptoms: NR HADS-Depression, mean (SD): 2 month follow up: 5.6 (2.9) vs. 7.7 (4.6); p=0.153
Roerink, 2017[57] RCT Low	**Anakinra vs. placebo** Overall Function: *SF-36 physical functioning (0 to 100, higher scores indicate better functioning)* : 4 weeks: 58.2 vs. 61.2, p=0.53 24 weeks: 60.8 vs. 64.8, p=0.47 *SIP (ranges from 0 to 5799, higher scores indicate worse health)* : 4 weeks: 1472.2 vs. 1353.7, p=0.47 24 weeks: 1351.5 vs. 1260.4, p=0.62 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *CIS-fatigue score (ranges from 8 to 56, higher scores indicate worse fatigue):* 4 weeks: 46.7 vs. 45.1, p=0.59 24 weeks:45.3 vs. 44.0, p=0.69 Outcomes related to associated symptoms: Pain: 4 weeks: 7.4 (6.5 to 8.3) vs. 6.3 (5.4 to 7.2), p=0.104 24 weeks: 6.9 (5.9 to 7.9) vs. 6.6 (5.6 to 7.6), p=0.63 Symptom Checklist-90: 4 weeks: 144.4 (136.6 to 152.2) vs. 139.9 (132.1 to 147.7), p=0.42 24 weeks: 143.5 (135.3 to 151.7) vs. 140.5 (132.3 to 148.7), p=0.63

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Rimes, 2013[56] Pilot RCT High	**MBCT vs. control** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: None reported	UK Department of Health via National Health Research Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry
Roerink, 2017[57] RCT Low	**Anakinra vs. placebo** Adverse Events: 24 vs. 14 Injection site reaction: 17 vs. 1 Infection: 6 vs. 4 Withdrawals due to adverse event: 1 vs. 0 1 from Anakinra group discontinued treatment due to a skin infection Serious Adverse Events: None	Interleukin Foundation and an independent anonymous donor

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Rowe, 1997[58] RCT Medium	Australia Single center Study year(s) NR Children's hospital clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Adolescents 11 to 18 years old meeting Fukuda criteria **Exclusion:** Receiving steroid medication, non-steroidal anti-inflammatory drugs, immunomodulatory agents, or had received IV immunoglobulin at any point; psychological or family issues salient in presenting symptomatology; improving at such a rate that they would be functioning by the end of the trail	**Intragram (n=36):** 3 once monthly IV infusions of 1 gm/kg (maximum 1 liter of 6 gm/100 mL) gammaglobulin in 10% weight by volume maltose solution Rowe 1999 also included 19 participants who all received study drug in pilot studies. **Placebo (n=35):** 3 once monthly IV infusions of 10% weight by volume maltose with 1% albumin solution, volume administered was calculated by patient weight For both groups, frusemide (40 mg orally) was given with infusions greater than 500 mL. Both groups received information about available services such as a visiting teacher service, distance education, social security support, and support groups. **Duration of treatment:** 3 months **Duration of followup:** 6 months after final infusion
See, 1996[59] Double-blind crossover study High	United States Single center Study year(s) NR	CDC (Holmes, 1988) criteria **Inclusion:** Referral by an internist or school of medicine faculty and fulfilling CDC diagnostic criteria **Exclusion:** Received immunologic therapy in the past year, diagnosis of a chronic infection, immunologic disorder, multiple sclerosis, thyroid disease, IgG deficiency or primary psychiatric illness	**Alfa-2a Interferon (n=15):** 3 million units subcutaneously 3 times per week after drinking 16 ounces of water. 650mg of acetaminophen was taken 2 hours following the dose. **Placebo (n=15):** 0.9% sodium chloride solution administered on the same schedule in the same way, with the same dose of acetaminophen. **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment (post-crossover data NR here)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Rowe, 1997[58] RCT Medium	**Intragram vs. placebo** Mean age: 15.3 vs. 15.6 years % Female: 58 (21/36) vs. 80 (28/35) Race: NR Mean duration of illness: 19.5 vs. 16.9 months Severity of symptoms: *Percentage functional score, calculated based on attendance at school or work, proportion of school or work attempted, proportion of normal physical activities attempted and proportion of normal social activities attempted, checked against records from parents and schools when possible*: 23.9 vs. 25.9 Comorbidities: NR	Number enrolled: 71 Number analyzed: 70	1% (1/71) for 6-month outcomes 1 placebo group
See, 1996[59] Double-blind crossover study High	Overall Mean age: 37.2 years % Female: 80 (24/30) Race: NR Mean duration of illness: 4.6 years (range 1 to 12) Severity of symptoms: NR Comorbidities: NR	Number enrolled: 30 Number analyzed: 26	None

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Rowe, 1997[58] RCT Medium	**Intragram vs. placebo** Overall Function: Returned to full function at 6 months, %: 25 (9/36) vs. 11 (4/34), p<0.04 Not improved (<25% mean functional improvement from baseline) at 3 months, %: 47.2 (17/36) vs. 68.6 (24/35) Improved (>25% mean functional improvement from baseline) at 3 months, %: 52 (19/36) vs. 31 (11/35) Not improved (<25% mean functional improvement from baseline) at 6 months, %: 27.8 (10/36) vs. 55.9 (19/34) Improved (>25% mean functional improvement from baseline) at 6 months, %: 72.2 (26/36) vs. 44.1 (15/34) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR
See, 1996[59] Double-blind crossover study High	**Alfa-2a Interferon (n=26) vs. placebo (n=13)** Overall Function: NR Quality of Life: Mean QOL score: difference between groups=NS Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Rowe, 1997[58] RCT Medium	**Intragram vs. placebo** Adverse Events: Severe headache following first infusion, %: 64 vs. 20, p<0.01 Significant differences between % of infusions in each group experiencing a ≥3 day headache after the first infusion, a ≥3 day fatigue or weakness after the second and third infusions, and a ≥3 day nausea after the third infusion Count of all: 145 vs. 98 Withdrawals due to adverse event: Serious Adverse Events: NR	Study drug and placebo provided by The Commonwealth Serum Laboratories Research supported by MR Society (Victoria) and The Commonwealth Serum Laboratories Research
See, 1996[59] Double-blind crossover study High	**Alfa-2a Interferon vs. placebo** Adverse Events: Flu-like symptoms: 4, all in interferon group at the time Diarrhea: 2, all in interferon group at the time Withdrawals due to adverse event: 4 (2 for neutropenia, 1 for palpitations, 1 for worsened fatigue), all in interferon group at the time Serious Adverse Events: None reported It is not clear which of these events occurred pre- or post- crossover.	NR Study drug obtained from Roche Pharmaceuticals

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sharpe 2015[60] pre-specified long-term followup of PACE trial	United Kingdom 2008 to 2011 By mail, with nonresponders reminded by telephone	**Included:** PACE trial participants who hadn't withdrawn from data collection or long-term followup. **Excluded:** Contact details not available.	31 median (range 24 to 53) month time from randomization to return of survey. After completing final trial outcome assessment 1 year after randomization, trial participants were offered an additional PACE therapy if they were still unwell, they wanted more treatment, and their PACE doctor agreed this was appropriate. The choice of treatment offered (APT, CBT or GET) was made by the patient's doctor, taking into account the patient's preference and their own opinion of which would be most beneficial. These choices were made with knowledge of the individual patient's treatment allocation, but before the overall trial findings were known. Patients were free to choose additional or different therapies from original assignments 1 year after randomization, and 44% (210/479) received at least 1 additional treatment session.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sharpe 2015[60] pre-specified long-term followup of PACE trial	Nature and amount of any additional PACE therapies that participants had received for CFS since their 1 year outcome assessment: **Overall; specialist medical care vs. APT vs. CBT vs. GET** Participants who received any additional sessions, n=479 (2 participants provided incomplete data; 1 in CBT group had additional GET and 1 in APT group had additional APT), %: 44 (210/479); 63 (73/115) vs. 50 (60/119) vs. 31 (36/118) vs. 32 (41/127), p<0.0001 Median number of additional sessions received (IQR): 0 (0 to 8); 6 (0 to 12) vs. 1 (0 to 8) vs. 0 (0 to 3) vs. 0 (0 to 6), p<0.0001 Participants who received an adequate number of (≥10) sessions of an additional therapy after 12 month trial, %: Received APT: 3 (15/479); 5 (6/115) vs. 0 (0/119) vs. 2 (2/118) vs. 6 (7/127), p=0.016 Received CBT: 14 (65/479); 20 (23/115) vs. 17 (20/119) vs. 2 (2/118) vs. 16 (20/127), p<0.0001 Received GET: 5 (26/479); 12 (14/115) vs. 6 (7/119) vs. 4 (5/118) vs. 0 (0/127), p=0.0001	Surveys sent to all 604 participants of the PACE trial, 481 (75% of full cohort and 80% of eligible participants) returned questionnaires: 115 originally assigned to specialist medical care alone 120 originally assigned to APT 119 originally assigned to CBT 127 originally assigned to GET Proportion of participants who returned questionnaires did not differ between treatment groups, p=0.37	122 questionnaires not returned, and 1 patient withdrew consent

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Sharpe 2015[60] pre-specified long-term followup of PACE trial	**Original assignments: Specialist medical care vs. specialist medical care with APT vs. CBT vs. GET** Overall Function: *SF-36 physical functioning subscale (higher scores indicate better functioning)* , mean score (SD): 57.4 (27.9) vs. 52.8 (30.2) vs. 62.2 (27.2) vs. 59.8 (27.6), mean difference between 52 weeks and long-term followup (95% CI): 7.1 (4.0 to 10.3), p<0.0001 vs. 8.5 (4.5 to 12.5), p<0.0001 vs. 3.3 (0.02 to 6.7), p=0.049 vs. 0.5 (-2.7 to 3.6), p=0.78 Compared with specialist medical care, mean (95% CI): APT: -3.6 (-9.6 to 2.4), p=0.24 vs. CBT 2.8 (-3.2 to 8.8), p=0.36 vs. GET 2.0 (-4.0 to 7.9, p=0.51; Compared with APT, mean (95% CI): CBT 6.4 (0.4 to 12.4, p=0.035 vs. 5.6 (-0.3 to 11.5), p=0.064 Self-rated impairment of daily activities: *Participant-rated work and social adjustment scale (range 0 to 40, with lower scores indicating less impairment)* mean (SD): 21.1 (11.5) vs. 22.9 (11.7) vs. 19.7 (10.2) vs. 19.4 (10.8); Compared with specialist medical care, mean difference (95% CI): APT 1.3 (-1.2 to 3.7), p=0.30 vs. CBT -1.1 (-3.6 to 1.4), p=0.38 vs. GET -0.8 (-3.2 to 1.6), p=0.51; Compared with APT, mean difference (95% CI): CBT -2.4 (-4.85 to 0.1), p=0.06 vs. GET -2.1 (-4.5 to 0.3), p=0.09 Quality of Life: Perceived change in overall health since trial enrollment: *Participant-rated clinical global impression of change score*: Positive change %: 42 (48/115) vs. 38 (45/118) vs. 42 (50/119) vs. 48 (61/127); Compared with specialized medical care, OR (95% CI): APT 0.8 (0.4 to 1.3), p=0.32 vs. CBT 0.9 (0.5 to 1.5), p=0.62 vs. GET 1.1 (0.6 to 1.8), p=0.85; Compared with APT, OR (95% CI): CBT 1.2 (0.7 to 2.0), p=0.59 vs. 1.4 (0.8 to 2.3), p=0.22 Minimum change %: 50 (58/115) vs. 38 (45/118) vs. 48 (57/119) vs. 47 (59/127) Negative change %: 8 (9/115) vs. 12 (14/118) vs. 10 (12/119) vs. 6 (7/127); Compared with specialized medical care, OR (95% CI): APT 1.8 (0.7 to 4.5), p=0.23 vs. CBT 1.6 (0.6 to 4.3), p=0.37 vs. GET 0.8 (0.3 to 2.2), p=0.67; Compared with APT, OR (95% CI): CBT 0.9 (0.4 to 2.2), p=0.81 vs. GET 0.5 (0.2 to 1.1), p=0.09 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Chalder Fatigue Questionnaire (lower scores indicate better health)*, mean score (SD): 20.2 (8.6) vs. 20.5 (8.4) vs. 18.4 (8.5) vs. 19.1 (7.8), mean difference between 52 weeks and long-term followup (95% CI): -3.9 (-5.3 to -2.6), p<0.0001 vs. -3.0 (-4.4 to -1.6), p<0.0001 vs. -2.2 (-3.7 to -0.6), p=0.006 vs. -1.3 (-2.7 to -0.1), p=0.059 Compared with specialist medical care, mean (95% CI): APT 0.3 (-1.7 to 2.3), p=0.78 vs. CBT -1.4 (-3.4 to 0.7), p=0.19 vs. GET -0.8 9-2.8 to 1.2), p=0.43; Compared with APT, mean (95% CI): CBT -1.6 (-3.6 to 0.3), p=0.11 vs. GET -1.1 (-3.0 to 0.9), p=0.28 Outcomes related to associated symptoms: NR No adjustment/penalty due to multiple analyses, so significant p-values are likely to be chance findings. Findings were similar in sensitivity analysis, which controlled for varying duration of followup, data NR.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sharpe 2015[60] pre-specified long-term followup of PACE trial	No significant worsening in perceived health occurred during the followup period after any of the trial treatments.	United Kingdom Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions, National Institute for Health and Research, National Institute for Health and Research Biomedical Research Centre for Mental Health at South London, Maudsley National Health Services Foundation Trust, King's College London

