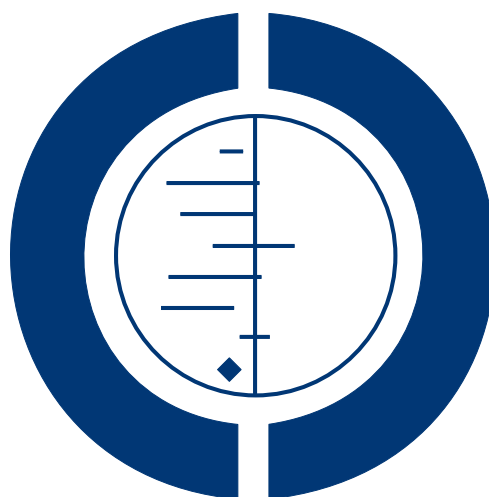


Exercise therapy for chronic fatigue syndrome (individual patient data) (Protocol)

Larun L, Odgaard-Jensen J, Brurberg KG, Chalder T, Dybwad M, Moss-Morris RE, Sharpe M, Wallman K, Wearden A, White PD, Glasziou PP



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Exercise therapy for chronic fatigue syndrome (individual patient data)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of exercise therapy, alone and in combination, for people with chronic fatigue syndrome (CFS) compared with treatment as usual control conditions and other interventions (psychological therapies, pharmacological treatment).

BACKGROUND

Description of the condition

Chronic fatigue syndrome (CFS) is an illness characterised by persistent, medically-unexplained fatigue, which is severe enough to result in substantial disability. Fatigue is usually accompanied by other symptoms such as musculoskeletal pain, sleep disturbance, headaches, and impaired concentration and short-term memory (Fukuda 1994; Prins 2006; Sharpe 1991). Some authors believe that myalgic encephalomyelitis (ME) is a separate condi-

tion (Carruthers 2011), while others believe that ME and CFS are the same (Medical Research Council 2003). However CFS is the term that has been adopted and clearly defined for research purposes and will be used in this review. The diagnosis requires alternative conditions to be excluded. The prevalence of CFS among adults ranges from 0.2% to 2.6% (Prins 2006; Ranjith 2005) and this variation might be related to heterogeneity in diagnostic procedures as there have been at least 20 sets of diagnostic criteria published since 1988 (Brurberg 2014; Christely 2012). The etiology and pathophysiology of CFS are controversial. Models of understanding can be broadly divided into biomedical and

biopsychosocial models. The biomedical model explains the illness as caused by abnormalities of the immune, central nervous (Nijls 2011) or endocrine systems and/or a persistent infectious agent. The multifactorial biopsychosocial model (Moss-Morris 2012) distinguishes between precipitating and maintaining factors. Precipitating factors may include acute infective illness and/or excessive stress, while the illness is maintained by the interaction of behavior, thoughts, emotions and physiology. For example, after a severe infection or other illness, attempts to get back to normal life may result in bursts of activity punctuated by the need to rest up to recover, known as all-or-nothing behaviour (Moss-Morris 2010; Spence 2005). These periodic bursts of activity may exacerbate symptoms and result in failure, which further reinforces sufferers' belief that they have a serious, ongoing illness. As time goes by, efforts to meet previous standards of achievement are abandoned and patients become increasingly inactive and distressed by their ongoing symptoms. Inactivity in turn leads to physiological changes such as cardiovascular and muscular deconditioning, dysregulation of the hypothalamic-pituitary-adrenal axis and disrupted circadian rhythms. In this deconditioned state, any activity is liable to produce symptoms, the experience of which reinforces the fearful beliefs and hence reinforces the avoidance of activity (fear avoidance).

Description of the intervention

There are no curative treatments for CFS and the primary goals of treatment are symptom, function and quality of life management (NICE 2007). Treatment strategies typically involve exercise therapy and cognitive behavioural therapy (CBT) in addition to symptom-specific treatments, such as activity pacing and sleep hygiene. Pharmacotherapy is not an indicated treatment for CFS other than for symptom management or comorbid conditions such as depression or sleep disruption (BMJ Best Practice 2013).

Exercise is physical activity that requires effort (OED 2012). Exercise therapy uses physical exercise to improve health and well-being in people who are unwell, and can include modalities such as strength training or endurance exercise given as a part of a goal-oriented, multidisciplinary approach (Rietberg 2004; Takken 2008). There are a number of different approaches to exercise therapy for CFS. These include aerobic exercise such as walking, jogging, swimming or cycling, as well as anaerobic exercise such as strength or stabilising exercises. It is important to look at all kinds of therapeutic exercise, not only aerobic exercise. Behavioral approaches which use carefully graded exercise as a form of systematic desensitisation focus on breaking the fear avoidance cycle and the tendency to interpret symptoms as signs of illness. These approaches usually set a low initial exercise level, which gives patients the opportunity to experience exercise which does not produce a large increase in symptoms. Exercise is then built up gradually in a programme agreed in advance with the patient. If patients experience

an increase in symptoms, then planned increases in exercise frequency, duration or intensity are temporarily deferred until symptoms are less intense. Exercise therapy based on improving fitness typically involves setting targets based on physiological indicators of baseline fitness (such as VO₂ max) and prescribing increases in exercise based on ongoing monitoring of measures of fitness. Whereas both of the above types of exercise therapy include gradual increases in activity over time, a third approach allows patients to reduce activity in response to symptom exacerbations.

Anaerobic exercise, such as pilates, the Mensendieck system and Qigong are stabilising exercises with slow movement, primarily targeting core muscles. Qigong exercise, a method taken from traditional Chinese medicine, is characterised by a low degree of intensity and slow movements, coordinated with breathing and a health-promoting meditative practice. Qigong has been suggested to improve the postural, stabilising muscular system which often gradually progresses to more complex movements (Tsang 2003). Strength training aims to build the strength, anaerobic endurance, and size of skeletal muscles by resistance training, weight training or isometric training, but is also an integral part of other exercise regimes. Strength training exercise is primarily anaerobic.