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sharpe, 1996[61] Block randomized RCT Medium	United Kingdom 2 centers Study years NR Hospitals, specific settings NR	Oxford (Sharpe 1991) criteria **Inclusion:** Ages 18 to 60 years, with major complaint of fatigue and symptoms unexplained by organic disease. **Exclusion:** Currently receiving psychotherapy or antidepressant drugs; unwilling to accept randomization or unavailable for followup; met criteria for severe depression or had history of bipolar disorder, schizophrenia, or substance misuse; or at significant risk of suicide or in need of urgent psychiatric treatment.	**CBT (n=30):** 16 1-hour sessions of individual CBT over 4 months emphasizing cognitive techniques questioning a simple disease explanation chronic fatigue syndrome and considering the role of psychological and social factors. It included strategies to reduce excessive perfectionism and self criticism, and an active problem solving approach to interpersonal and occupational difficulties was also employed. Patients were invited to evaluate the effect of gradual and consistent increases in activity and to try strategies other than avoidance. **Control (n=30):** Patients were followed by their General Practitioner in their usual way. **Duration of treatment:** 4 months **Duration of followup:** 12 months after entry into study
Strayer, 1994[62] RCT Medium	United States 4 centers Study years NR Specialty clinics	CDC (Holmes,1988) criteria **Inclusion:** CFS diagnosed ≥12 months before study; severe debilitation (Karnofsky Performance Score 20 to 60). **Exclusion:** Diagnostic workup, brain MRI, and CSF analyses were performed to exclude other disorders.	**Rintatolimod (n=45):** IV rintatolimod 200 mg twice weekly 4 times, then 400 mg twice weekly for a total of 24 weeks **Placebo (n=47):** IV saline twice weekly for 6 months **Duration of treatment:** 6 months (24 weeks) **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sharpe, 1996[61] Block randomized RCT Medium	**CBT vs. control** Mean age (SD): 34 (9.1) vs. 38 (11.8) years % Female: 60 (18/30) vs. 77 (23/30) Race: NR Duration of illness: Mean (SD): 33.6 (9.1) vs. 29.7 (24.1) months Severity of symptoms: Mean disability on Karnofsky scale (SD): 71 (3.3) vs. 72 (3.4) Number of days in bed each week (SD): 3.3 vs. 1.6 (1.5) Fatigue severity (patient rated on a 1-10 scale): 7.8 (1.5) vs. 7.9 (1.9) % Not working or studying: 87 (26/30) vs. 50 (15/30) Comorbidities: % Major depressive disorder: 20 (6/30) vs. 20 (6/30) % Any depressive disorder: 53 (16/30) vs. 57 (17/30) % Any anxiety disorder: 47 (14/30) vs. 50 (15/30) % Any anxiety or depression disorder: 67 (20/30) vs. 67 (20/30) % Somatization disorder: 10 (3/30) vs. 10 (3/30)	Number approached: NR Number screened: 123 Number eligible: 62 Number enrolled: 60 (30 CBT, 30 control) Number analyzed: 60 (30 CBT, 30 control)	1/60 did not complete 12 month followup
Strayer, 1994[62] RCT Medium	**Rintatolimod vs. placebo** Mean age: NR, groups "well matched" % Female: 64 (29/45) vs. 85 (40/47); p=0.003 Race: NR Duration of illness: Mean: 6.1 vs. 4.4 years Severity of symptoms: *Karnofsky Performance Score (100 to 0, 0 is most severe)* mean: 51 to 50; p=0.64 Comorbidities: Prior Depression %: 24 (11/45) vs. 23 (11/47); p=0.91 MRI abnormality % (n=89): 38 vs. 43 (n by group NR); p=0.60 HHV-6-infected giant cells % (n=39): 68 vs. 71 (n by group NR); p=0.82	Number enrolled: 92 Number analyzed: 76 to 84 varies by outcome	9% (8/92) 4 from each group

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Sharpe, 1996[61] Block randomized RCT Medium	**CBT vs. control** Overall Function: *Achieved KPS score of ≥80* 5 months: 27% (8/30) vs. 20% (6/30); difference of 7 (95% CI, -15 to 28) 8 months: 53% (16/30) vs. 30% (9/30); difference of 23 (95% CI, 0 to 48) 12 months: 73% (22/30) vs. 27% (8/30); difference of 47 (95% CI, 24 to 69); p<0.001 *Improvement of ≥10 points on KPS* 5 months: 23% (7/30) vs. 7% (2/30); difference of 17 (95% CI, 0 to 34) 8 months: 60% (18/30) vs. 20% (6/30); difference of 40 (95% CI, 17 to 63) 12 months: 73% (22/30) vs. 23% (7/30); difference of 50 (95% CI, 28 to 72); p<0.001 Quality of Life: NR Work/School Days: Improvement in work status at 12 months, %: 63 (19/30) vs. 20 (6/30) Proportion full/part-time work: NR Fatigue: Fatigue severity (0 to 10), mean: 12 months: 4.3 vs. 6.3 Change from baseline, -3.5 vs. -1.6; difference 1.9, 95% CI 0.5 to 3.3 Outcomes related to associated symptoms: HADS-Depression: 12 months: 3.6 vs. 5.8 Change from baseline: -3.1 vs. -1.0; difference 2.0, 95% CI 0.0 to 4.1 Control group outcomes: One patient was referred to behavioral psychotherapy and was prescribed full-dose antidepressants, one patient was diagnosed as suffering from celiac disease and began a gluten free diet, two were referred to psychiatry services and received supportive psychotherapy.
Strayer, 1994[62] RCT Medium	**Rintatolimod vs. placebo** Overall Function: % change in *KPS score from baseline (0-100 scale, higher scores indicate better health)* +20 vs. 0; p=0.023 % change in *Activities of Daily Living score from baseline (0-100 scale, higher scores indicate better health)* +23.1 vs. 14.1; p=0.034 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Exercise duration* % change from baseline: +10.3 vs. +2.1; p=0.007 *Exercise work* % change from baseline: +11.8 vs. +5.8; p=0.011 Outcomes related to associated symptoms: SCL-90-R changes were similar between groups (scoring NR) Decreased used of medications for relief of CFS symptoms declined for rintatolimod but not compared with placebo; p<0.05

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sharpe, 1996[61] Block randomized RCT Medium	**CBT vs. control** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Wellcome Trust
Strayer, 1994[62] RCT Medium	**Rintatolimod vs. placebo** Adverse Events: 706 vs. 711 events; p>0.90 Insomnia more frequent among placebo and dry skin among rintatolimod; p<0.05 Withdrawals due to adverse event: None Serious Adverse Events: None	HEM Pharmaceuticals Corporation

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Strayer, 2012[63] Crossover RCT Medium	United States 12 centers 1998 to 2004 Specialty clinics	CDC (Holmes,1988) and (Fukuda, 1994) criteria **Inclusion:** Adults 18 to 60 years of age with diagnosis of CFS ≥ 12 months resulting in significant debilitation as measured by KPS, with ability to walk on the treadmill. Patients must have baseline laboratory documentation of euthyroid status, negative antinuclear antibody or negative anti-ed DNA, negative rheumatoid factor, and an erythrocyte sedimentation rate. **Exclusion:** Medical need to continue taking aspirin or NSAIDs, treatment with glucocorticoids, mineralocorticoids, interferons, interleukin-2, systemic antivirals, gamma globulin or investigational drugs within the 8 weeks prior to study baseline, ability to exercise >18 minutes during baseline exercise tolerance tests, history of alcohol or substance abuse within 2 years before the onset of CFS or anytime afterward, history of suicidal ideation, past or current diagnosis of major depressive disorder, schizophrenia, bipolar affective disorder, delusional disorders, dementia, or eating disorder.	**Rintatolimod (n=117):** IV rintatolimod 200 mg twice weekly for 2 weeks, followed by 400 mg twice weekly for 40 weeks **Placebo (n=117):** Placebo IV saline solution twice weekly for 42 weeks *Block randomization by treadmill duration (≤ 9 minutes vs. >9 minutes)* **Duration of treatment:** 42 weeks **Duration of followup:** End of treatment
Stubhaug, 2008[64] Medium	Norway Single center 2001 Specialty clinic	Diagnostic criteria: 65/72 (90%) patients met Oxford, 29/72 (40%) patients met Fukuda criteria Included: Chronic fatigue complaints, ICD-10 code F48.0 for neurasthenia Allowed mild depressive or anxiety symptoms independent or secondary to fatigue symptoms	**Mirtazapine first 12 weeks (n=28) plus comprehensive CBT after 12 weeks** (n=22) **Placebo first 12 weeks (n=24) plus comprehensive CBT after 12 weeks** (n=24) **Comprehensive CBT first 12 weeks (n=23, same individuals in C and D),** mirtazapine only second 12 weeks (n=11) **Comprehensive CBT first 12 weeks (n=23, same individuals in C and D),** placebo only second 12 weeks (n=12) Duration of follow up: 24 weeks

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Strayer, 2012[63] Crossover RCT Medium	**Rintatolimod vs. placebo** Mean age: 43 vs. 44 years % Female: 67 (79/117) vs. 78 (91/117) % White: 93 (109/117) vs. 92 (107/117) Duration of illness: Mean: 9.6 vs. 9.7 years Severity of symptoms: NR Comorbidities: NR	Number enrolled: 240 Number analyzed: 201	19.2% (46/240)
Stubhaug, 2008[64] Medium	**Marzitapine vs. placebo vs. CBT/marzitapine vs. CBT/placebo** Age, mean years: 45 vs. 45 vs. 47 vs. 51 % Female: 76 vs. 88 vs. 82 vs. 83 Race: NR Duration of illness: NR Severity of symptoms: Fatigue scale score (Chalder 0 to 33), mean: 24.76 vs. 25.54 vs. 24.91 vs. 24.33	Enrolled: 72 Analyzed: 72	All patients included in data analysis, using last observation carried forward

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Strayer, 2012[63] Crossover RCT Medium	**Rintatolimod vs. placebo, results prior to crossover portion of the study** Overall Function: KPS score, Activities of Daily Living scores, Vitality Score (SF-36), and General Health Perception (SF-36) measured with some significant differences pre and post, but not compared between rintatolimod and placebo groups Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Cardiopulmonary exercise tolerance (primary outcome)* Increase from baseline: 36.5% vs. 15.2%; p=0.047 Outcomes related to associated symptoms: Decreased used of medications for relief of CFS symptoms: 68% vs. 55%; p=0.048
Stubhaug, 2008[64] Medium	**12- week follow up, mean (95% CI)** **Marzitapine vs. placebo vs. CBT/marzitapine+CBT/placebo:** CGI score: 4.0 (3.7 to 4.3) vs. 4.4 (3.9 to 4.9) vs. 4.4 (3.9 to 4.9), A vs. C+D p=0.046, B vs. C+D, p=0.001 Fatigue Scale score: 22.7 (21.4 to 24.1) vs. 23.7 (21.0 to 26.5) vs. 23.7 (21.0 to 26.5), A vs. C+D p=0.34, B vs. C+D, p=0.014 HRSD (Hamilton Rating Scale for Depression): 12.6 (11.4 to 13.8) vs. 13.5 (10.9 to 16.1) vs. 13.5 (10.9 to 16.1), A vs. C+D, p=0.36, B vs. C+D, p=0.54

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Strayer, 2012[63] Crossover RCT Medium	**Rintatolimod vs. placebo** Adverse Events: 99% rintatolimod and 97% placebo reported symptoms, flu-like syndrome, chills, vasodilatation, and dyspnea were more frequent in rintatolimod vs. placebo ($p<0.05$) Withdrawals due to adverse event: 4 (2 in each group) Serious Adverse Events: 3 in each group with no differences between rintatolimod and placebo	Hemispherx Biopharma
Stubhaug, 2008[64] Medium	**Mirtazapine vs. Placebo** At least one adverse event: 100% vs. 45% Sedation: 56% vs. 11% Increased appetite: 31% vs. NR Weight increase: 33% vs. 11% Restless leg syndrome: 19% vs. NR Headache: NR vs. 17% Insomnia: NR vs. 11%	Organon AS provided unrestricted grant, medication, and placebo

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	**Country Number of Centers Study Years Setting (primary care, specialty clinic or other)**	**Diagnostic criteria Inclusion/ Exclusion criteria**	**Interventions (n) Duration of treatment Duration of followup**
Stulemeijer, 2005[65] RCT Medium	The Netherlands Single center 1999 to 2002 Pediatric outpatient clinic in department of child psychology	CDC (Fukuda, 1994) criteria **Inclusion:** Aged 10 to 17.2 years, referred to clinic for complaint of fatigue and meeting CDC criteria for CFS. **Exclusion:** Psychiatric comorbidity.	**CBT (n=36):** 10 individual sessions of cognitive behavioral therapy administered by a child therapist. These patients agreed to undertake no further treatments or assessments during therapy. Therapy differed for physically active and physically passive patients; active patients were taught to reduce their levels of activity to respect their limitations, then build the activity level in a controlled way. Passive patients began activity building immediately, with no regard to reinforcing the patients' need to respect limitations. Both groups included active involvement from parents, and focused on the specific developmental tasks of adolescents. The goal was a return to full-time school. **Control (n=35):** Waiting list for therapy, with no limitations on other assessments or therapies. **Duration of treatment:** 5 months **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Stulemeijer, 2005[65] RCT Medium	**CBT vs. control** Mean age: 15.6 vs. 15.7 years % Female: 89 (31/35) vs. 91 (31/34) Race: NR Duration of illness: 16.0 vs. 18.0 months Severity of symptoms: Fatigue Severity (Checklist individual strength): 52.5 vs. 51.6 Comorbidities: NR	Number randomized: 71 Number analyzed: 69 (35 CBT, 34 control)	13% (9/71) overall CBT: 19% (6/36) Control: 8.6% (3/35)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Stulemeijer, 2005[65] RCT Medium	**CBT vs. control** Overall Function: Mean (SD) *physical functioning subscale of the SF-36 (0 to 100 range with higher scores indicating better functioning*): 69.4 (28.0) vs. 55.3 (21.1), treatment effect 14.5 (95% CI, 7.4 to 21.6), p=0.001 Quality of Life: NR Work/School Days: Mean (SD) school attendance (number of hours attended divided by the number of hours that should have been attended) (2 participants were left out of the analysis because they'd completed final exams and weren't required to attend school for 5 months): 74.7 (37.8) vs. 66.7 (36.0), treatment effect 18.2 (95% CI, 0.8 to 35.5), p=0.040 Proportion full/part-time work: NA Fatigue: Mean (SD) Fatigue severity subscale of the checklist of individual strength: 30.2 (16.8) vs. 44.0 (13.4), treatment effect 17.3 (95% CI, 6.2 to 28.4), p=0.003 Outcomes related to associated symptoms: Mean patient-indicated symptom scores (SD): Unrefreshing sleep: 2.5 (1.1) vs. 3.2 (0.8), treatment effect -1.2 (-1.8 t0 -0.6), p=0.001 Muscle pain: 2.4 (1.0) vs. 2.4 (0.8), treatment effect -1.1 (95% CI, -1.6 to -0.6), p=0.001 Impaired concentration: 2.4 (1.2) vs. 2.7 (0.8), treatment effect -1.1 (95% CI, -1.5 to -0.65), p=0.001 Tiredness after exercise: 2.5 (1.1) vs. 2.9 (0.3), treatment effect -1.0 (95% CI, -1.5 to -0.5), p=0.001 Headache: 2.6 (0.9) vs. 2.5 (0.8), treatment effect -0.05 (95% CI, -0.9 to 0.0), p=0.033 Impaired memory: 1.8 (1.1) vs. 2.4 (1.0), treatment effect -0.4 (95% CI, -0.93 to 0.1), p=0.12 Multi-joint pain: 2.0 (1.2) vs. 2.3 (0.9), treatment effect -0.2 (95% CI, -0.7 to 0.3), p=0.38 Sore throat: 1.6 (0.8) vs. 1.9 (0.7), treatment effect 0.2 (95% CI, -0.3 to -0.7), p=0.40 Sensitive lymph nodes: 1.6 (0.9) vs. 1.5 (0.9), treatment effect 0.0 (95% CI, -0.4 to 0.6), p=0.72

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Stulemeijer, 2005[65] RCT Medium	**CBT vs. control** Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	Foundation for Children's Welfare Stamps Netherlands and the ME Society

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	**Country Number of Centers Study Years Setting (primary care, specialty clinic or other)**	**Diagnostic criteria Inclusion/ Exclusion criteria**	**Interventions (n) Duration of treatment Duration of followup**
Sulheim 2014[66] Combined cross-sectional and RCT Medium	Norway Single center 2010 to 2012 Referral center recruiting nationwide from all 20 pediatric hospital departments in Norway, assessments made at one single research unit	CDC (Fukuda, 1994) criteria, only 75% met criteria **Inclusion:** Patients with CFS (3 months of unexplained, disabling, chronic/relapsing fatigue of new onset) aged 12 to 18 years. **Exclusion:** Psychiatric or medical disorder that might explain the fatigue, concurrent demanding life event.	**Clonadine (n=60):** Clonadine hydrochloride in lactose capsules (25µg or 50µg twice daily for body weight <35kg or >35kg respectively. A half-dose was given for the first 3 days and for the last week. **Placebo (n=60):** Empty lactose capsules twice daily **Duration of treatment:** 9 weeks **Duration of followup:** 30 weeks
Surawy, 2005[67] RCT High	United Kingdom Single center Study year(s) NR Hospital clinic	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients with a diagnosis of CFS and meeting the Oxford criteria, following a thorough initial screening for infecions and physical diseases who were assessed for suitability for CBT and placed on the waiting list, due to wait more than 3 months **Exclusion:** Did not have a primary diagnosis of CFS, unable to travel to the group, or had a diagnosis of major depression or schizophrenia	**CBT (n=9):** 8 weekly group sessions, given at the same time each week **Control (n=9):** Waiting list for therapy, including standard care that may have included visits to the general practitioner and alternative therapies such as homeopathy and acupuncture, but not CBT or mindfulness. Questionnaires were sent by mail to the control group. **Duration of treatment:** 8 weeks **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sulheim 2014[66] Combined cross-sectional and RCT Medium	**Clonadine vs. placebo** Mean age: 15.2 vs. 15.5 % Female: 78 (47/60) vs. 65 (39/60) Race: 98% Scandinavian overall Median duration of illness: 17.5 vs. 18 months Severity of symptoms: Mean Functional Disability Inventory: 24.0 vs. 23.1 Mean Chalder Fatigue Questionnaire11-item (0 to 33): 19.1 vs. 19.2 Comorbidities: % Adhering to Fukuda criteria: 76 (45/60) vs. 74 (43/60)	Number enrolled: 120 Number analyzed at 30 weeks: Modified intention to treat analysis; 120	None
Surawy, 2005[67] RCT High	**CBT vs. control** Mean age: NR % Female: 44 (4/9) vs. 44 (4/9) Race: NR Duration of illness: NR Severity of symptoms: Mean (SD) *Chalder Fatigue Scale (14-item, 0 to 42, with higher scores indicating worse fatigue)* : 21.25 (9.16) vs. 25.33 (6.24) Comorbidities: NR; major depression and schizophrenia excluded	Number randomized: 18 Number analyzed: 17 (9 CBT, 8 control)	5.6% (1/18) overall CBT: 0 Control: 11% (14/9)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Sulheim 2014[66] Combined cross-sectional and RCT Medium	**Clonadine vs. placebo** Overall Function: Mean Functional Disability Inventory at 30 weeks: 17.5 vs. 16.8, difference 0.2, 95% CI: -13.3 o 13.6, p=0.98 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean Chalder Fatigue Questionnaire at 30 weeks: 11.1 vs. 13.5, difference 0.5, 95% CI: -14.7 to 15.7, p=0.95 Outcomes related to associated symptoms: Pain (BPI): 8 weeks: 17.9 vs. 16.4, p=0.24 30 weeks: 11.1 vs. 13.5, p=0.95 NS at week 8 and 10-week follow-up Sleep (KSQ Insomnia Score): 8 weeks: 3.7 vs. 3.8, p=0.54 30 weeks: 3.6 vs. 3.6, p=0.74NS at week 8 and 10-week follow-up
Surawy, 2005[67] RCT High	**CBT vs. control** Overall Function: Mean (SD) *physical function subscale of the SF-36 (0 to 100 range with higher scores indicating better functioning)* : 40.00 (16.78) vs. 35.50 (27.00), p=0.58 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean (SD) *Chalder Fatigue Scale (14-item, 0 to 42, with higher scores indicating worse fatigue)* :18.56 (8.13) vs. 20.38 (8.26), p=0.08 Outcomes related to associated symptoms: HADS Anxiety mean (SD): 8.22 (2.99) vs. 8.63 (4.57), p=0.01 HADS Depression mean (SD): 8.33 (1.66) vs. 9.50 (3.96), p=0.28

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sulheim 2014[66] Combined cross-sectional and RCT Medium	**Clonadine vs. placebo** Adverse Events: Total: 75% (43/57) vs. 65% (33/51), p=0.223 Dizziness when rising: 28% (16/57) vs. 10% (5/51), p=0.17 (although 23 adverse event analyses were performed) Withdrawals due to adverse event: Headache: 2 vs. 0 Syncope: 1 vs. 0 Suspected suicidality: 0 vs. 1 Abdominal discomfort: 0 vs. 1 Serious Adverse Events: NR	Health South-East Hospital Trust, University of Oslo, Oslo and Akershus University College of Applied Sciences, the Norwegian Competence Network of Paediatric Pharmacotherapy, Simon Fougner Hartmann's Family Foundation, Eckbo's Family Foundation
Surawy, 2005[67] RCT High	**CBT vs. control** Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	Linbury Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sutcliffe, 2010[68] Pilot RCT Medium	United Kingdom Number of centers NR Study year(s) NR Setting NR, exercises performed in home	CDC (Fukuda, 1994) criteria **Inclusion:** Ages ≥18 years with diagnosis of CFS under Fukuda criteria. **Exclusion:** Use of drugs which can affect the autonomic nervous system that cannot be safely discontinued, inability to stand up for 40 minutes, or pregnancy.	**Orthostatic training (n=19)**: Daily training consisting of standing with upper back against a wall, heels 15 cm from the wall with a cushioned 'drop zone', maintained position without movement for 40 minutes or until symptoms of CFS occur. **Control (n=19):** Standing against a wall as described above for only 10 minutes, also taught to perform gentle flexion and extension exercises with their calf muscles while standing against the wall, to enhance believability, counter venous pooling and prevent any possible orthostatic training effect. **Duration of treatment:** 6 months **Duration of followup:** End of treatment
Taylor, 2004[69] RCT Medium	United States Single center Study year(s) NR Center for independent living	CDC (Fukuda, 1994) **Inclusion:** Adults with CFS by Fukuda criteria **Exclusion:** Psychiatric illness that would rule out CFS diagnosis, untreated hyperthyroidism	**Counseling (n=23):** 8 sessions of a group illness-management program using empowerment theory occurring every other week over 4 months. These sessions consisting of check-ins, reporting of self-monitored goal attainment, educational lecture and discussion of participant-selected, CFS-relevant topics including activity pacing using the Envelope Theory, cognitive coping skills training, relaxation and meditation training, employment issues and economic self-sufficiency, personal relationships, traditional and complementary medical approaches, and nutritional approaches. After a post-group assessment that occurred during a 1 month break period, participants received 7 months of 1-on-1 peer counseling, which consisted of self-advocacy training, continued monitoring of goal attainment, and ongoing case coordination services. $300 was also given to each participant after they supplied statements of how their planned expenditure would facilitate their goal attainment and independent living. **Wait list (n=24):** On waiting list for 12 months, then given program as described above. Results of this group after they received the program are NR. **Duration of treatment:** 12 months **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sutcliffe, 2010[68] Pilot RCT Medium	**Orthostatic training vs. control** Mean age: 48 vs. 48 years % Female: 79 (15/19) vs. 84 (16/19) Race: NR Duration of illness: NR Severity of symptoms: NR Comorbidities: NR	Number enrolled: 38 Number analyzed: 36 (18 orthostatic training, 18 control)	**Overall:** 26% (10/38) **Orthostatic training vs. control:** NR
Taylor, 2004[69] RCT Medium	**Counseling vs. wait list** Mean age (SD): 49.0 (10.9) vs. 44.9 (9.7) years % Female: 91 (21/23) vs. 100 (24/24) % Minority: 17 (4/23) vs. 17 (4/24) % Working full-time: 9 (2/23) vs. 21 (5/24) % Working part-time: 22 (5/23) vs. 8 (2/24) % Unemployed: 70 (16/23) vs. 71 (17/24) Duration of illness: NR Severity of symptoms: *Mean symptom severity (scale NR, higher ratings indicate worse health) (SD):* 15.1 (3.0) vs. 14.2 (2.8) Comorbidities: NR	Number enrolled: 47 (23 counseling, 24 wait list) Number analyzed: 47 (23 counseling, 24 wait list)	None dropped out

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Sutcliffe, 2010[68] Pilot RCT Medium	**Orthostatic training vs. control** Overall Function: Difference in mean (SD) blood pressure drop with active stand at 6 months: 6 mmHg; 95% CI, 0.0 to 12.6; p=0.05 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Improvement of ≥10 points on FIS at 6 months: 50% (7/14) vs. 38% (5/13); p=NR Outcomes related to associated symptoms: NR
Taylor, 2004[69] RCT Medium	**Counseling vs. wait list** Overall Function: NR Quality of Life: *Mean (SD) QLI scores (0-30 scale, higher scores indicate better life quality)* Overall at 4 months: 13.2 (3.8) vs. 14.6 (4.8) Overall at 12 months: 15.7 (3.7) vs. 14.6 (4.1) Change in score at 12 months from baseline: 2.6 vs. 0.6; p<0.05 Health and function subscale at 4 months: 12.8 (1.8) vs. 13.6 (2.1) Health and function subscale at 12 months: 14.1 (1.7) vs. 13.6 (1.8) Social and economic subscale at 4 months: 15.2 (0.8) vs. 15.5 (1.0) Social and economic subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Psychological and spiritual subscale at 4 months: 15.0 (1.1) vs. 15.2 (1.3) Psychological and spiritual subscale at 12 months: 15.5 (1.1) vs. 15.1 (1.2) Family subscale at 4 months: 15.4 (1.0) vs. 15.5 (1.0) Family subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Change in score at 12 months from baseline: 0.2 vs. -0.2; p<0.05 Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: *Mean symptom severity (scale NR, higher ratings indicate worse health) (SD):* 4 months: 14.4 (3.5) vs. 14.3 (2.7) 12 months: 13.9 (3.5) vs. 14.8 (2.8) Change in score at 12 months from baseline: -1.2 vs. 0.6; p<0.05

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sutcliffe, 2010[68] Pilot RCT Medium	**Orthostatic training vs. control** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Northern Regional CFS/ME Clinical Network
Taylor, 2004[69] RCT Medium	**Counseling vs. wait list** Adverse Events: NR Withdrawals due to adverse event: None Serious Adverse Events: NR	U.S. Department of Education National Institute on Disability and Rehabilitation Research Grant #H133G000097

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
The, 2007[70] RCT Medium	The Netherlands Single center 2003 to 2005 Specialty clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18 to 65 years, IGFBP3/IGF1 ratio >2.5 **Exclusion:** Psychiatric comorbidities, pregnant or lactating women, lactose intolerance, or taking psychotropic drugs or experimental medications. *Note: Healthy controls were included to compare hormone blood levels, outcome NR here*	**Acclydine (n=30):** Acclydine (increases IGF1 levels) capsules on a decreasing dosage schedule (from 1,000 mg every day to 250 mg every 2 days) with amino acid supplement **Placebo (n=27):** Placebo capsules with placebo amino acid supplement **Duration of treatment:** 14 weeks **Duration of followup:** End of treatment
Tummers, 2012[71] Tummers, 2013[35] RCT Medium	The Netherlands Single center Study year(s) NR Tertiary care facility	CDC (Fukuda, 1994) criteria **Inclusion:** Age 18 to 65 years, were severely fatigued (≥35 on the fatigue severity subscale of the CIS), were fatigued for ≥6 months, were severely disabled (≤70 on physical and/or social functioning subscale of SF-36), reported ≥4 of 8 additional symptoms: unrefreshing sleep, post exertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes, impairment of concentration or memory. **Exclusion:** Those with the presence of somatic diseases or psychiatric disorders and the use of medication that could explain the fatigue; BMI >40.	**Self-instruction (n=62):** 20 weeks of guided self-instruction which included setting goals, reviewing of precipitating and perpetuating factors, challenging of fatigue-related cognitions, reducing focus on fatigue, sleep routine setting, physical activity level adapted for either relatively-active person or a low-active person, gradually asked to increase activity or divide activities more evenly, challenging of beliefs that activity would exacerbate symptoms, begin plan for resuming work, modifying excessive expectations regarding the response of their social environment to their symptoms, learn how to communicate about CFS, gradually increase mental and social activities, and relapse prevention and improve self control. **Wait list (n=61):** Waitlist control for duration of intervention. **Duration of treatment:** 20 or more weeks **Duration of followup:** 6 months after baseline assessment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
The, 2007[70] RCT Medium	**Acclydine vs. placebo** Mean age (SD): 40.9 (9.4) vs. 43.4 (11.2) years % Female: 77 (23/30) vs. 59 (16/27) Race: NR Duration of illness: NR Severity of symptoms: *Mean (SD) Checklist Individual Strength-fatigue (8-56 scale, lower scores indicate better health)*: 46.5 (7.4) vs. 46.2 (7.9) *Mean (SD) Sickness Impact Profile-8 (0-5,799 scale, lower scores indicate better health)*: 1,484 (520.4) vs. 1,317 (481.7) *Mean (SD) CDC symptoms*: 7.6 (1.4) vs. 7.5 (1.3) Comorbidities: NR	Number enrolled: 57 Number analyzed: 57	**Overall:** 3.5% (2/57) **Acclydine vs. placebo:** 3.3% (1/30) vs. 3.7% (1/27)
Tummers, 2012[71] Tummers, 2013[35] RCT Medium	**Self-instruction vs. wait list** Mean age (SD): 36.3 (12.1) vs. 36.4 (13.6) years % Female: 74 (46/62) vs. 82 (50/61) Race: NR Mean (range) duration of illness: 48 (6 to 464) vs. 60 (6 to 625) months Severity of symptoms: *Mean (SD) CIS Fatigue severity (8 to 56 scale with lower scores indicating less fatigue):* 51 (5.3) vs. 51.6 (5.5) *Mean (SD) SF-36 physical functioning (0 to 100 scale with lower score indicating greater disability)*: 50.0 (22.2) vs. 51.6 (22.6) *Mean (SD) SF-36 social functioning (0 to 100 scale with lower score indicating greater disability):* 37.7 (22.3) vs. 41.0 (21.7) Comorbidities: NR	Number enrolled: 123 (62 self-instruction, 61 wait list) Number analyzed: 111 (55 self-instruction, 56 wait list)	**Self-instruction vs. wait list** 11% (7/62) vs. 8% (5/61)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
The, 2007[70] RCT Medium	**Acclydine vs. placebo** Overall Function: *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* 14 weeks: 1,228.1 (619.7) vs. 1,120.2 (543.0); 59.1, 95% CI -201.7 to 319.8, p=0.65 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) CIS-fatigue severity scores (8-56 scale, lower scores indicate better health)* 14 weeks: 42.4 (11.6) vs. 43.0 (12.6); mean difference in change from baseline 1.1, 95% CI -4.4 to 6.5, p=0.70 Daily fatigue level: 8.0 vs. 7.0, p=0.76; average daily fatigue rating for 14 days, range 0-16, higher scores indicate more fatigue Outcomes related to associated symptoms: *Mean (SD) physical activity level over a 12-day period (measured by actometer attached to the ankle)* 14 weeks: 64.9 (23.4) vs. 64.9 (23.5); mean difference in change from baseline 4.1, 95% CI -5.9 to 14.0, p=0.42
Tummers, 2012[71] Tummers, 2013[35] RCT Medium	**Self-instruction vs. wait list** Overall Function: *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 65.4 (24.9) vs. 59.3 (22.9); p=0.08 **Subanalysis of baseline group with SF-36 physical functioning score ≤70** **Self-instruction (n=53) vs. wait list (n=50)** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 63.0 (25.9) vs. 53.4 (18.7) Change from baseline: 18.5 vs. 9.6, difference: 9.05 (95% CI, 0.2 to 17.9); p<0.05 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue*: Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 39.6 (14.1) vs. 48.3 (8.1); p<0.01 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 33 (18/55) vs. 9 (5/56); OR 5.0 (95% CI 1.69 to 14.57) **Subanalysis of baseline group with SF-36 physical functioning score ≤70** **Self-instruction (n=53) vs. wait list (n=50)** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 38.9 (14.3) vs. 50.1 (6.2) Change from baseline: -12.4 vs. -2.4; difference: -9.9 (95% CI, -5.4 to -14.3); p<0.01 Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
The, 2007[70] RCT Medium	**Acclydine vs. placebo** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: None	Optipharma and GlaxoSmithKline
Tummers, 2012[71] Tummers, 2013[35] RCT Medium	**Self-instruction vs. wait list** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Dutch Medical Research Council ZonMW