How the intervention might work

Various models exist to explain why exercise therapy might be a viable treatment for CFS. The deconditioning model suggests that CFS is perpetuated by a chronic reduction and avoidance of activity leading to reversible physiological changes of deconditioning (Clark 2005; White 2011). In support of the model, CFS patients show a decreased exercise capacity when compared to sedentary controls (Fulcher 2000), but to date, improvements in fitness following exercise therapy have not been linked to improvements in fatigue in people with CFS (Fulcher 2000; Moss-Morris 2005). The biopsychosocial model emphasises the role of patients' cognitions and behaviours in the perpetuation of CFS. One variant of this model suggests exercise therapy reduces the focus on symptoms and avoidance of feared activity through showing that gradual increases in activity do not unduly exacerbate symptoms (Moss-Morris 2005), thereby engendering belief change. Reductions in beliefs about harmful effects of exercise have also been related to improved outcomes in CFS (Deale 1997). A second variant suggests that graded exposure to the previously-avoided exercise extinguishes the conditioned response to exercise. Further research is needed to verify different hypothesis, but effective treatments may be discovered without knowledge of the effective pathway or underlying cause.

Why it is important to do this review

Exercise therapy is often used as treatment for CFS both on its own and as part of a treatment program. The available evidence

(Edmonds 2004; Larun 2011) strongly suggests that exercise therapy might be effective in the treatment of CFS. However it has been reported in one trial that health-related quality of life does not improve with exercise (Nunez 2011) and argued in a review that rest, pacing and conserving energy are better treatments (Twisk 2009). People with CFS should have the opportunity to make decisions about their treatment informed by robust research evidence. This review will examine the effectiveness of exercise therapy, either as a stand-alone intervention or as one part of a treatment plan. Cochrane reviews address many aspects of treatments for CFS. A review of CBT was published in 2008 (Price 2008), and of traditional Chinese herbal medicine in 2009 (Adams 2009).

A meta-analysis of individual participant data (IPD) may be a more reliable method than using only aggregate data meta-analyses. The use of IPD facilitates standardisation of analyses and reporting of results across studies, and allows direct derivation of outcomes, independent of how these were reported (Riley 2010). IPD also increases the power to detect differential treatment effects between the individual participants, providing additional information on who is most likely to respond.

Analysis based on IPD also enables us to use a wider range of statistical and analytical approaches (Higgins 2011a). In particular, it will allow us to explore more thoroughly the relative importance of the aspects of heterogeneity such as type of exercise, intensity, incremental procedures, treatment provided to participants in the control group, baseline illness, and selection criteria, and ensure that missing data and baseline differences are dealt with in standardised ways. Access to IPD also allows subgroup analyses that were not previously reported.

OBJECTIVES

To assess the effects of exercise therapy, alone and in combination, for people with chronic fatigue syndrome (CFS) compared with treatment as usual control conditions and other interventions (psychological therapies, pharmacological treatment).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials, including cluster-randomised trials and cross-over trials, published or unpublished. While every effort will be made to obtain individual participant data (IPD) for trials which meet the selection criteria, an eligible

trial will not be excluded if we cannot obtain access to the raw data.

Types of participants

We will include male and female participants over the age of 17, irrespective of culture and setting. As several sets of criteria are currently used to diagnose CFS (Sharpe 1991; Fukuda 1994; Carruthers 2011) we will include trials given that the patients fulfil the following diagnostic criteria for CFS:

- Fatigue or a synonym is a prominent symptom;
- Fatigue is medically unexplained (i.e. other diagnosis known to cause fatigue such as psychiatric disorders and cancer should be excluded);
- Fatigue is sufficiently severe to significantly disable or distress the patient; and
- Fatigue has persisted for at least six months.

We will include trials which include patients with disorders other than CFS as long as more than 90% of the patients had a primary CFS diagnosis according to the criteria above. Trials in which less than 90% of participants had a primary diagnosis of CFS will only be included in the analysis of this review if data for CFS are reported separately.

Comorbidities

Studies involving participants with comorbid physical or common mental disorders are eligible for inclusion, as long as the diagnoses of CFS is not excluded by the comorbid condition.

Types of interventions

Experimental intervention

Exercise therapy as monotherapy or as an adjunctive treatment (e.g. exercise combined with pharmacological treatment). We define exercise therapy as aerobic or anaerobic interventions aimed at exercising big muscle groups, for example walking, swimming, jogging, strength or stabilising exercises. Both individual and group treatment modalities are eligible, but interventions should be clearly described and supported by appropriate references. We do not impose restrictions with regard to the duration of each treatment session, number of sessions or time between each session. Trials presenting data from one of the following comparisons are eligible for inclusion:

Comparator interventions

1. Standard care - to include passive conditions of treatment as usual and waiting list, and active conditions of relaxation/flexibility, pacing and supportive listening.

2. Psychological therapies - to include cognitive behavioural therapies, psychodynamic therapies and humanistic/supportive therapies.

3. Pharmacological treatments - to include antidepressants, hypnotics, antiviral drugs and immunotherapy.

A non-active supportive listening is regarded as non-active by the trialists and active by participants, whereas a supportive therapy is regarded as active by both trialists and participants.

Types of outcome measures

Note: 'Validated' is defined as having undergone psychometric development and having been published in a peer-reviewed journal.

Primary outcomes

Effectiveness

1. Fatigue, measured using a validated scale (e.g. Fatigue Scale (FS) (Chalder 1993) or the Fatigue Severity Scale (FSS) (Krupp 1989)).
2. Drop out from treatment.