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Tummers, 2012[71] Tummers, 2013[35] Continued	See Tummers 2012/2013	See Tummers 2012/2013	See Tummers 2012/2013
Vercoulen, 1996[72] RCT Medium	The Netherlands Single center Study year(s): NR Specialty clinic	Oxford (Sharpe, 1991) criteria **Inclusion:** Fatigue for more than 1 year with substantial impairment in daily life (≥35 on subjective fatigue subscale of the checklist individual strength). **Exclusion:** Score <16 and >11 on modified Beck depression inventory, any physical illness the could explain complaints, any psychiatric diagnosis besides major depressive disorder in depressed patients, pregnancy or lactation, lack of contraception in women of childbearing age, exposure to fluoxetine in a clinical trial, previous lack of satisfactory response to an adequate course of fluoxetine, participation in a recent clinical trial, use of any prescribed medication except clinical analgesics that could not be stopped , current psychotherapy.	**Fluoxetine (n=54):** One 20 mg capsule once a day. **Placebo (n=53):** Not described. **Duration of treatment:** 8 weeks **Duration of followup:** 10 weeks after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Tummers, 2012[71] Tummers, 2013[35] Continued	See Tummers 2012/2013	See Tummers 2012/2013	See Tummers 2012/2013
Vercoulen, 1996[72] RCT Medium	**Fluoxetine depressed vs. fluoxetine non-depressed vs. placebo depressed vs. placebo non-depressed** Mean age (years): 39.9 vs. 39.8 vs. 38.5 vs. 37.8 % Female: 83 (15/18) vs. 67 (12/18) vs. 72 (13/18) vs. 53 (10/19) Race NR Mean duration of illness (range): 5 (1 to 30) vs. 5 (1 to 20) vs. 6 (2 to 20) vs. 6 (2 to 30) Severity of symptoms: *Subjective fatigue, daily observed fatigue score, measured 4 times a day on a 4-point scale, and combined, with higher scores indicating worse fatigue*: 10.2 vs. 8.6 vs. 9.8 vs. 9 (estimated from Figure 2) Comorbidities: Major depressive disorder %: 100 vs. 0 vs. 100 vs. 0	Enrolled: 107 Analyzed: 96	**Fluoxetine vs. placebo** 10.3% (9/54) vs. 4 (2/53)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Tummers, 2012[71] Tummers, 2013[35] Continued	**Tummers, 2013** Interaction tests for potential moderators from linear regression models (95% CI) Age (years): 0.15 (0.01 to 0.045); p<0.05 Depression: 0.15 (0.04 to 1.95); p=0.04 Self-efficacy: -0.06 (-1.18 to 0.56); p=0.48 Somatic attribution: 0.10 (-0.32 to 1.43); p=0.21 Avoidance of activity: 0.17 (0.03 to 1.78); p=0.04 Focus on bodily symptoms: -0.02 (-0.61 to 0.52); p=0.88 Interaction tests for potential moderators from logistic regression models (95% CI) Age (years): 1.06 (0.99 to 1.13); p=0.10 Depression: 1.40 (1.08 to 1.82); p=0.01 Self-efficacy: 0.81 (0.62 to 1.05); p=0.11 Somatic attribution: 1.13 (0.87 to 1.46); p=0.36 Avoidance of activity: 1.34 (1.03 to 1.74); p=0.03 Focus on bodily symptoms: 1.02 (0.87 to 1.20); p=0.80
Vercoulen, 1996[72] RCT Medium	**Fluoxetine depressed vs. fluoxetine non-depressed vs. placebo depressed vs. placebo non-depressed** Overall Function: NR Quality of Life: *Self-reported change:* Recovered: 0 vs. 0 vs. 0 vs. 0 Improved, %: 14 (3/21) vs. 21 (5/24) vs. 13 (3/23) vs. 7% (2/28) Unchanged, %: 62 (13/21) vs. 71 (17/24) vs. 52 (12/52) vs. 79 (22/28) Worse, %: 24 (5/21) vs. 8 (2/24) vs. 35 (8/23) vs. 14 (4/28) Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Subjective fatigue, daily observed fatigue score, measured 4 times a day on a 4-point scale, and combined, with higher scores indicating worse fatigue*: 10.3 vs. 8.2 vs. 9.2 vs. 8.8 (estimated from figure) Mean difference between fluoxetine and placebo in improvement in fatigue severity: -0.164 (95% CI, 0.64 to 0.31), p=NS Outcomes related to associated symptoms: Mean difference between fluoxetine and placebo in improvement in depression severity: -0.186 (95% CI, 0.35 to 0.02), p=NS

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Tummers, 2012[71] Tummers, 2013[35] Continued	See Tummers 2012/2013	See Tummers 2012/2013
Vercoulen, 1996[72] RCT Medium	**Fluoxetine vs. placebo** Adverse events: Tremor: NR, but fluoxetine group greater p=0.006 Perspiration: NR, but fluoxetine group greater p=0.008 Withdrawals due to adverse events, %: 15 (8/54) vs. 4 (2/53) Serious adverse events: NR	Eli Lilly, Netherlands

Appendix E2. Evidence Table for Key Question 3

Author, year **Study Design** **Risk of Bias**	**Country** **Number of Centers** **Study Years** **Setting (primary care, specialty clinic or other)**	**Diagnostic criteria** **Inclusion/ Exclusion criteria**	**Interventions (n)** **Duration of treatment** **Duration of followup**
Vermeulen, 2004[73] Open-label randomized study Medium	The Netherlands Single center Study year(s) NR CFS clinic	CDC (Fukuda, 1994) criteria **Inclusion:** Meet CDC criteria for CFS, no other criteria described. **Exclusion:** Patients with an underlying organic cause, substance misuse, and severe psychiatric disorder.	**Acetyl-L-carnitine (n=30):** Acetyl-L-carnitine 2g/day **Propionyl-L-carnitine (n=30):** Propionyl-L-carnitine 2 g/day **Combination (n=30):** Acetyl-L-carnitine 2g/day + propionyl-L-carnitine 2 g/day **Duration of treatment:** 24 weeks **Duration of followup:** 2 weeks after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Vermeulen, 2004[73] Open-label randomized study Medium	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Mean age (SD): 37 (11) vs. 38 (11) vs. 42 (12) years % Female: 77 (23/30) vs. 77 (23/30) vs. 77 (23/30) Race: NR Duration of illness: Median (range): 5.5 (1.0 to 23.0) vs. 3.0 (0.5 to 25.0) vs. 6.0 (1.0 to 21.0) years Severity of symptoms: *Mean (SD) General fatigue, Multidimensional fatigue inventory-20 (5-20 scale, lower scores indicate better health)* : 18.6 (1.9) vs. 18.4 (18) vs. 19.1 (1.4) *Mean (SD) Physical fatigue, Multidimensional fatigue inventory-20 (5-20 scale, lower scores indicate better health)* : 18.1 (2.6) vs. 17.8 (2.3) vs. 18.5 (1.6) *Mean (SD) Mental fatigue, Multidimensional fatigue inventory-20 (5-20 scale, lower scores indicate better health)* : 17.0 (3.3) vs. 16.3 (2.5) vs. 15.7 (3.9) Comorbidities: NR	Number enrolled: 90 Number analyzed: 89	**Overall:** 20% (18/90) **Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination:** 27% (8/30) vs. 13% (4/30) vs. 20% (6/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Vermeulen, 2004[73] Open-label randomized study Medium	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Overall Function: NR Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) MFI-20 scores (5-20 scale, lower scores indicate better health)* General fatigue at 24 weeks: 15.9 (4.2) vs. 16.5 (3.1) vs. 17.3 (3.3); mean differences: ALC vs. PLC, 0.60, 95% 2.52 to -1.32; ALC vs. ALC/PLC, 1.40, 95% CI 3.37 to -0.57; PLC vs. ALC/PLC, 0.80, 95% CI 2.45 to -0.85 Physical fatigue at 24 weeks: 15.7 (4.4) vs. 16.4 (3.2) vs. 16.5 (3.4) mean differences: ALC vs. PLC, 0.70, 95% CI 2.70 to -1.30 ALC vs. ALC/PLC, 0.80, 95% CI 2.85 to -1.25 PLC vs. ALC/PLC, 0.10, 95% CI 1.81 to -1.61 Mental fatigue at 24 weeks: 15.1 (3.6) vs. 13.9 (3.5) vs. 14.6 (4.0) mean differences: ALC vs. PLC, -1.20, 95% CI 0.65 to -3.05 ALC vs. ALC/PLC, -0.50, 95% CI 1.49 to -2.49 PLC vs. ALC/PLC, 0.70, 95% CI 2.64 to -1.24 Outcomes related to associated symptoms: *% Improved on CGI* 24 weeks: 59 (17/29) vs. 63 (16/25) vs. 37 (11/30); ALC vs. PLC, RR 1.02, 95% CI 0.54 to 1.90 ALC vs. ALC/PLC, RR 0.65, 95% CI 0.39 to 1.09 PLC vs. ALC/PLC, RR 0.64, 95% CI 0.38 to 1.09

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Vermeulen, 2004[73] Open-label randomized study Medium	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Adverse Events: NR Withdrawals due to adverse event: 10% (3/29) vs. 7% (2/30) vs. 10% (3/30) Overstimulated feeling and sleeplessness Serious Adverse Events: NR	Sigma-Tau Ethifarma

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Vollmer-Conna, 1997[74] RCT Medium	Australia 2 centers Study year(s): NR Hospital inflammation research units	CDC (Fukuda, 1994) criteria **Inclusion:** No other explanation of chronic fatigue. **Exclusion:** Pregnant; taking steroid medication, nonsteroidal anti-inflammatory drugs, immunomodulatory agents, or choline esterase inhibitors; had previously received immunologic therapy; recent history of asthma	**Immunoglobulin 0.5 g/kg (n=22):** 3 monthly IV infusions each lasting 24 hours **Immunoglobulin 1 g/kg (n=28):** 3 monthly IV infusions each lasting 24 hours **Immunoglobulin 2 g/kg (n=23):** 3 monthly IV infusions each lasting 24 hours **Placebo (n=26):** 1% albumin in 10% weight/volume maltose, 3 monthly IV infusions each lasting 24 hours **Duration of treatment:** 3 months **Duration of followup:** 3 months after the final infusion
Walach, 2008[75] Partially-blinded RCT Low	Germany and Austria 14 centers 2001 to 2003 Private practices for environmental medicine specializing in CFS	CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) criteria **Inclusion:** Patients 18 years or older who met the Fukuda or Oxford Criteria **Exclusion:** Patients with other chronic conditions of co-morbidities that typically rule out a diagnosis of CFS (cancer, hepatitis, or depression), pregnancy, patients with a serious acute illness or hospital admission in the 3 months prior to entry	**Distant healing (n=207):** Received distant healing from 3 healers who were allowed to use whichever techniques they used in their normal practice; techniques included either prayer or imagining the transmission of 'healing energy, 'light', or 'healing power' **Usual care (n=206):** No healing as "deferred treatment" *Note: Patients were also randomized to being blinded or unblinded to treatment allocation:* *Blinded distant healing n=105* *Unblinded distant healing n=102* *Blinded usual care n=95* *Unblinded usual care n=109* **Duration of treatment:** 6 months **Duration of followup:** 6 months after end of treatment; 18 months total for patients recruited at beginning of study