Secondary outcomes

3. Physical functioning, measured using a validated scale (e.g. SF-36, physical functioning sub scale (Ware 1992)).

Safety

4. Serious adverse reactions and events, measured using any reporting system (e.g. Serious Adverse Reactions (SAR) (European Union Clinical Trials Directive 2001)).
5. Pain, measured using a validated scale (e.g. Visual Analogue Scale for Pain (VAS_{pain}) (Finch 2002)).
6. Mood disorders, measured using a validated scale (e.g. Hospital Anxiety and Depression Scale (Zigmond 1983)).
7. Sleep duration and quality, measured using a validated scale (e.g. Pittsburgh Sleep Quality Index (Buysse 1989)).
8. Self-perceived changes in overall health, measured using a validated scale (e.g. Global Impression Scale (Guy 1976)).
9. Symptom severity, treatment response and efficacy, measured using a validated scale (e.g. Clinical Global Impression - Severity scale (CGI-S) (Guy 1976)).
10. Overall functional status, measured using a validated scale (e.g. Work and Social Adjustment Scale (Mundt 2002)).
11. Objective measures of fitness e.g. VO₂max or VO₂ at subjective maximal effort, measured for example by 100 watts on an exercise bicycle or running at six miles per hour.

Timing of outcome assessment

Data on each outcome will be extracted for short-term (end of treatment), medium-term follow up (three to nine months) and long-term follow up (nine months or more).

Search methods for identification of studies

Electronic searches

The Cochrane Collaboration's Depression, Anxiety and Neurosis (CCDAN) Review Group's Trials Search Coordinator (TSC) will search their Group's Specialized Register (CCDANCTR-Studies and CCDANCTR-References). This register is created from routine generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-). Details of [CCDAN's generic search strategies](#), used to inform the CCDANCTR can be found on the Group's website.

The CCDANCTR-Studies Register will be searched using the following terms:

Diagnosis = ("Chronic Fatigue Syndrome" or fatigue) and Free Text = (exercise or sport* or relaxation or "multi convergent" or "tai chi")

The CCDANCTR-References Register will be searched using a more sensitive list of free-text search terms to identify additional untagged/uncoded references, e.g. fatigue*, myalgic encephalomyelitis*, exercise, physical active* and taiji. Full search strategy listed in [Appendix 1](#).

A complementary search of the following bibliographic databases and international trial registers will also be conducted (see [Appendix 2](#)):

- SPORTSDiscus (1985 to present);
- The Cochrane Central Register of Controlled Trials (CENTRAL, all years); and
- WHO International Clinical Trials Portal.

Searching other resources

We will contact the authors of included studies, and screen reference lists to identify additional published or unpublished data. We will also conduct citation searches using the ISI Science Citation Index on the Web of Science.

Data collection and analysis

Selection of studies

Two review authors will screen the titles and abstracts obtained from the searches, independently. Trials that appear to fulfil the selection criteria will be noted and full-text articles retrieved. Two

review authors will independently assess the full-text articles for adherence to the selection criteria. In the case of disagreement, we will attempt to reach a resolution through discussion. Should this prove unsuccessful, a third review author or staff at the CCDAN editorial base will be consulted.

The trialists of the included trials will be invited to take part in a collaborative group by a letter ([Appendix 3](#)) stating the main aims and purpose, importance of contribution, publication policy and confidentiality of data. The trialists who provide data will be offered co-authorship according to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals ([ICMJE 2014](#)). The local secretariat will be based at the Norwegian Knowledge Centre of the Health Services, and the first author will act as project manager. The CCDAN editorial group will act as advisory board. We will ask the trialists to provide their raw data to enable us to assemble the most complete data set possible, including all randomised participants, using flexible data formats containing pseudo-anonymised patient data. The data will be kept and used in accordance with the Norwegian Data Inspectorate's recommendations, and the parties will sign a contract ([Appendix 4](#)) to this end. An eligible trial will not be excluded if we cannot obtain access to the raw data.

We will prepare a flow diagram depicting the flow of references/studies through the different phases of the review in accordance with the PRISMA statement ([Mother 2009](#)). The flow diagram will map out the number of records identified, included and excluded and reasons for exclusion.

Data extraction and management

Trialists of included studies will be invited to collaborate in accordance with section 18.2 of the *Cochrane Handbook* ([Stewart 2011](#)). They will be offered authorship and asked to provide IPD for all randomised participants to be used in the review. A list of variables that we will particularly request is attached ([Appendix 5](#)), but we will accept data sets containing more variables than requested. We will accept all data sent in data formats that can be read by SAS or SPSS, Microsoft Access databases, Excel and delimited or (comma-)separated text-files. The review authors will adopt data security measures to ensure data protection, and to ensure that the data cannot be violated or tracked. All data sets will be stored securely and pseudo-anonymously; that is, all identifiers that potentially could be linked directly to the actual participants will be deleted, and identifiers will only be identifiable to the original investigators.

Descriptive data (methodology, treatment, comparator, and instruments used for measuring outcomes) for each of the included studies will be independently extracted by JO-J and LL using a standardised data collection form ([Appendix 6](#)) which will include the following variables.

Study methodology specific:

- Diagnostic criteria used for identifying eligible patients;

- Method of recruitment for trial;
- Randomisation method;
- Allocation concealment; and
- Blinding.

Treatment specific:

- Deliverer of intervention;
- Explanation and material;
- Type of exercise;
- Schedule, therapist;
- Schedule, home;
- Duration of sessions;
- Initial exercise level;
- Increment steps;
- Patient self monitoring; and
- Criteria for (non) increment.

Outcome specific:

Scales used for assessment

- Fatigue;
- Pain;
- Physical functioning;
- Depression;
- Anxiety; and
- Quality of life.

Measurement time points/follow-up will be collected and study authors contacted to provide additional information where gaps have been identified.

For included studies from which we are not able to gain access to IPD, relevant information (both the above-mentioned data and results for the prespecified outcomes) will be extracted. For adverse events, we will extract the number of events and number of participants in each group. For the remaining (continuous) outcomes, we will extract N, mean and standard deviation.

Planned comparisons

1. Exercise therapy versus treatment as usual/waiting list/supportive listening/pacing/cognitive treatment. We also plan to conduct subgroup comparisons for each comparison above to see if one of the more passive comparators is more effective than another.

2. Exercise therapy (as monotherapy or adjunctive therapy) versus cognitive behavioural therapy. Monotherapy and adjunctive therapy will be analysed separately.

3. Exercise therapy (as monotherapy or adjunctive therapy) versus pharmacological treatment.

If there are several drug trials we will divide the comparators into antidepressants, hypnotics, antiviral and immunotherapy. Monotherapy and adjunctive therapy will be analysed separately.

Data checking and cleaning

To reduce potential bias (Tierney 2005), we will request information for all randomised patients including those who had been excluded from the investigators' original analyses. A number of standard checks will be applied to all incoming trials, including checks for missing values, data validity and consistency across variables. To assess the randomisation integrity, we will look for unusual patterns in the sequencing of allocation or imbalances in baseline characteristics between treatment arms. Follow-up of patients will be assessed to ensure that it was balanced in the treatment arm, and as up-to-date as possible.

All incoming data will be checked thoroughly for consistency and completeness of follow-up. We will tabulate summary measures (frequencies for categorical variables and mean, standard deviations, minimum, maximum, median, 25th and 75th percentile for continuous variables) for the individual parameters (demographic variables, illness-specific variables and outcomes) for each study to identify missing data and outliers, and to describe differences in distribution between the studies. We will analyse patient and disease characteristics and treatment outcome by trial and treatment arm to check consistency with published results. If we encounter any problems regarding missing data, obvious errors, discrepancies (e.g. between published data and raw data), inconsistencies between variables or extreme values or inability to replicate the results presented in the retrieved papers, we will resolve these in discussion with the original investigator. We will maintain a log of all changes made to the data originally supplied by the trialists, and the reasons for these changes. Any queries will be resolved and the final database entries verified by the responsible trial investigator or statistician.

As the summary statistics for outcomes in this review may differ from the summary statistics presented in the retrieved papers due to the possible use of imputed data in the original analyses by trial investigators, we will present summary statistics for all outcomes by trial and treatment arm in a table (showing sample size, mean, standard deviation, minimum and maximum).

Assessment of risk of bias in included studies

Two authors (LL and JO-J) will use the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011a), published in the most recent version of the *Cochrane Handbook* (Higgins 2011b). This tool encourages consideration of how the allocation sequence was generated, how allocation was concealed, the integrity of blinding at outcome level, the completeness of outcome data, selective outcome reporting (only applicable in cases where we do not gain access to complete data sets) and other potential sources of bias. When it comes to blinding, we will distinguish between performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessors; for outcomes not reported/assessed by the participants). As all the outcomes we intend to look at are subjective (self report by participants, or the

use of scales that are based on judgements) we will include an item for objective outcomes. Each item in the 'Risk of bias' assessment will be assessed as low, high or unclear risk of bias using the guidelines outlined in the *Cochrane Handbook* (Higgins 2011a). In addition, we will make an overall assessment of the risk of bias across all items for each included study. If one or more of the items sequence generation, allocation concealment or completeness of outcome data are assessed as being at high risk of bias, the overall assessment of the study will be high risk of bias.

We will perform sensitivity analyses in which studies assessed to be at high risk of bias (across all items) are excluded. The reasons for the judgement 'high risk of bias' might vary between studies where IPD are available and studies where IPD are not available. Selective outcome reporting will only be a problem for non IPD-studies as we have access to all data from the included studies with IPD. Furthermore we can reduce the risk of bias due to non-completeness of outcome data for studies with IPD by using statistical methods that do not exclude participants based on missing data (such as analysis of longitudinal data, or the use of censoring when analysing time-to-event data).

Measures of treatment effect

1. Binary data

We will calculate the odds ratio (OR) and its 95% confidence interval (CI).

2. Continuous data

When the same scale has been used in all included studies, we will calculate the mean differences (MD) and their 95% CI, as it preserves the original units and is therefore easier to interpret. Where different scales are used for the same outcome, effect sizes will be calculated separately for each scale.

2.1 Change versus endpoint data

Mean differences will primarily be based on endpoint data. For studies where IPD are not available, we will only use change data when endpoint data are not available. In cases where results from some studies are based on change data and results from other studies are based on endpoint data, all studies will be included in the same meta-analysis with change data and endpoint data as subgroups.

Unit of analysis issues

Cluster-randomised trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain the intra-class correlation co-efficient (ICC) of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering is incorporated, we will present the data as if from a parallel-group randomised study, but adjusted for the clustering effect. We will additionally exclude such studies using a sensitivity analysis.

If cluster studies are appropriately analysed taking into account ICC and relevant data documented in the report, synthesis with other studies will be possible using the generic inverse variance technique.

Cross-over trials

A major concern of cross-over trials is the potential for carryover effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in CFS/ME, randomised cross-over studies will be eligible for inclusion, but only data up to the point of first cross-over will be used, while data from the following (second) period of the cross-over trial will not be considered for analysis. This might introduce bias due to the possibility of selectively reporting results from the first period based on the results. We will exclude cross-over studies using a sensitivity analysis.

Studies with multiple treatment groups

1. Multiple dose groups

We expect that some studies will address the effects of different levels of supervision and follow-up in regards to the exercise intervention to the comparator (e.g. sessions for designing exercise therapy, sessions for designing exercise therapy and planned telephone contacts, sessions for designing exercise therapy and seven face to face treatment sessions, and usual care). In the case of dichotomous outcomes we will sum up the sample sizes and the number of people with events across all intervention groups. For

continuous outcomes, we will combine means and standard deviations using methods described in Chapter 7 (section 7.7.3.8) of the *Cochrane Handbook* (Higgins 2011b).

2. Multiple medications

We expect that some other studies will combine several interventions with one comparison group. In this case we will analyse the effects of each intervention group versus placebo separately, but will divide up the total number of participants in the placebo group. In the case of continuous outcomes the total number of participants in the placebo group will again be divided up, but the means and standard deviations will be left unchanged (see chapter 16, section 16.5.4 in Higgins 2011b).