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Vollmer-Conna, 1997[74] RCT Medium	**Immunoglobulin 0.5 g/kg vs. Immunoglobulin 1 g/kg vs. Immunoglobulin 2 g/kg vs. Placebo** Mean age (years): 41 vs. 40 vs. 38 vs. 40 % Female: 74 (17/23) vs. 79 (22/28) vs. 61 (14/23) vs. 85 (22/26) Race NR Mean duration of illness (years): 6 vs. 7 vs. 5 vs. 7 Severity of symptoms: *Mean Karnofsky Performance Scores, 0 to 100 (higher scores indicate better health):* 73 vs. 70 vs. 67 vs. 71, p=NS *Profile of Mood States (POMS) energy score (calculated by subtracting the POMS fatigue score from the POMS vigor score for each patient):* -13.0 vs. -9.3 vs. -7.3 vs. -16.0, p-0.005, NS (Bonferroni adjusted p-critical was 0.004 due to multiple comparisons) Comorbidities: NR	Enrolled: 99 Analyzed: 99	4 patients left the study, but were analyzed on an intention-to-treat basis.
Walach, 2008[75] Partially-blinded RCT Low	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Mean age (SD): 47.5 (10.7) vs. 48.1 (10.0) vs. 46.2 (10.9) vs. 50.4 (12.8) years % Female: 74.3 (78/105) vs. 76.5 (78/102) vs. 76.6 (72/94) vs. 75.0 (81/108) Mean length of unemployment (SD): 36.3 (38.2) vs. 34.8 (49.6) vs. 27.7 (22.3) vs. 28.7 (27.4) months Race: NR Duration of illness: Mean (SD): 11.3 (9.4) vs. 9.6 (6.7) vs. 9.6 (8.6) vs. 11.9 (9.9) years Severity of symptoms: *% Severe idiopathic CFS:* 7.6 (8/105) vs. 2.9 (3/102) vs. 4.3 (4/94) vs. 3.7 (4/108) *Mean (SD) Fatigue severity score (1-7 scale, lower scores indicate better health):* 6.2 (0.9) vs. 6.1 (0.9) vs. 6.1 (1.1) vs. 6.0 (1.1) Comorbidities: NR	Number enrolled: 411 Number analyzed: 409	**Overall:** 3.6% (15/411) **Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care**: 1.9% (2/105) vs. 5.9% (6/102) vs. 3.2% (3/95) vs. 3.7% (4/109)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Vollmer-Conna, 1997[74] RCT Medium	**Immunoglobulin 0.5 g/kg vs. Immunoglobulin 1 g/kg vs. Immunoglobulin 2 g/kg vs. Placebo** Overall Function: *Investigator-rated Median Karnofsky Performance Score, 0 to 100, higher scores indicate better health:* By group, median (1st to 3rd IQR): 80.0 (80 to 70) vs. 80.0 (80 to 70) vs. 75.0 (80 to 70) vs. 77.5 (80 to 70), difference in change between groups: p>0.13 Quality of Life: *Visual Analog Scale:* Trend toward improvement in all groups, but no significant difference between groups, data NR, p>0.09 Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Profile of Mood States (POMS) energy score (calculated by subtracting the POMS fatigue score from the POMS vigor score for each patient):* No significant difference between groups, data NR Outcomes related to associated symptoms: Nonsedentary activity hours per day: No significant difference between groups, data NR
Walach, 2008[75] Partially-blinded RCT Low	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Overall Function: *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)* 6 months: 34.69 (9.77) vs. 34.79 (10.41) vs. 35.08 (10.01) vs. 33.46 (9.68); p=NR Change from baseline: 3.66 (6.83) vs. 3.04 (7.38) vs. 3.29 (7.28) vs. 0.75 (7.85); p=NR *Mean (SD) SF-36 mental health subscale scores (0-100 scale, lower score indicates better health)* 6 months: 36.37 (11.98) vs. 36.61 (10.75) vs. 38.44 (12.01) vs. 35.97 (11.56); p=NR Change from baseline: -0.29 (9.54) vs. 1.74 (10.25) vs. 1.16 (11.07) vs. 0.81 (10.45); p=NR Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Vollmer-Conna, 1997[74] RCT Medium	**Immunoglobulin 0.5 g/kg vs. Immunoglobulin 1 g/kg vs. Immunoglobulin 2 g/kg vs. Placebo** Adverse events: Moderate to severe constitutional symptoms including headache, fatigue, malaise, and concentration impairment typically reported 12 to 2 hours after the completion of the infusion and persisting for up to 10 days, %: 88 (18/22) vs. 71 (20/28) vs. 78 (18/23) vs. 88 (23/26), p=0.49 Withdrawals due to adverse events: 3 immunoglobulin patients (group[s] NR) withdrew after either a severe constitutional symptom reaction (2 patients) or a vesiculopapular skin eruption on hands and feet (1 patient) to infusion 1 or 2 Serious adverse events: NR	Commonwealth Serum Laboratories and the Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis Society of New South Wales
Walach, 2008[75] Partially-blinded RCT Low	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	European Commission "Quality of Life and Living Resources" grant, Bundesamt fur Wissenschaft und Bildung, Switzerland, and the Samueli Institute

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Wallman, 2004[76] RCT High	Australia Single center Study year(s) NR University human performance laboratory	CDC (Fukuda, 1994) criteria **Inclusion:** Physician's written confirmation of diagnosis using Fukuda criteria. **Exclusion:** Alternative diagnosis or failure to provide written confirmation of diagnosis	**Graded exercise (n=32):** Aerobic activity using all the large muscles of the body, beginning with 5 to 15 minutes, with intensity based on mean HR value, every other day unless they had a relapse. Subjects could choose between walking, cycling, or swimming. **Flexibility/relaxation (n=29):** Relaxation/flexibility therapy; listening to a relaxation tape and stretching exercises every other day over 12 weeks. Requested not to participate in any extra physical activity. Both groups used a diary to record their sessions and were assessed once a week for 4 weeks before and 4 weeks after the intervention, with the average scores used for pre-and post-treatment data. Both groups were contacted by phone every other week to review progress and determine next exercise regimen. **Duration of treatment:** 12 weeks **Duration of followup:** End of treatment
Wearden, 2010[77] Wearden, 2012[78] Wearden, 2013[79] FINE Trial Block-randomized and stratified RCT Medium	United Kingdom 186 centers 2005 to 2007 Primary care; therapies delivered in-home	Oxford (Sharpe ,1991) **Inclusion:** Ages ≥18 years, scored ≤70% on SF-36 physical functioning scale, scored ≥4 on Chalder fatigue scale. **Exclusion:** Fit criteria for antisocial, borderline, or paranoid personality disorders; active suicidal ideation; unable to read or write English; currently undertaking systemic psychological therapies for CFS/ME; had received pragmatic rehabilitation in the past year. All patients were referred from general practitioners, who performed a list of exclusionary tests based on Fukuda, 1994 criteria.	**Graded exercise (pragmatic rehabilitation) (n=95):** 10 sessions over an 18-week period of a program of graded return to activity; designed collaboratively by the patient and therapist, which encourages patients to regularize their sleep patterns and includes relaxation exercises to address somatic symptoms of anxiety. An additional component to address concentration and memory problems was also included. **Supportive listening (n=101):** 10 sessions over an 18-week period of listening therapy based on non-directive counseling, with therapist aiming to provide an empathic and validating environment in which the patient can discuss his or her concerns and work towards resolution of whichever problems the patient wishes to prioritize. **Usual care (n=100):** Practitioners managed their patients as they saw fit, but were not referred for systematic psychological therapies for CFS/ME during the 18-week treatment period. **Duration of treatment:** 18 weeks **Duration of followup:** 70 weeks total

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Wallman, 2004[76] RCT High	**Graded exercise vs. flexibility/relaxation** Mean age: NR by group, range overall 16 to 74 % Female: 84% (27/32) vs. 69% (20/29) Race: NR Duration of illness: "No initial difference," data NR Severity of symptoms: Mental fatigue, maximum score 12, average score (range): 6.3 (5.6 to 7.0) vs. 5.6 (5.0 to 6.1) Physical fatigue, maximum score 21, average score (range): 11.6 (10.1 to 13.0) vs. 11.4 (10.4 to 12.3) Comorbidities: 6 subjects had a major depressive disorder in the previous 12 months, group NR 2 subjects had dysthymia, group NR	Number enrolled: 68 7 excluded post-randomization, 6 for reasons not associated with the study, and one because her BMI (44) prevented her from participating in the exercise test. Number analyzed: 61 (32 exercise, 29 relaxation/flexibility)	**Overall:** 10% (7/68) **Graded exercise vs. flexibility/relaxation:** 6% (2/34) vs. 15% (5/34) patients received neither intervention and were not included in baseline or end of treatment testing
Wearden, 2010[77] Wearden, 2012[78] Wearden, 2013[79] FINE Trial Block-randomized and stratified RCT Medium	**Graded exercise vs. supportive listening vs. usual care** Mean age: 43.74 vs. 45.13 vs. 44.92 years % Female: 78 (74/95) vs. 79 (80/101) vs. 76 (76/100) Race: NR Duration of illness: Median (range): 7 (0.5-51.7) years Severity of symptoms: All scored ≤70% on SF-36 physical functioning scale and scored ≥4 on 0 to 11 Chalder fatigue scale % Ambulatory: 90 (85/95) vs. 87 (88/101) vs. 88 (88/100) % Met London ME criteria: 30 (28/95) vs. 31 (31/101) vs. 33 (33/100) Comorbidities: % Any anxiety diagnosis: 27 (21/95) vs. 20 (17/101) vs. 26 (22/100) % Any depression diagnosis: 19 (18/95) vs. 15 (15/101) vs. 20 (20/100) % With ≥2 comorbidities: 34 (32/95) vs. 32.7 (33/101) vs. 43 (43/100) % With 1 comorbidity: 22 (21/95) vs. 28 (29/101) vs. 24 (24/100) % With no comorbidities: 44 (42/95) vs. 39 (39/101) vs. 33 (33/100) Comorbidities: musculoskeletal disorders 21% (63/296), gastrointestinal problems including irritable bowel syndrome 5% (45/296), and cardiovascular diseases such as hypercholesterolemia 14% (41/296)	Number enrolled: 296 (95 graded exercise, 101 supportive listening, 100 usual care) Number analyzed: 274 at 20 weeks (85 graded exercise, 97 supportive listening, 92 usual care) and 257 at 70 weeks (81 graded exercise, 90 supportive listening, 86 usual care)	**Overall:** 13.2% (39/296) **Graded exercise vs. supportive listening vs. usual care:** 14.7% (14/95) vs. 10.9% (11/101) vs. 14.0% (14/100) 1 in supportive listening group subsequently received diagnosis of multiple sclerosis (misdiagnosis)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Wallman, 2004[76] RCT High	**Graded exercise vs. flexibility/relaxation** Overall Function: Ratings of perceived exertion (estimated from figure): 1.3 vs. 1.8 (p=0.013) Quality of Life: *Self-rated clinical global impression change scores after completing treatment:* 1: Very much better: 16% (5/32) vs. 7% (2/29) 2: Much better: 44% (14/32) vs. 34% (10/29) 3: A little better: 31% (10/32) vs. 34% (10/29) 4: No change: 9% (3/32) vs. 21% (6/29) 5: A little worse: 0 vs. 3% (1/29) 6: Much worse: 0 vs. 0 7: Very much worse: 0 vs. 0 Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mental fatigue, maximum score 12, average score (range): 4.5 (3.9 to 5.2) vs. 4.8 (4.2 to 5.5) Physical fatigue, maximum score 21, average score (range): 8.1 (6.9 to 9.4) vs. 9.6 (8.3 to 10.9) Outcomes related to associated symptoms: HADS depression: 4.8 (6 to 5.9) vs. 6.5 (5.5 to 7.6), p=0.041
Wearden, 2010[77] Wearden, 2012[78] Wearden, 2013[79] FINE Trial Block-randomized and stratified RCT Medium	Overall Function: **Graded exercise vs. supportive listening vs. usual care** *Mean percentage scores (SD) on SF-36 physical functioning scale (0-100 scale, higher scores indicate better outcomes)* 20 weeks: 39.94 (25.21) vs. 33.28 (22.94) vs. 40.27 (26.45); treatment effect estimate -7.54, 95% CI -12.96 to -2.33; p=0.005 for supportive listening vs. usual care; 70 weeks: 43.27 (27.38) vs. 35.72 (25.94) vs. 39.83 (27.77); p=NS Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: **Graded exercise vs. supportive listening vs. usual care** *Mean (SD) Chalder fatigue scale scores (items scored dichotomously; lower scores indicate better outcomes)* 20 weeks: 8.39 (3.67) vs. 9.67 (2.76) vs. 9.32 (3.18); treatment effect estimate -1.18, 95% CI -2.18 to -0.18; p=0.021 for graded exercise vs. usual care; 70 weeks: 8.72 (3.65) vs. 9.39 (3.21) vs. 9.48 (2.71). **Graded exercise vs. usual care** *Mean (SD) Chalder fatigue scale scores (items scored 0-3 and summed to total of 0-33; lower scores indicate better outcomes)* 20 weeks: 22.78 (8.56) vs. 26.27 (7.68); 70 weeks: 23.90 (8.34) vs. 26.02 (7.11) **Graded exercise vs. usual care vs. supportive listening** Outcomes related to associated symptoms: *HADS-Depression, mean (SD):* 20 weeks: 7.28 (4.02) vs. 8.48 (4.47) vs. 8.85 (4.01) 70 weeks: 7.88 (4.45) vs. 8.06 (4.75) vs. 8.67 (4.51)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Wallman, 2004[76] RCT High	**Graded exercise vs. flexibility/relaxation** Adverse Events: 0 vs. 3% (1/29) felt a little worse after completing treatment Withdrawals due to Adverse Events: NR Serious Adverse Events: NR	NR
Wearden, 2010[77] Wearden, 2012[78] Wearden, 2013[79] FINE Trial Block-randomized and stratified RCT Medium	Adverse Events: Overall: 4 (herpes simplex infection, attempted suicide, bleeding peptic ulcer, and recurrence of cancer; all deemed unrelated to interventions) Withdrawals due to adverse event: Unclear, 2 each in graded exercise and supportive listening withdrew due to nurse therapist or researcher safety concerns, not otherwise described Serious Adverse Events: None reported	United Kingdom Medical Research Council and the United Kingdom Department of Health; and the University of Manchester