Dealing with missing data

Analyses of all endpoints, subsets and subgroups will be carried out on the basis of the intention-to-treat principle but based on the available data; that is, participants will be analysed according to their allocated treatment, irrespective of whether they received that treatment or not, but no attempt will be made to impute missing data. In our request for the raw data from the included trials it will be made clear that data are needed for all randomised participants.

Assessment of heterogeneity

We will assess clinical heterogeneity across the included trials in terms of interventions, participants and settings. We expect that the trials might differ when it comes to the ingredients of the active interventions and the components of the passive controls (treatment as usual, waiting list, etc.). We furthermore anticipate that the severity and duration of CFS might differ between the trials. If we judge that the included trials are too heterogeneous (e.g. we expect the effect sizes across trials to be unrelated) to warrant a formal meta-analysis, we will not perform meta-analysis but present the results of the included trials narratively.

We will assess statistical heterogeneity on the basis of the *Cochrane Handbook* recommendations (I^2 values of 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). In addition to the I^2 value (Higgins 2003), we will present the χ^2 and its P value and consider the direction and magnitude of the treatment effects. As in meta-analysis with few studies, the χ^2 test is underpowered to detect heterogeneity should it exist; a P value of 0.10 is used as a threshold of statistical significance.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These biases included publication bias and selective outcome reporting bias.

Funnel plots can be useful in reporting biases (Sterne 2011, section 10.4). It is important to bear in mind when interpreting a funnel plot, that publication and selective outcome reporting biases are not the only reasons for asymmetry. Poor methodological quality of studies, inappropriate analysis and true heterogeneity between trials can also lead to funnel plot asymmetry.

We will only produce funnel plots if at least 10 studies are included for that specific outcome and the studies are not similar in size. Funnel plots will be inspected visually and Egger's test for asymmetry (Egger 1997) used to assess the risk of reporting bias. We will interpret the results with caution; all test results will be assessed in light of the visual inspection. We acknowledge that tests for funnel plot symmetry in general have relatively low power to detect funnel plot asymmetry. Thus bias cannot be excluded even if the test does not provide evidence of funnel plot asymmetry.

For studies where we obtain IPD, we do not consider selective outcome reporting to be a problem, as we have access to all data collected. For the remaining non-IPD studies, selective outcome reporting can be an issue, which will be addressed during the 'Risk of bias' assessment.

Data synthesis

Data from the included studies will be analysed using a two-step approach (Riley 2008).

At the first step, we will analyse the IPD for each trial, separately. For continuous outcomes the study-level analyses will be based on repeated measurements with a reference group coding of independent factors, thus taking into account the correlation between baseline and post-intervention measurements. Data from all measurement points will be included in one single model. The post intervention measurements will be modelled as depending on the baseline measurement, time, group (intervention or control) and the interaction between time and group. The repeated measurements (from the same person) will be assumed to have an unstructured covariance structure. The analyses of data from the individual included trials will be conducted using the MIXED procedure in SAS (SAS 2009). For each trial the estimate of effect at any given measurement point will be calculated as the difference between the estimated value of the dependent variable in the intervention and control groups, respectively (at that measurement point); the corresponding 95% confidence intervals will also be calculated.

If a study has performed more than one measurement of the same outcome at baseline, the baseline value for our analysis will be defined as the last value. If measurement of an outcome has been performed more than once at each measurement point, then we will base our analysis on the first-measured value.

For studies where no IPD are available, the estimate of effect (MD with standard error) will be based on the sample sizes, means, standard deviations, confidence intervals and P values extracted from papers.

At the second step we will combine the estimates of effect across

studies in meta-analysis. The primary analyses will be based on all included studies, both IPD and non-IPD, but we will conduct sensitivity analyses in which studies where IPD are not available will be excluded. The estimates of effect from all included studies will be pooled using the generic inverse variance technique in a random-effects model.

Adverse events will be counted and reported for each study using odds ratios (ORs) and their 95% confidence intervals. A random-effects model will be used to estimate effects across studies.

We will use GRADE to examine the quality of evidence and the strength of recommendations. Judgment of the strength of a recommendation will require consideration of the following factors: the balance between benefit and harm, the quality of the evidence, translation of the evidence into specific circumstances and the certainty of the baseline risk (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

To examine the potential impact of trial design and the treatments used, we plan to group trials by important aspects that might influence the effect of exercise therapy.

Heterogeneity will be explored on the following trial-specific items:

- Control groups (treatment as usual/waiting list versus relaxation/flexibility);
- Diagnostic criteria used for assessing eligibility of participants (Oxford (Sharpe 1991) versus CDC1994 (Fukuda 1994) versus London ME criteria (Dowsett 1994) versus ICC (Carruthers 2011)); and
- Setting (primary versus secondary versus tertiary care).

For each of these analyses a pooled measure of treatment effects will be calculated for each group of trials and for all trials together.

Participant-specific items:

- Age (less than 45 years of age versus 45 years or older);
- Gender;
- Length of syndrome history (less than 5 years versus more than 5 years);
- Baseline illness severity (dichotomised);
- Baseline anxiety (Yes/No);
- Baseline depression (Yes/No);
- Comorbidity (Yes/No);
- Diagnostic criteria met (Met least strict criteria versus met two sets of criteria versus met three sets of criteria versus met all four sets of criteria); and
- Illness beliefs (virus/psychological/combo).

We will furthermore explore heterogeneity on the following intervention-specific items:

- Baseline (no determination/patient-centred/physiological);
- Type of exercise (aerobic/anaerobic-strengthening/anaerobic-non-strengthening);

- Explanations and materials (no cognitive component/ educational-didactic/educational-didactic plus therapist using cognitive approaches); and
- Incremental steps (none/pacing/mutually planned and expected/physiological response to exercise).

For the participant-specific items we will calculate separate estimates of treatment effect for each subgroup using the same methods as for the main analyses. Pooled measures of treatment effect will be calculated for each subgroup of the population, but not across subgroups due to the dependency between estimates of effect from the same trial.

If enough trials are included (a minimum of 10 studies with all relevant data available per comparison), meta-regression (random-effects) will be performed to formally explore heterogeneity or differences between subgroups of trials or populations. We will perform one meta-regression for each variable we wish to explore (not adjusted for the other proposed subgroup variables). The meta-regression will be conducted using the MIXED procedure with random error terms for each trial in SAS (SAS 2009). Due to the number of subgroup analyses we will adjust the level of significance to 0.05/(#number of subgroup analyses) using the Bonferroni correction method.

Sensitivity analysis

Sensitivity analysis will be performed, separately, by excluding:

- studies assessed as being at high risk of bias on one or more of the 'Risk of bias' items: sequence generation, allocation concealment or completeness of outcome data;
- cluster-randomised trials;
- cross-over trials (possible selective reporting of results from first period in non-IPD studies); and
- studies where IPD are not available (estimates of treatment effect depends on the method of analysis).

We will, in addition, perform sensitivity analyses based on standardised mean differences (SMD) for continuous outcomes that have been measured using different instrument/scales in the included studies. For the outcome Clinical Global Impression Scale (CGI) we will perform sensitivity analyses based on dichotomised values:

- Participant became better (1 and 2 versus 3 to 7); and

- Participant became worse (6 and 7 versus 1 to 5).

'Summary of findings' tables

We will prepare 'Summary of findings' tables to summarise the key findings of the systematic review in line with the standard methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) using GRADEpro (Brozek 2008).

These findings will include:

- Fatigue;
- Drop out rates;
- Physical functioning; and
- Self-perceived changes in overall health.

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Disclaimer

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategy - CCDANCTR-References

CCDANCTR-References Register

(fatigue* or asthenia or “muscular disorder*” or neurasthenia* or “infectious mononucleos*” or “myalgic encephalomyelit*” or “royal free disease*” or lassitude or “muscular weakness*” or “akureyri disease” or “atypical poliomyelitis” or CFIDS or CFS or (chronic and mononucleos*) or “epidemic neuromyasthenia” or “iceland disease” or “post infectious encephalomyelitis” or PVFS or tiredness or adynamia or legasthenia or (perspective and asthenia) or neurataxia or (“muscle strength” and loss) or “muscle* weak*” or “weak* muscle*” or (muscular and insufficiency) or (neuromuscular and fatigue))

and

exercise or “physical fitness” or “physical education” or “physical condition*” or “physical train*” or “physical mobility” or “physical activ*” or “physical exertion” or “physical effort*” or (breathing and (therap* or exercise*)) or (respiration and therap*) or “gi gong” or gigong or *kung or tai or thai or taiji or taijiquan or taichi or walking or yoga or relaxation* or gymnastics or calisthenics or aerobic or danc* or jumping or hopping or running or jogging or ambulat* or “muscle strengthening” or (muscular and (strength or resistance)) or ((weight or weights) and lifting) or weightlifting or “power lifting” or “weight train*” or pilates or stretching or plyometric* or “cardiopulmonary conditioning” or “motion therap*” or “neuromuscular facilitation*” or “movement therap*” or ((recreation or

activity) and therap*) or “isometric training” or climbing or cycling or bicycle* or “lifting effort*” or swim* or (training and (technical or course or program*)) or writing or kinesi* or gardening or multiconvergent)

Appendix 2. Other search strategies

SPORTSDiscus (EBSCOHost)

1. exp Exercise/
2. exp Exercise Therapy/
3. exp Exercise Movement Techniques/
4. Physical Fitness/
5. exp "Physical Education and Training"/
6. (exercise\$ or exercising).tw.
7. ((breathing or respiration) adj (therap\$ or exercise\$)).tw.
8. (gi gong or gigong).tw.
9. relaxation\$.tw.
10. ((tai adj ji) or ((tai or thai) adj chi) or taiji or taijiquan or taichi).tw.
11. walking.tw.
12. yoga.tw.
13. (physical adj (fitness or condition\$ or education or training or mobility or activit\$ or exertion or effort)).tw.
14. gymnastics.tw.
15. calisthenics.tw.
16. aerobic danc\$.tw.
17. danc\$.tw.
18. (jumping or hopping).tw.
19. (running or jogging).tw.
20. ambulat\$.tw.
21. muscle strengthening.tw.
22. (muscular adj (strength or resistance) adj training).tw.
23. ((weight\$1 adj2 lifting) or weightlifting or power lifting or weight training).tw.
24. pilates.tw.
25. stretching.tw.
26. plyometric\$.tw.
27. cardiopulmonary conditioning.tw.
28. motion therap\$.tw.
29. neuromuscular facilitation\$.tw.
30. movement therap\$.tw.
31. ((recreation or activity) adj therap\$).tw.
32. gymnastic therap\$.tw.
33. isometric training.tw.
34. climbing.tw.
35. cycling.tw.
36. lifting effort\$.tw.
37. swimming.tw.
38. writing.tw.
39. technical training.tw.
40. (training adj (course\$ or program\$)).tw.
41. (training adj (course\$ or program\$)).tw.
42. kinesi?therap\$.tw.
43. gardening.tw.
44. multiconvergent.tw.
45. exp Sports/
46. or/1-45