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	**Country Number of Centers Study Years Setting (primary care, specialty clinic or other)**	**Diagnostic criteria Inclusion/ Exclusion criteria**	**Interventions (n) Duration of treatment Duration of followup**
Wearden, 1998[80] RCT Medium	England and Wales Single center 1993 to 1995 University department of medicine out-patient clinic	Oxford (Sharpe, 1991) criteria **Inclusion:** Ages ≥ 18 years, meeting Oxford criteria, principle complaint of fatigue lasting six months and exacerbated by exercise, impairment in 3 out of 4 areas of activity. **Exclusion** Medical cause of fatigue; unable to come off of depressants; requiring orthopedic treatment.	**GET + fluoxetine (n=33)**: Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3x/week, with low initial intensity that was gradually increased based on heart rate plus fluoxetine 20 mg daily. **Fluoxetine (n=35)**: Fluoxetine 20 mg daily plus placebo exercise program of being told to keep doing what they were doing, rest when needed, and no other advice. **GET (n=34):** Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3x/week, with low initial intensity that was gradually increased based on heart rate plus placebo drug. **Attention control (n=34):** Placebo drug plus placebo exercise program of being told to keep doing what they were doing, rest when needed, and no other advice. **Duration of treatment:** 26 weeks **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Wearden, 1998[80] RCT Medium	**Overall, GET + fluoxetine vs. GET vs. fluoxetine vs. attention control** Mean age: 38.7, 38.2 vs. 40.4 vs. 38.8 vs. 37.6 years % Female: 71 (97/136), 67 (22/33) vs. 79 (27/34) vs. 77 (27/35) vs. 62 (21/34) Race: NR Duration of fatigue median: 28.0, 29.5 vs. 34.5 vs. 30.5 vs. 22.0 months Severity of symptoms: *Fatigue: Mean (95% CI) Chalder fatigue scale scores (0 to 42, lower scores indicate better health):* 35.9 vs. 33.7 vs. 34.4 vs. 34.0 Comorbidities: NR by group; % overall: Current psychiatric diagnosis: 46 (62/136) Major depression: 10 (14/136) Either dysthymia or a depressive disorder not otherwise specified: 24 (32/136) Various anxiety disorders: 10 (14/136) Somatization disorder: 2 (2/146)	Number enrolled: 136 Number analyzed: ITT: 136 (33 GET + fluoxetine, 34 fluoxetine, 35 GET, 34 attention control) Completed trial: 96 (19 GET + fluoxetine, 23 fluoxetine, 25 GET, 29 attention control)	**Overall:** 29% (40/136) **GET + fluoxetine vs. fluoxetine vs. GET vs. attention control** 42% (14/33) vs. 32% (11/34) vs. 29% (10/35) vs. 17% (5/29)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Wearden, 1998[80] RCT Medium	**GET + fluoxetine vs. GET vs. fluoxetine vs. attention control** Overall Function: *Mean (SD) functional work capacity (amount of O2 consumed in the final minute of exercise per kg of body weight)* 0-12 weeks: 2.2 (1.0 to 3.4) vs. 2.6 (1.0 to 43) vs. 0.4 (-1.2 to 2.0) vs. 0.4 (-0.9 to 1.7) 26 weeks: 2.0 (0.4 to 3.5) vs. 2.8 (0.8 to 4.8) vs. 1.0 (-0.9 to 3.0) vs. -0.1 (-1.7 to 1.6) *Effect of exercise on functional work capacity* Mean change 0-12 weeks: 2.0 (95% CI 0.60 to 3.49), p=0.005 Mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (95% CI) Chalder fatigue scale scores (0 to 42, lower scores indicate better health)* 0-12 weeks: -5.7 (-9.2 to -2.2) vs. -2.1 (-4.9 to 0.6) vs. -1.6 (-4.4 to 1.2) vs. -2.0 (-4.1 to 0.1) 26 weeks: -6.0 (-9.7 to -2.3) vs. -5.7 (-9.5 to -1.9) vs. -3.0 (-5.9 to -0.2) vs. -2.7 (-5.4 to 0.01) *% non-cases of fatigue (Chalder fatigue scale score <4)* 12 weeks: 18 (6/33) vs. 1 (3/34) vs. 1 (3/35) vs. 6 (2/34) 26 weeks: 18 (6/33) vs. 18 (6/34) vs. 6 (2/ 35) vs. 6 (2/34) p=0.025 for exercise interventions combined vs. others *Exercise improved fatigue scale scores* Mean change 0 to12 weeks: 2.1 (95% CI -0.6 to 4.8), p=0.13 Mean change 26 weeks: 2.9 (95% CI -0.2 to 6.1), p=0.07 Outcomes related to associated symptoms: HADS-Depression, mean change (95% CI) at 26 weeks: -2.0 (3.3 to -0.7) vs. -1.2 (-2.5 to 0.2) vs. -1.7 (-3.0 to -0.5) vs. -1.3 (-2.3 to -0.3)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Wearden, 1998[80] RCT Medium	**GET + fluoxetine vs. GET vs. fluoxetine vs. attention control** Adverse Events: Overall unclear, only reported drop-outs due to adverse events Withdrawals due to adverse event: 11 medication side-effects (2 reported with placebo) Serious Adverse Events: NR	Linbury Trust; study drug provided by Eli Lily

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Weatherley-Jones, 2004[81] RCT Medium	United Kingdom 2 centers 1998 to 2000 1 specialty clinic in CFS and 1 in infectious disease	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients over 18 years of age, meeting the Oxford criteria **Exclusion:** Clinically significant abnormalities in full blood count, liver function tests, thyroid stimulating hormone, acute phase protein, urea and electrolytes; protein or sugar in urine; primary major depression; current engagement in individual psychotherapy or counseling; pregnancy; bipolar disorders; psychosis; eating disorders; substance abuse/dependence; somatization disorders; patients already receiving homeopathy or CBT or who had completed a course of homeopathy of CBT for CFS.	**Homeopathy (n=53):** Homeopathic prescriptions (including cacinosin, polycrest remedies, antidotes to specific viruses and vaccinations and bowel nosodes) given after approximately monthly consultations, single remedies prescribed at each consultation, and occasionally >1 remedy; remedies changed throughout, but must be only those remedies which have been proved **Placebo (n=50):** Placebo prescribed in the same manner as homeopathy **Duration of treatment:** 6 months **Duration of followup:** 1 month after end of treatment; 7 months total after randomization

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Weatherley-Jones, 2004[81] RCT Medium	**Homeopathy vs. placebo** Mean age (SD): 38.9 (10.6) vs. 38.8 (11.2) years % Female: 57 (30/53) vs. 62 (31/50) Race: NR Duration of illness: Mean (SD): 4.8 (4.3) vs. 3.7 (2.4) years Severity of symptoms Mean (SD): *Multidimensional fatigue inventory (4-20 scale, lower scores indicate better health)* General fatigue: 18.4 (1.7 vs. 18.1 (2.2) Physical fatigue: 18.0 (2.2) vs. 17.5 (3.1) Mental fatigue: 16.7 (3.7) vs. 16.5 (3.0) Reduced activity: 16.1 (3.1) vs. 13.2 (3.7) Reduced motivation: 13.0 (3.9) vs. 13.2 (3.7) *Fatigue Impact Scale (0-40 scale, lower scores indicate better health)* Cognitive dimension: 24.1 (9.0) vs. 24.2 (8.0) Physical dimension: 27.3 (6.8) s. 27.4 (7.1) *Functional Limitations Profile, a version of the Sickness Impact Profile (scale unclear, higher scores indicate better health)* Physical dimension: 20.4 (14.1) vs. 22.1 (14.9) Psychosocial dimension: 35.1 (14.8) vs. 36.3 (15.0) Comorbidities: NR	Number enrolled: 103 Number analyzed: 86	**Overall:** 11% (11/103) **Homeopathy vs. placebo:** 10% (5/50) vs. 11% (6/53)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Weatherley-Jones, 2004[81] RCT Medium	**Homeopathy vs. placebo** Overall Function: *Mean change from baseline (SD) Functional Limitations Profile scores (scale unclear, higher score indicates better health)* Physical dimension: 5.11 (8.82) vs. 2.72 (8.40), p=0.04 Psychosocial dimension: 9.81 (14.19) vs. 6.76 (10.67); p=0.14 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean change from baseline (SD) MFI-20 scores (4-20 scale, lower score indicates better health); likelihood for improvement (RR, 95% CI)* General fatigue: 2.70 (3.93) vs. 1.35 (2.66); RR 1.67, 95% CI 0.94 to 2.97 Physical fatigue: 2.13 (4.00) vs. 1.28 (2.74); RR 1.42, 95% CI 0.77 to 2.60 Mental fatigue: 2.70 (4.01) vs. 2.05 (2.86); RR 1.25, 95% CI 0.76 to 2.07 Reduced activity: 2.72 (4.47) vs. 1.81 (2.82); RR 1.27, 95% CI 0.75 to 2.15 Reduced motivation: 1.35 (4.15) vs. 1.65 (3.02); RR 0.89, 95% CI 0.53 to 1.50 *Mean change from baseline (SD) FIS (0-40 scale for each subscale, except 0-80 scale for social subscale, lower score indicates better health)* Cognitive dimension: 4.88 (9.3) vs. 4.21 (7.18); p=0.61 Physical dimension: 4.98 (8.5) vs. 5.30 (6.69); p=0.98 Social dimension: 7.92 (18.02) vs. 8.20 (14.06); p=0.79 Outcomes related to associated symptoms: NR Likelihood of improvement on MFI-20: General fatigue

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Weatherley-Jones, 2004[81] RCT Medium	**Homeopathy vs. placebo** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Linbury Trust grant

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
White, 2011[82] White, 2013[83] Dougall, 2014[84] PACE Trial RCT Medium	United Kingdom 6 centers 2005 to 2010 Specialist CFS clinics	Oxford (Sharpe, 1991) criteria **Inclusion:** Bimodal score of ≥6 out of 11 on Chalder fatigue scale and score of ≤60 on SF-36 physical function subscale (after 11 months this was changed to ≤65). **Exclusion:** Ages <18 years, at significant risk of self-harm, unable to attend hospital appointments, unable to speak and read English, had medical needs that made participation inappropriate, had previously received a trial treatment for their present illness at a PACE trial clinic.	**Adaptive pacing therapy + specialist medical care (APT) (n=160):** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual adaptive pacing therapy with the aim of achieving optimum adaptation to the illness, this was done by helping the participant to plan and pace activity to reduce or avoid fatigue, achieve prioritized activities and provide the best conditions for natural recovery. Strategies consisted of: identifying links between activity and fatigue; encouragement to plan activity to avoid exacerbation; developing awareness of early warnings of exacerbation; limiting demands and stress; regularly planning rest and relaxation; and alternating different types of activities; with advice not to undertake activities that demand >70% of participant's perceived energy envelopes. **Cognitive behavioral therapy + specialist medical care (CBT) (n=161):** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual CBT with the aim of changing the behavioral and cognitive factors assumed to be responsible for perpetuation of the participant's symptoms and disability. Strategies guided participants to address unhelpful cognitions, including fears about symptoms or activity by testing them in behavioral experiments, consisting of gradual increases in both physical and mental activity. **Graded exercise + specialist medical care (GET) (n=160):** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual GET with the aim of helping the participant gradually return to appropriate physical activities, reverse the deconditioning, and thereby reduce fatigue and disability. Strategies consisted of establishment of baseline achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active; target heart rate ranges set when necessary to avoid overexertion; which aimed at 30 minutes of light exercise 5 times a week; with mutually agreed upon gradual increases in intensity and aerobic nature of exercises. The most commonly chosen exercise was walking. **Control (n=160):** Specialist medical care (SMC), consisting of information about chronic fatigue syndrome, generic advice, and symptomatic pharmacology. **Duration of treatment:** 23 weeks **Duration of followup:** 12 months

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
White, 2011[82] White, 2013[83] Dougall, 2014[84] PACE Trial RCT Medium	**APT vs. CBT vs. GET vs. control** Mean age (SD): 39 (11) vs. 39 (12) vs. 39 (12) vs. 37 (11) years % Female: 76 (121/159) vs. 80 (129/161) vs. 77 (123/160) vs. 76 (122/160) % White: 92 (146/159) vs. 94 (151/161) vs. 93 (148/160) vs. 94 (150/160) Duration of illness: Median (IQR): 33 (16 to 69) vs. 36 (16 to 104) vs. 35 (18 to 67) vs. 25 (15 to 57) months Severity of symptoms: *Mean (SD) Chalder fatigue scale scores (0 to 33 scale, lower scores indicate better health*: 28.5 (4) vs. 27.7 (3.7) vs. 28.2 (3.8) vs. 28.3 (3.6) *Mean (SD) SF-36 physical functioning subscale scores (0 to 100 scale, higher scores indicate better health)*: 37.2 (16.9) vs. 39.0 (15.3) vs. 36.7 (15.4) vs. 39.2 (15.4) Comorbidities: % Any depressive disorder: 35 (55/159) vs. 34 (55/161) vs. 34 (54/160) vs. 34 (55/160) % Any psychiatric disorder: 47 (75/159) vs. 47 (75/161) vs. 46 (73/160) vs. 48 (77/160)	Number enrolled: 641 (160 APT, 161 CBT, 160 GET, 160 control) Number analyzed: 630 (159 APT, 155 CBT, 159 GET, 157 control)	**Overall:** 1.7% (11/641) **APT vs. CBT vs. GET vs. control:** 0.6% (1/160) vs. 3.7% (6/161) vs. 0.6% (1/160) vs. 1.9% (3/160)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
White, 2011[82] White, 2013[83] Dougall, 2014[84] PACE Trial RCT Medium	**APT vs. CBT vs. GET vs. control** Overall Function: *Mean (SD) SF-36 physical functioning subscale scores (0 to 100 scale, higher scores indicate better health)* 12 weeks: 41.7 (19.9) vs. 51.0 (20.7) vs. 48.1 (21.6) vs. 46.6 (20.4) 24 weeks: 43.2 (21.4) vs. 54.2 (21.6) vs. 55.4 (23.3) vs. 48.4 (23.1) 52 weeks: 45.9 (24.9) vs. 58.2 (24.1) vs. 57.7 (26.5) vs. 50.8 (24.7) Mean difference from control at 52 weeks: APT: -3.4 (-8.4 to 1.6) p=NS; CBT: 7.1 (2.0 to 12.1) p=0.0068; GET: 9.4 (4.4 to 14.4) p=0.0005 Mean difference from APT at 52 weeks: CBT: 10.5 (5.4 to 15.6) p=0.0002; GET: 12.8 (7.7 to 17.9) p<0.0001 % Improved from baseline (by ≥8 points): 49 (75/153) vs. 71 (105/148) vs. 70 (108/154) vs. 58 (88/152) % Within normal range (score ≥60): 35 (53/153) vs. 52 (77/148) vs. 53 (81/154) vs. 41 (62/152) *Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)* 52 weeks: 24.5 (8.8) vs. 21.0 (9.6) vs. 20.5 (9.4) vs. 23.9 (9.2); p=0.0001 for CBT vs. control p=0.0006 for GET vs. control; p=0.0001 for CBT vs. APT; p=0.0004 for GET vs. APT Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Mean (SD) Chalder fatigue scale scores (0 to 33 scale, lower scores indicate better health)* 12 weeks: 24.2 (6.4) vs. 23.6 (6.5) vs. 22.8 (7.5) vs. 24.3 (6.5) 24 weeks: 23.7 (6.9) vs. 21.5 (7.8) vs. 21.7 (7.1) vs. 24.0 (6.9) 52 weeks: 23.1 (7.3) vs. 20.3 (8.0) vs. 20.6 (7.5) vs. 23.8 (6.6) Mean difference (95% CI) from control at 52 weeks: APT: -0.7 (-2.3 to 0.9) p=NS; CBT: -3.4 (-5.0 to -1.8) p=0.0001; GET: -3.2 (-4.8 to -1.7) p=0.0003 Mean difference (95% CI) from APT at 52 weeks: CBT: -2.7 (-4.4 to -1.1) p=0.0027; GET: -2.5 (-4.2 to -0.9) p=0.0059 % Improved from baseline (by ≥2 points): 65 (99/153) vs. 76 (113/148) vs. 80 (123/154) vs. 65 (98/152) % Within normal range (score ≤18): 22 (34/153) vs. 41 (60/148) vs. 33 (51/154) vs. 21 (32/152) Depression: HADS-Depression, mean (SD) 52 weeks: 7.2 (4.5) vs. 6.2 (3.7) vs. 6.1 (4.1) vs. 7.2 (4.7); CBT vs. control: p=0.0003; GET vs. control: p=0.0035; CBT vs. APT: p=0.382, GET vs. APT: p=0.23