47. Fatigue Syndrome, Chronic/
48. exp Fatigue/
49. Asthenia/
50. Neurasthenia/
51. chronic fatigue\$.tw.
52. fatigue syndrom\$.tw.
53. infectious mononucleos\$.tw.
54. postviral fatigue syndrome\$.tw.
55. chronic fatigue-fibromyalgia syndrome\$.tw.
56. myalgic encephalomyelit\$.tw.
57. royal free disease\$.tw.
58. neurasthenic neuroses.tw.
59. akureyri disease.tw.
60. atypical poliomyelitis.tw.
61. benign myalgic encephalomyelitis.tw.
62. (CFIDS or CFS).tw.
63. (chronic adj4 mononucleos\$).tw.
64. epidemic neuromyasthenia.tw.
65. iceland disease.tw.
66. post infectious encephalomyelitis.tw.
67. PVFS.tw.
68. (perspective adj4 asthenia).tw.
69. neurasthenic syndrome\$.tw.
70. neurataxia.tw.
71. neuroasthenia.tw.
72. (neuromuscular adj6 fatigue).tw.
73. or/47-72
74. randomized controlled trial.pt.
75. controlled clinical trial.pt.
76. randomi#ed.ab.
77. placebo\$.ab.
78. randomly.ab.
79. trial.ab.
80. (clinic\$ adj3 (trial\$ or study or studies\$)).ti,ab.
81. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
82. ((singl\$ or doubl\$ or tripl\$) adj (blind\$ or mask\$ or dummy)).ti,ab.
83. or/74-82
84. (animals not (humans and animals)).sh.
85. 83 not 84
95. 46 and 73 and 85

Cochrane Central Register of Controlled Trials (CENTRAL)

- #1 MeSH descriptor Exercise
- #2 MeSH descriptor Exercise Therapy
- #3 MeSH descriptor Exercise Movement Techniques
- #4 MeSH descriptor Physical Fitness
- #5 MeSH descriptor Physical Education and Training
- #6 exercis*
- #7 breathing NEAR/2 (therap* or exercis*)
- #8 respiration NEAR/2 (therap* or exercis*)
- #9 (gi gong or gigong)
- #10 relaxation*
- #11 tai or thai or taiji or taijiquan or taichi

#12 walking
 #13 yoga
 #14 (physical NEAR/2 (fitness or condition* or education or training or mobility or activit* or exertion or effort))
 #15 gymnastics
 #16 calisthenics
 #17 aerobic*
 #18 danc*
 #19 jumping or hopping
 #20 ambulat*
 #21 muscle strengthening
 #22 (muscular NEAR/2 (strength or resistance))
 #23 (weight or weights) NEAR/2 lift*
 #24 weightlifting or power lifting or weight training
 #25 (Pilates or stretching or plyometric* or cardiopulmonary conditioning or motion therap* or neuromuscular facilitation* or movement therap* or gymnastic therap* or isometric training or climbing or cycling or lifting effort* or swimming or writing) #26 ((recreation or activity) NEAR/2 therap*)
 #27 technical training
 #28 (training NEAR/2 (course* or program*))
 #29 (training adj (course* or program*))
 #30 kinesi*
 #31 gardening
 #32 multiconvergent
 #33 MeSH descriptor Sports explode all trees
 #34 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)
 #35 MeSH descriptor Fatigue Syndrome, Chronic
 #36 MeSH descriptor Fatigue
 #37 MeSH descriptor Asthenia
 #38 MeSH descriptor Neurasthenia
 #39 chronic fatigue*
 #40 fatigue syndrom*
 #41 infectious mononucleos*
 #42 postviral fatigue syndrome*
 #43 chronic fatigue-fibromyalgia syndrome*
 #44 myalgic encephalomyelit*
 #45 royal free disease*
 #46 neurasthenic neuroses
 #47 akureyri disease
 #48 atypical poliomyelitis
 #49 benign myalgic encephalomyelitis
 #50 CFIDS or CFS
 #51 chronic NEAR/5 mononucleos*
 #52 epidemic neuromyasthenia
 #53 iceland disease
 #54 post infectious encephalomyelitis
 #55 PVFS
 #56 perspective NEAR/5 asthenia
 #57 neurasthenic syndrome*
 #58 neurataxia
 #59 neuroasthenia
 #60 neuromuscular NEAR/6 fatigue

#61 (#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60)
#62 (#34 AND #61)

International Trial Registers

WHO International Clinical Trials Portal available at: <http://apps.who.int/trialsearch/>, incorporating the following International trials registers/registries:

- Australian New Zealand Clinical Trials Registry
- ClinicalTrials.gov
- EU Clinical Trials Register (EU-CTR)
- ISRCTN
- Brazilian Clinical Trials Registry (ReBec)
- Chinese Clinical Trial Registry
- Clinical Trials Registry - India
- Clinical Research Information Service - Republic of Korea
- Cuban Public Registry of Clinical Trials
- German Clinical Trials Register
- Iranian Registry of Clinical Trials
- Japan Primary Registries Network
- Pan African Clinical Trial Registry
- Sri Lanka Clinical Trials Registry
- The Netherlands National Trial Register
- Thai Clinical Trials Register (TCTR)

Appendix 3. Letter of invitation

Dear Dr XXX,

Following up our previous communication on the need to follow up and elaborate on the the Cochrane review 'Chronic Fatigue Syndrome and graded exercise therapy' from 2004; your study, XXXX, is one of the studies to be included.

As previously mentioned we intend to conduct an Individual Participant Data (IPD) review. The reason for the IPD review is to enable in-depth analyses by performing subgroup analyses. This will be carried out using variables such as patient, illness and treatment characteristics. We are able to handle data delivered in the following formats:

- Excel
- SAS
- SPSS/PASW Statistics
- Delimited or fixed-width files provided that a detailed file-description with variable-names, formats and maximum width of each column is provided.

Please don't hesitate to contact us if you need more information. Enclosed is a memorandum which should be returned to us with the datafiles.

We would like to invite you to participate as co-author(s) in line with your contribution. Should you not wish to be listed as a co-author you will of course be mentioned under Acknowledgments for the provision of your raw data.

The review will be undertaken in collaboration with representatives from Uni Health Bergen and The Norwegian Knowledge Centre for the Health Services, Oslo, as well as the authors of the included studies.

Yours sincerely

Lillebeth Larun

Attachments

- Memorandum to be signed
- List of background variables
- Data extraction template

Appendix 4. Memorandum

Exercise therapy for chronic fatigue syndrome (individual patient data)

Whereas:

The parties have agreed to provide information which they consider to be confidential in nature (the “Confidential Information”) to write the review: ‘Exercise Therapy for Chronic Fatigue Syndrome (Individual Patient Data)’, hereafter called the “Purpose”;

It is agreed as follows:

1. In consideration of each of the parties disclosing to the other Confidential Information for the Purpose the parties hereby undertake that they shall:
 - i) not communicate, disclose or make available all or any of the part of the Confidential Information to any third party
 - ii) not directly or indirectly use, or permit others to use, the Confidential Information other than for the Purpose;
 - iii) not make any announcements or disclosure in connection with the Confidential Information or the Purpose without prior consent of the other party.
2. The obligation of the confidentiality and non-use will not apply to any of the following:
 - i) information which is generally available to the public at the date of this agreement;
 - ii) information which is subsequently disclosed by third parties having no obligation of confidentiality;
 - iii) information which is or will become generally available to the public in printed publications in general circulation through no act or default on the parties.
3. Without prejudice to the generality of clause 2 information shall not be deemed to be generally available to the public by reason only that it is known to only a few of those people to whom it may be of commercial interest and a combination of two or more parts of the Confidential Information shall not be deemed to be generally available to the public by reason only of separate part being so available.
4. The parties shall each ensure that all measures necessary are taken to secure the confidentiality of the other party’s Confidential Information including but not limited to:
 - i) keeping separate all Confidential Information and all information generated based on the Confidential Information from all other documents and records;
 - ii) keeping all documents and any other material bearing or incorporating any of the Confidential Information at the party’s usual place of business;
 - iii) not using, reproducing, transforming or storing any of the V in an external accessible computer or electronic information retrieval system, not transmitting it in any form or by any means outside the party’s usual place of business and not copying all or any part of the Confidential Information without the prior consent and then only to the extent that the same is required for the Purpose;
 - iv) allowing access to the Confidential Information only to those employees and/or to the professional advisers who have reasonable need to see or use it for the Purpose and informing each of the said employees and professional advisers of the confidential nature of the Confidential Information and of the obligations in respect of the Confidential Information and ensuring such employees and professional advisers comply with the confidentiality and non-disclosure obligations in this agreement;
 - v) obtaining from employees having access to the Confidential Information their undertakings to maintain the same as confidential and taking such steps as may be reasonable to enforce such obligations;
 - vi) delivering all documents and other materials in the possessions, custody or control of the party, employees or professional advisers that bear or incorporate any part of the Confidential Information of the other party;
 - vii) delivering all data material encrypted wherever possible and make sure that individual participants cannot be identified from the data provided.
5. The failure by any party to enforce at any time any one or more of the terms or conditions of this agreement shall not be a waiver of them or of the right at any time subsequently to enforce all terms and conditions in this agreement.
6. The parties agree that damages might not be sufficient remedy to any breach of the terms of this agreement and that as a result injunctive or other equitable relief may be obtained in respect of any breach or anticipated breach.
7. All right in the Confidential Information are reserved by the party to which it belongs and no rights or obligations other than those expressly set out in this agreement are granted or to be implied from this agreement. In particular no license is granted directly or indirectly by this agreement relating to any intervention, discovery, patent, copyright or other industrial or intellectual property right now or in future held, made, obtained or licensable by either party.

8. The rights, duties and obligations of the parties and the validity, interpretation, performance and legal effect of this agreement shall be governed and determined by the laws of country of residence.

AGEED by the parties:

SIGNED by

Name (print)

Position

Date (Day/Month/Year)

SIGNED by

Name (print)

Position

Date (Day/Month/Year)

Appendix 5. List of variables requested from original investigators

Gender (M/F)
Age (years)
Education
Marital status
Income
Employment status
Complied with protocol (Y/N)
Completed follow-up (Y/N)
Number of sessions attended
Duration of illness (years)
Illness severity
Previous diagnosis (specify)
Co-morbidity (specify)
previous treatment
Adjunctive treatment
Illness perception
Medication

(Continued)

Physical fatigue
Mental fatigue (all measurements)
Total fatigue (all measurements)
Perceived exertion (all measurements)
Depression (all measurements)
Anxiety (all measurements)
Pain (all measurements)
Functional impairment (all measurements)
Quality of life (all measurements)
Adverse outcomes (specify)

Appendix 6. Data collection form - descriptive data

Study specific			
Diagnostic criteria for identifying eligible patients			
Methods of recruitment for trial			
Randomisation method			
Allocation concealment			
Blinding (who was blinded to what)			
Treatment specific			
Deliverer of intervention			
Explanation and material			
Type of exercise			

(Continued)

Schedule, therapist			
Schedule, home			
Duration of sessions			
Initial exercise level			
Increment steps			
Patient self monitoring			
Criteria for (non) increment			
Scales used for assessment	Name	Self-reported or clinician-reported (please state by whom and whether the clinician was blinded to treatment allocation)	When measured
Fatigue			
Pain			
Functional impairment			
Depression			
Anxiety			
Quality of life			

CONTRIBUTIONS OF AUTHORS

Lillebeth Larun (LL), Jan Odgaard-Jensen (JOJ) and Kjetil Gundro Brurberg (KGB) developed and drafted the protocol.

Hugh McGuire and Sarah Dawson, CCDAN Trials Search Coordinators developed the search with input from LL.

Jan Odgaard-Jensen developed and drafted the statistical analysis.

All the co-authors have contributed to the final draft of the protocol.

DECLARATIONS OF INTEREST

KB: none known.

TC: none known.

MD: none known.

PG is on the board of Therapeutic Guidelines Limited, and holds a research grant from the NHMRC on screening and diagnostic testing.

LL: none known.

REM-M: none known.

JO-J: none known.

MS has done occasional consultancy for Aegon Insurance Ltd.

KW: none known.

AW: none known.

PDW has undertaken both voluntary and paid consultancy work for the UK government and a re-insurance company.

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- Norwegian Knowledge Centre for the Health Services, Norway.
- Wages for JOJ, KGB and LL

External sources

- No sources of support supplied