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
White, 2011[82] White, 2013[83] Dougall, 2014[84] PACE Trial RCT Medium	*Outcomes related to associated symptoms: Patients with self-rated CGI changes* *12 weeks % Positive change: 13 (20/153) vs. 21 (32/153) vs. 25 (37/151) vs. 5 (7/151)* *12 weeks % Minimum change: 82 (126/159) vs. 74 (113/161) vs. 74 (111/151) vs. 88 (133/160)* *12 weeks % Negative change: 5 (7/153) vs. 5 (8/153) vs. 2 (3/151) vs. 7 (11/151)* *24 weeks % Positive change: 24 (37/155) vs. 38 (56/149) vs. 37 (54/148) vs. 19 (28/151)* *24 weeks % Minimum change: 72 (111/155) vs. 55 (82/149) vs. 60 (89/148) vs. 71 (107/151)* *24 weeks % Negative change: 5 (7/155) vs. 7 (11/149) vs. 3 (5/148) vs. 11 (16/151)* *52 weeks % Positive change: 31 (47/153) vs. 41 (61/147) vs. 41 (62/152) vs. 25 (38/152)* *52 weeks % Minimum change: 63 (96/153) vs. 52 (77/147) vs. 53 (80/152) vs. 66 (100/152)* *52 weeks % Negative change: 7 (10/153) vs. 6 (9/147) vs. 7 (10/152) vs. 9 (14/152)* *OR (95% CI) positive change vs. negative change* *Compared with control: 1.3 (0.8 to 2.1) p=NS vs. 2.2 (1.2 to 3.9) p=0.011 vs. 2.0 (1.2 to 3.5) p=0.013 vs. NR* *Compared with APT: NR vs. 1.7 (1.0 to 2.7) p=0.034 vs. 1.5 (1.0 to 2.3) p=0.028 vs. NR* *Recovery based on different criteria at 52 weeks* % Within the normal range on both the Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60): 16 (25/153) vs. 30 (44/148) vs. 28 (43/154) vs. 15 (22/152) % No longer meeting case definitions CDC (Fukuda, 1994) criteria: 49 (74/150) vs. 67 (97/144) vs. 65 (93/144) vs. 51 (76/149) Oxford (Sharpe, 1991) criteria: 43 (64/149) vs. 54 (77/143) vs. 56 (81/144) vs. 41 (62/150) London ME criteria: 68 (100/147) vs. 76 (107/140) vs. 77 (106/138) vs. 66 (97/148) *Cumulative criteria for recovery at 52 weeks* Normal range on both Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60), and not meeting Oxford (Sharpe, 1991) criteria: 15 (23/149) vs. 28 (40/143) vs. 28 (41/144) vs. 14 (21/150) Normal range on both Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60), not meeting Oxford (Sharpe, 1991) criteria, and CGI of very much better or much better (this cumulative criteria considered meeting "trial recovery criteria"): 8 (12/149) vs. 22 (32/143) vs. 22 (32/143) vs. 7 (11/150) *Meeting "trial recovery criteria" in subgroups meeting alternate definitions of CFS or ME at baseline* CDC (Fukuda, 1994) criteria: 9 (9/102) vs. 19 (17/89) vs. 22 (20/93) vs. 6 (6/98) London ME criteria: 11 (8/75) vs. 21 (15/70) vs. 21 (16/75) vs. 10 (7/73) OR (95% CI) for composite "trial recovery" CBT vs. APT: 3.36 (1.64 to 6.88); p=0.001 CBT vs. control: 3.69 (1.77 to 7.69); p<0.001 GET vs. APT: 3.38 (1.65 to 6.93); p=0.001 GET vs. control: 3.71 (1.78 to 7.74); p<0.001 APT vs. control: 1.10 (0.47 to 2.58); p=NS

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
White, 2011[82] White, 2013[83] Dougall, 2014[84] PACE Trial RCT Medium	**APT vs. CBT vs. GET vs. control** Adverse Events: % With ≥1 non-serious adverse event‡: 96 (152/159) vs. 89 (143/161) vs. 93 (149/160) vs. 93 (149/160); p=NS Number of non-serious adverse events‡: 949 vs. 848 vs. 992 vs. 977, p=0.0081 for CBT vs. APT and p=0.0016 for CBT vs. control Median (quartiles) non-serious adverse events‡ per person-year: 4 (2, 9) vs. 4 (2, 7) vs. 5 (2, 8) vs. 4 (3, 8); p=NS % with physical function worse: 25 (39/159) vs. 9 (15/161) vs. 11 (18/160) vs. 18 (28/160); p=0.0007 % with worse fatigue: 13 (21/159) vs. 9 (14/161) vs. 7 (11/160) vs. 14 (22/160); p=NS % with worse function and fatigue: 7 (11/159) vs. 2 (4/161) vs. 3 (5/160) vs. 5 (8/160); p=NS Withdrawals due to adverse event: % Withdrawn due to worsening: 2 (3/159) vs. 0 vs. 1 (2/160) vs. <1 (1/160) Serious Adverse Events: % With ≥1 SAE*: 9 (15/159) vs. 4 (7/161) vs. 8 (13/160) vs. 4 (7/160); p=NS Number of serious adverse events: 16 vs. 8 vs. 17 vs. 7, p=0.0433 for GET vs. control SAEs per 100 person-years (95% CI): 10.1 (5.8 to 16.3) vs. 5.0 (2.2 to 9.8) vs. 10.6 (6.2 to 17.0) vs. 4.4 (1.8 to 9.0) % With ≥1 serious adverse reactions†: 1 (2/159) vs. 2 (3/161) vs. 1 (2/160) vs. 1 (2/160); p=NS Number of serious adverse reactions†: 2 vs. 4 vs. 2 vs. 2 Serious adverse reactions† per 100 person-years (95% CI): 1.3 (0.2 to 4.5) vs. 2.5 (0.7 to 6.4) vs. 1.3 (0.2 to 4.5) vs. 1.3 (0.2 to 4.5) *Serious adverse events were defined in the PACE trial as an event that resulted in one of the following outcomes: a) death, b) threat to life (i.e., an immediate, not hypothetical, risk of death at the time of the event), c) required hospitalization except for elective treatment of a pre-existing condition, d) increased severity and persistent disability, defined as: (i) severe, i.e. significant deterioration in the participant's ability to carry out their important activities of daily living (e.g. employed person no longer able to work, caregiver no longer able to give care, ambulant participant becoming bed bound); and (ii) symptom and disability persistent, i.e. of at least 4 weeks continuous duration, e) any other important medical condition which, though not included in the above, might require medical or surgical intervention to prevent one of the outcomes listed, and f) any episode of deliberate self-harm. †Serious adverse reactions were considered in the PACE trial to be a reaction to one of the supplementary therapies or a drug prescribed as part of usual care. ‡Non-serious adverse events were defined in the PACE trial as 'any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial.'	United Kingdom Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Wiborg, 2015[85] RCT Medium	The Netherlands Single center 2008 to 2011 Outpatient clinic	CDC (Fukuda, 1994) criteria **Inclusion:** ≥18 years of age, referred to clinic for management of chronic fatigue, willing to receive group therapy. **Exclusion:** In a dispute over a disability pension, already undergoing CBT treatment, clinical reason for exclusion (i.e. they received specifically tailored interventions because they were unsuccessfully treated with CBT for CFS outside the study clinic, or were between 18 and 21 years of age and the family had to be involved in the therapy)	**CBT 8/2 (n=68):** Cognitive behavioral therapy in a group of 8 patients and 2 therapists. 14 2-hour group sessions over 6 months. Topics covered included personal goal setting, fixing sleep-wake cycles, reducing the focus on bodily symptoms, a systematic challenge of fatigue-related beliefs, regulation and gradual increase in activities, and accomplishment of personal goals. Patients were encouraged to give feedback to fellow participants. **CBT 4/1 (n=68):** Cognitive behavioral therapy in a group of 4 patients and 1 therapist. 14 2-hour group sessions over 6 months with same topics as those listed above. **Wait list (n=68):** Wait list for individual CBT **Duration of treatment:** 6 months **Duration of followup:** End of treatment
Williams, 2002[86] Crossover RCT Medium	United Kingdom Number of centers unclear Study year(s) NR University hospital	Oxford (Sharpe, 1991) Criteria **Inclusion:** Patients diagnosed with CFS by the Oxford criteria **Exclusion:** Anemia, inadequately replaced hypothyroidism, various reasons including diagnostic uncertainty and reluctance to meet the practical demands of the protocol.	**Melatonin (n=42):** Oral melatonin 5 mg daily **Phototherapy (n=42):** Phototherapy with 2500 Lux lightbox 30 minutes in morning **Duration of treatment:** 60 weeks: 12 weeks placebo, 12 weeks treatment, 12-week washout or placebo, then 12-week crossover and 12-week washout or placebo **Duration of followup:** End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Wiborg, 2015[85] RCT Medium	**CBT 8/2 vs. CBT 4/1 vs. wait list** Mean age: 36.4 vs. 39.9 vs. 37.3 % Female: 75 (51/68) vs. 74 (50/68) vs. 82 (56/68) Duration of illness, mean (SD): 8.6 (9.5) vs. 7.6 (9.7) vs. 10.0 (10.6) years Severity of symptoms: Mean CIS fatigue severity, (SD): 51.4 (4.8) vs. 50.5 (4.5) vs. 49.9 (4.8) Comorbidities: NR	Number enrolled: 204 Number analyzed: 204	**Overall:** 17% (34/204) **CBT 8/2 vs. CBT 4/1 vs. wait list:** 15% (10/68) vs. 24% (16/68) vs. 12% (8/68)
Williams, 2002[86] Crossover RCT Medium	Overall, for those completing study Mean age (SD): 44.5 (11.1) years % Female: 57 (17/30) Race: NR Duration of illness: Mean (SD): 3.6 (3.3) years Severity of symptoms: NR Comorbidities: NR	Number enrolled: 42 Number analyzed: 30	**Overall:** 29% (12/42) **Melatonin first vs. phototherapy first:** 27% (6/22) vs. 30% (6/20)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Wiborg, 2015[85] RCT Medium	**CBT 8/2 plus CBT 4/1 vs. wait list** Overall Function: Mean physical functioning (SD): 747.7 (22.0) vs. 63.3 (21.1), treatment effect 14.1 (95% CI, 9.0 to 19.3), p<0.001 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: Mean fatigue severity (SD): 33.5 (13.6) vs. 46.6 (8.5), treatment effect -13.8 (95% CI, -17.2 to -10.3), p<0.001 Improvement in fatigue severity: 49.3% (67/139) vs. 8.8% (6/68), OR 10.0 (95 CI, 4.1 to 24.8), p<0.001 Normal functioning in fatigue severity: 32.4% (44/136) vs. 2.9% (2/68), OR 15.8 (95% CI, 3.7 to 67.4), p<0.001 Outcomes related to associated symptoms: Mean overall impairment (SD): 800 (664) vs. 1,389 (561), treatment effect -623 (95% CI, -788 to -458), p<0.001 Mean psychological distress (SD): 135 (32.0) vs. 153 (38.5), treatment effect -22.1 (95% CI, -29.9 to -14.4), p<0.001
Williams, 2002[86] Crossover RCT Medium	**Melatonin vs. phototherapy** Overall Function: *Median (IQR) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)* After treatment: 42.5 (16.3 to 53.8) vs. 45 (22.5 to 60.0); p=NS Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Median (IQR) visual analog scale score for How fatigued are you? (1-10 scale, lower score indicates better health)* After treatment: 6.1 (4.8 to 8.0) vs. 7.2 (5.5 to 8.3); p=NS *Median (IQR) Mental Fatigue Inventory scores (0-36 scale, lower score indicates better health)* After treatment: 23 (15.0 to 27.0) vs. 24 (21.0 to 29.0); p=NS *Median (IQR) SF-36 vitality subscale scores (0-100 scale, lower score indicates better health)* After treatment: 20 (10.0 to 40.0) vs. 20 (10.0 to 25.0); p=NS Outcomes related to associated symptoms: NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Wiborg, 2015[85] RCT Medium	**CBT 8/2 vs. CBT 4/1 vs. wait list** Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NR
Williams, 2002[86] Crossover RCT Medium	**Melatonin vs. phototherapy** Adverse Events: NR Withdrawals due to adverse event: None Serious Adverse Events: NR	Linbury Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Windthorst, 2017[87] Pilot RCT High	Germany Single center Study year(s) NR Outpatient treatment center	CDC (Fukuda, 1994) criteria **Inclusion:** Females currently diagnosed with CFS meeting CDC criteria. **Exclusion:** Somatic or medical conditions explaining fatigue, substance abuse, primary psychiatric disorder, ongoing psychotherapy or activation program, BMI <18.5 or >35.	**Graded exercise (n=15):** 8 50-minute sessions consisting of 20 to 30 minutes of slow walking adapted to a heart rate at 70% of individual anaerobic threshold, discussion of diary, and review of session. Patients were encouraged to reduce resting and avoiding behavior, but simultaneously to watch carefully for symptoms and feelings of overload. Homework was 2 to 3 20 to 30-minute walking sessions per week at home, controlled by a pulse watch. **Heartrate variability biofeedback therapy (n=13):** 8 50-minute sessions consisting of 20 to 30 minutes of heartrate variability biofeedback therapy, discussion of diary, and review of biofeedback results. Homework was twice daily 5 to 10-minute practice sessions without the biofeedback device. Participants in both groups kept a daily diary of fatigue intensity, activity, and individual training at home. First session for both groups was introductory only, with no treatment administered. **Duration of treatment:** 8 weeks **Duration of followup:** 5 months
Wright, 2005[88] High	United Kingdom Single center Unclear study dates Specialty clinic	Oxford criteria, modified for children with three months fatigue Excluded other fatiguing medical conditions, and pre-existing ongoing CFS treatment	**Pacing (n=6)**: pacing activity to the changing needs and responses of the body, managing energy within an overall limit, resting when necessary, avoiding physically and/or emotionally stressful situations until ready, tailoring return to school to the needs of the young person **STAIRway to Health programme (n=7)**: structured tailored incremental rehabilitation program. Provided holistic understanding of CFS, explaining vicious cycles that exacerbate illness, bolstering adaptive coping strategies. Tailored gradual return to school and normal social activity. Treatment duration of 1 year: weekly for 1 month, every 2 weeks for three months, every 3 weeks for two months, every 4 weeks for six months

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Windthorst, 2017[87] Pilot RCT High	**Graded vs. heartrate variability biofeedback therapy** Mean age: 50.0 vs. 51.4 100% female Duration of illness: >2 years: 100% vs. 84.5% (11/13) >1 year: 0 vs. 7.7% (1/13) 6 months: 0 vs. 7.7% (1/13) Severity of symptoms: *German Multidimensional Fatigue Inventory total, range 20 to 100, with lower scores indicating better health:* 68.8 vs. 61.5, p=NS Comorbidities: NR	Number enrolled: 28 Number analyzed: 24 (11 graded exercise training, 13 biofeedback therapy)	**Overall:** 29% (8/28) **Graded exercise vs. heartrate variability biofeedback therapy:** NR
Wright, 2005[88] High	Age: 0 to 11: 1; 12 to 14: 7; 15 to 19: 5 % Female: 62% Race: NR Duration of illness, median months: 14.5 vs. 12.0	Enrolled: 13 Analyzed: 11	15%

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Windthorst, 2017[87] Pilot RCT High	**Graded exercise vs. heartrate variability biofeedback therapy** Overall Function: SF-36 Physical mean score (SD): after treatment: 44.8 (9.7) SES=0.92 vs. 45.2 (9.9) SES=0.28 5 month follow up: 46.6 (7.1) SES=1.14 vs. 47.1 (12.2) SES=0.49 SF-36 Mental mean score (SD): after treatment: 41.7 (10.9) SES=0.06 vs. 48.6 (9.0) SES=0.50 5 month follow up: 38.3 (15.3) SES=0.30 vs. 51.0 (8.9) SES=0.73 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: *Multidimensional Fatigue Inventory total (SD), range 20 to 100, with lower scores indicating better health:* Outcomes related to associated symptoms: after treatment: 56.6 (18.8) SES=1.21 vs. 48.2 (15.9) SES=1.37 5 month follow up: 55.6 (21.3) SES=1.31 vs. 43.6 (15.9) SES=1.84 Depression: PHQ-9 baseline vs. after treatment vs. 5 month follow up: GET: 8.9 (5.4) vs. 8.3 (4.6) vs. 8.8 (6.0), p=0.656 Biofeedback: 7.5 (3.1) vs. 4.3 (3.0) vs. 4.2 (3.1), p=0.006
Wright, 2005[88] High	Differences, with all showing improvement in STAIRway arm than pacing arm: Child Health Questionnaire (1 = excellent, 5 = poor): 21.8 (20.94 to 22.74); F=23.4; p= 0.002 School attendance comparing six months prior to study to last six months of treatment (percentage): 45.1 (21.8 to 92.0); F= 4.9; p= 0.057 School attendance comparing six months prior to study to six months post study (percentage): 56.1 (6.3 to 105.7); F=6.8; p= 0.032 Difficulty doing highly exertional activities (child rated) (0-4, 4 being fully healthy): 1.46 (20.33 to 3.25); F= 3.7; p= 0.095 Difficulty doing moderately exertional activities such as swimming (0-4, 4 being fully healthy): 1.56 (20.20 to 2.33); F=4.4; p= 0.075 Difficulty walking and climbing several flights of stairs (0-4, 4 being fully healthy): 0.93 (0.02 to 1.84); F= 5.8; p= 0.046 Difficulty climbing one flight of stairs (0-4, 4 being fully healthy): 0.71 (20.18 to 1.61); F= 3.5; p= 0.10 Difficulty getting in and out of bed (0-4, 4 being fully healthy): 0.31 (20.17 to 0.78); F= 2.4; p= 0.17 Young Person Functional Ability Scale (percentage score rated by pediatrician): 17.0 (217.0 to 51.0) F=1.3; p= 0.28 HADS Anxiety (0–21 child rated): 21.60 (28.31 to 5.10); F= 0.30; p= 0.60 Birleson Depression Rating Scale (0–36): 22.99 (210.0 to 4.06); F= 1.0; p= 0.36 Fatigue score (Chalder 0 to 42 14 item version): 25.2 (219.8 to 9.49); F= 0.67; p= 0.44

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Windthorst, 2017[87] Pilot RCT High	**Graded exercise vs. heartrate variability biofeedback therapy** Adverse Events: 1 increased appetite and weight gain in graded exercise therapy 1 change in daily routine and role perception in biofeedback therapy, 1 stress from conversations about symptoms and individual issues, 1 development of a depressive episode due to external individual reasons in graded exercise therapy group Withdrawals due to adverse events: NR Serious Adverse Events: NR	Alfred-Teufel Foundation
Wright, 2005[88] High	NR	NR

Note: Refer to Appendix G for abbreviations and acronyms.

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Al-Haggar, 2006[8]	Yes	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Yes	Yes	Yes	High
Arnold, 2015[9]	Unclear	Unclear	Yes, except for social functioning, mental health and emotional scores	Unclear	Unclear	Yes	Yes	No/No	No	No	Yes	Medium
Blacker, 2004[10]	Yes	NR	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	No	Yes	Medium
Blockmans, 2003[11]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	No	Yes	Yes	Medium
Burgess, 2012[13]	Yes	Yes	Yes	No	No	No	Yes	Yes/Yes	Yes	No	Yes	Medium
Chalder, 2010[14]	Yes	Yes	No	No	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Chan, 2013[16] Ho, 2012[17]	Yes	Unclear	Yes	No	No	No	Yes	No/Yes	Yes	No	Yes	Medium
Clark, 2017[18]	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium
Crawley, 2019[19]	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium
Deale, 1997[20] Deale, 2001[21]	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	No	Yes	Medium
Dybwad, 2007[22]	Yes	Yes	No, duration of illness	Yes ("testing person")	No	No	Yes	No/No	Yes	No	Yes	Medium
Fluge, 2011[23]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	No	No	Yes	Medium
Fluge, 2019[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	No	Yes	Low
Friedberg, 2016[25]	Yes	Unclear	Yes	Unclear	No	No	Yes	No/No	Yes	Yes	Yes	Medium
Fulcher, 1997[26]	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Hobday, 2008[27]	Yes	No	Yes	No, outcome assessors were not blinded. Data analysts were	No	No	Yes	Yes	No	Yes	Yes	High
Huanan, 2017[28]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Medium
Janse, 2018[29]	Yes	Unclear	Yes	Yes	No	No	Yes	No/No	Yes	No	Yes	Medium
Jason, 2007[30] Hlavaty, 2011[32] Jason, 2009[31]	Yes	Unclear	Yes	Unclear	No	No	No	Unclear	Yes	No	Yes	Medium
Knoop, 2008[33] Tummers, 2010[34] Tummers, 2013[35]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	Medium
Li, 2015[36]	NR	NR	Yes	No	No	No	Yes	No/No	No	No	Yes	High
Lopez, 2011[37]	Unclear	Unclear	Unclear	Unclear	No	No	Yes	No/No	Yes	No	Yes	High
Malaguarnera, 2008[38]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	Yes	Medium
McKenzie, 1998[39] McKenzie, 2000[40]	Yes	NR	Yes	Unclear	Unclear	Yes	Yes	No	Unclear	No	Yes	Medium
Montoya, 2013[41]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No/No	Yes	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Montoya, 2018[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No 27% (37/135)/Yes 34% (26/67) vs. 21% (14/68)	No	Yes	Yes	Medium
Moss-Morris, 2005[43]	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium
Nijhof, 2012[44] Nijhof, 2013[45] Crawley, 2012[46]	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	No	Yes	Medium
Ockerman, 2000[47]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Yes	No	Yes	High
O'Dowd, 2006[48]	Unclear	Yes	No (sex)	Yes	No	No	Yes	No/No	Yes	No	Yes	Medium
Oka, 2014[49]	Yes	Yes	Yes	No	No	No	Yes	No/No	Unclear	No	Yes	Medium
Ostojic, 2016[50]	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	High
Peterson, 1990[51]	Yes	Yes	Yes, except for age	Yes	Unclear	Yes	Yes	No/No	Yes	No	Yes	Medium
Pinxsterhuis, 2017[52]	Yes	Unclear	Yes	Yes	No	No	Yes	No/No	No	No	Yes	Medium
Powell, 2001[53] Bentall, 2002[54] Powell, 2004[55]	Yes	Yes	Yes	Unclear	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Rimes, 2013[56]	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes/No	Yes	No	Yes	High
Roerink, 2017[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Low
Rowe, 1997[58]	Unclear	Unclear	Yes, except for sex	Yes	Unclear	Yes	Yes	No	No	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
See, 1996[59]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Unclear	Unclear	Yes	High
Sharpe, 1996[61]	Yes	Yes	Yes	Unclear	Unclear	No	No	No/No	Yes	No	Yes	Medium
Strayer, 2012[63]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	No	Yes	Medium
Strayer, 1994[62]	Unclear	Yes	Yes, except for sex	Yes	Unclear	Yes	Yes	No	No	No	Yes	Medium
Stubhaug, 2008[64]	Yes	Unclear	Yes	Yes	Yes (to medication only)	Yes (to medication only)	Yes (to medication only)	Yes/Yes	Yes	No	Yes	Medium
Stulemeijer, 2005[65]	Yes	Yes	Yes	No	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Sulheim, 2014[66]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No	No; 20% of randomized subjects did not fulfill all criteria	No	Yes	Medium
Surawy, 2005[67]	Unclear	Unclear	Unclear	Unclear	No	No	Yes	No/No	Yes	No	Yes	High
Sutcliffe, 2010[68]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	No	Yes	Medium
Taylor, 2004[69]	Yes	Unclear	Yes	No	No	No	No	Unclear	Yes	No	Yes	Medium
The, 2007[70]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Medium
Tummers, 2012[71]	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	No	Yes	Medium
Vercoulen, 1996[72]	Unclear	Unclear	Yes, except for sex	NA	Yes	Yes	Yes	No	No	No	Yes	Medium
Vermeulen, 2004[73]	Yes	Yes	Yes	Unclear	No	No	Yes	No	Yes	No	Yes	Medium
Vollmer-Conna, 1997[74]	Yes	Unclear	Yes, except for POMS-fatigue	Unclear	Unclear	Yes	Yes	No	Yes	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Walach, 2008[75]	Yes	Yes	Yes	Yes	Yes	50%, by design	Yes	No	Yes	No	Yes	Low
Wallman, 2004[76]	Unclear	Unclear	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	High
Wearden, 1998[80]	Yes	Unclear	Yes	Unclear	Unclear	Partial (to medication)	Yes	No/No	Yes	No	Yes	Medium
Wearden, 2010[77] Wearden, 2012[78] Wearden, 2013[79]	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Yes	No	Yes	Medium
Weatherley-Jones 2004[81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Medium
White, 2011[82] White, 2013[83] Dougall, 2014[84] Bourke, 2014[12]	Yes	Yes	Yes	Partial (statistician)	No	No	Yes	No/No	Yes	No	Yes	Medium
Wiborg, 2015[85]	Yes	Yes	Yes	No	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Williams, 2002[86]	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	Medium
Windthorst, 2017[87]	Unclear	Unclear	Yes	Unclear	No	No	Yes	No	No	No	Yes	High
Wright, 2005[88]	Unclear	Yes	Yes	Yes	No	No	No	Unclear	Yes	No	Yes	High

Note: Refer to Appendix G for abbreviations and acronyms.

Appendix G. Abbreviations and Acronyms

Abbreviation	Definition
ACT	anaerobic activity therapy
ADL	activities of daily living
AHRQ	Agency for Healthcare Research and Quality
AMD	adjusted mean difference
ANOVA	analysis of variance
AP	anteroposterior
APT	adaptive pacing therapy
ARD	adjusted risk difference
BMI	body mass index
CBT	cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CDs	compact discs
CFS	chronic fatigue syndrome
CGI	Clinical Global Impression of Change
CGS-S	Clinical Global Impression Severity Score
CHQ-CF	child health questionnaire-child form
CI	confidence interval
CIBEROBN	Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion
CIS	checklist individual strength
CNS	central nervous system
COG	cognitive therapy
COPD	Chronic Obstructive Pulmonary Disease
DF	degrees of freedom
DSM-III-R	Diagnostic Statistical Manual third edition revised
DSM-IV	Diagnostic Statistical Manual IV
EPC	Evidence-based Practice Center
ESS	Epworth Sleepiness Scale
FDA	U.S. Food and Drug Administration
FINE	Fatigue Intervention by Nurses Evaluation
FIQ	Fibromyalgia Impact Questionnaire
FIS	Fatigue Impact Scale
FITNET	fatigue in teenagers on the internet
FSM	fatigue self-management
FSM:ACT	fatigue self-management with web diaries and actigraphs
FSM:CTR	fatigue self-management with paper diaries and step counters
FSS	fatigue severity scale
GAA	guadidinoacetic acid
GES	guided graded exercise self-help
GET	graded exercise therapy
GETSET	guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome
GHQ	general health questionnaire
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-anxiety
HADS-D	Hospital Anxiety and Depression Scale-depression
HHV-6	human herpes virus-6
HRSD	Hamilton Rating Scale
HTA	Health Technology Assessment
iCBT	internet-based cognitive-behavioral therapy
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10th revision

Appendix G. Abbreviations and Acronyms

IGF1	insulin-like growth factor-1
IGFBP3	insulin like growth factor binding protein 3
IgG	immunoglobulin G
IOM	Institute of Medicine
IQR	interquartile range
ITT	intention to treat
IV	intravenous
KFSS	Krupp Fatigue Severity Scale
KPS	Karnofsky Performance Scale
MBCT	mindfulness-based cognitive therapy
MCT	multi convergent therapy
MD	mean difference
MDD	major depressive disorder
ME	myalgic encephalomyelitis
MFI	Multidimensional Fatigue Inventory
M-H	Mantel-Haenszel test
MOS	Medical Outcome Study
MRI	magnetic resonance imaging
NAFKAM	Norway's National Research Center in Complementary and Alternative Medicine
NH&MRC	National Health and Medical Research Council
NHS	National Health Service
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NNT	number needed to treat
NR	not reported
NS	not significant
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PACE	pacing, graded activity, cognitive behavior therapy
PF	physical function
PHQ	patient health questionnaire
PICOTS	populations, interventions, comparators, outcomes, timing, and setting/study design
POMS	profile of mood states
QLI	quality of life index
QLS	quality of life score
QOL	Quality of Life
QOLI	quality of life inventory
QOL-SF	quality of life short form
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SCL-90-R	symptom checklist 90-revised
SD	standard deviation
SE	standard error
SEID	systemic exertion intolerance disease
SEM	standard error of the mean
SES	standardized effect sizes
SF-12	12-item Short Form Health Survey
SF-36	36-item Short Form Health Survey
SGR	support the activities of research groups

Appendix G. Abbreviations and Acronyms

SIP	Sickness Impact Profile
SIP-8	Sickness Impact Profile 8-item
SMC	specialist medical care
SMD	standardized mean difference
SOE	strength of evidence
SSRI	selective serotonin reuptake inhibitor
VAS	visual analogue scale
WMD	weighted mean difference
ZonMW	ZorgOnderzoek Nederland and Medische wetenschappen

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