Author's response to reviews

Title: One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with Multiple Sclerosis.

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Author's response to reviews: see over
Dr Calabrese

Thank you for the invitation to revise our manuscript and for the helpful reviewers’ comments. We appreciate the opportunity to revise and improve our manuscript. Please find below the reviewers’ comments with our point-by-point response. Please do not hesitate to contact us should you require any further clarification on any response.

Yours sincerely

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Editor’s comments
As also some reviewer suggested, the paper is difficult to be read since many information are lacking (referring to the main paper). The Methods section is too limited. As an independent paper please include all details that can help the readers to understand it properly. Also Discussion seems to me too short.

The discussion is longer now that we have addressed the reviewers’ comments.

Referee 1
This is a pragmatic non-pharmacological three-centre RCT aimed to evaluated the long-term (1 year) effects of a manualised group-based program plus current local practice (FACETS) vs current local practice alone (CLP) for managing MS-fatigue.

The topic is relevant since it is well known that both pharmacological and non-pharmacological interventions have only a weak effect in limiting perceived fatigue in MS patients.

Some comments and suggestions:
Minor essential revisions
1. The authors refer to the published protocol for method details; however, the reader would appreciate some information to remind inclusion and exclusion criteria or trial conduction (e.g. were the drugs against fatigue allowed during the trial?)

We have added a summary of the trial inclusion and exclusion criteria as follows:

Participants were recruited in three UK centres (Poole, Bristol, Southampton/Portsmouth) from primary or secondary care, or via MS Society newsletters/websites. Recruitment took place from May 2008 to November 2009.

The main inclusion criteria were: (1) clinically definite MS diagnosis, (2) fatigue impacting on daily life (Fatigue Severity Scale total score >4) and (3) ambulatory. The main exclusion criteria were: (1) having taken part in a fatigue programme in the last year, (2) cognitive impairments, (3) a relapse in the previous 3 months or (4) having started treatment with disease modifying or antidepressant drugs within the previous 3 months. The full eligibility criteria are described in the protocol.

In keeping with our pragmatic approach we did not exclude individuals who were taking a drug for MS-fatigue (such as Amantadine or Modafinil) as we wanted the results to be as generalisable as possible to individuals with MS experiencing fatigue.

2. A brief description of the experimental and, in particular, of the control intervention would also be desirable

We have added a description as follows:

Intervention (FACETS)

The manualised group-based FACETS programme is described elsewhere and is based upon a conceptual framework integrating elements from cognitive behavioural, social-cognitive, energy effectiveness, self-management and self-efficacy theories. The aim of the intervention is to help people normalise their fatigue experiences, learn helpful ways of thinking about fatigue and use available energy more effectively. The intervention consists of six sessions (~90 min duration) held weekly and facilitated in groups of 6-12 by two health professionals with experience of working with people with
MS and group-work (such as occupational therapists, nurses or physiotherapists). Each session follows the same general format, namely, facilitator-delivered presentations, flipchart discussions, group activities and homework. The facilitator manual provides guidance on preparation and delivery, detailed session content, notes and suggested timings, and a checklist of facilitator objectives as well as signposts to additional resources. Sessions are delivered via PowerPoint; hence can be easily replicated. A companion participant handbook, along with existing information booklets, reinforces programme content.

FACETS was delivered in hotel meeting-room facilities, with the exception of one centre, where it was held in a rehabilitation hospital. Apart from one MS specialist nurse, facilitators were either occupational therapists or physiotherapists. Facilitators were trained to deliver the intervention at one-day workshops and psychological advice and debriefing were available for facilitators throughout the trial.

To increase external validity, no attempt was made in the FACETS arm to restrict or control participants’ access to current local practice or to standardise it across healthcare settings or treatment arms. When we refer to the FACETS arm, participants in this arm also received current local practice.

We have added this to the description of the control group:

This could have ranged from general advice and information provision about MS-fatigue to more detailed individualised management advice from a variety of health professionals. Inevitably, there will have been variations in the exact composition of what was usually provided, within and between centres, depending on local resources and patient need. Collecting detailed information at an individual level on the type and quantity of advice received as part of current local practice was not deemed feasible. However, this real world variation increases applicability to a wider range of centres.

All participants in the ‘usual care’ arm received current local practice as our pragmatic approach to this trial meant that we made no attempt to control or standardise what participants received in this
arm. Our research question was whether adding the fatigue management programme to what is currently happening in the NHS would confer patient benefit. Thus we feel that the variations in the composition of usual care (we have called this ‘current local practice’ to reflect this local variation) increase the generalisability of the findings to a range of healthcare settings.

3. Again, a brief paragraph describing patient characteristics (e.g. age, type of MS, EDSS score, etc) definitely affecting the outcome should be added in the Results

We have now included the original table of patient characteristics. Certain patient characteristics (age, gender, marital status, education level, type of MS, time since diagnosis, level of disability) were among those that were pre-specified in the published protocol as important variables to include in supplementary analyses involving covariates which we reported in the manuscript in the text below.

The mixed model approach taken as specified in the protocol included 1 year and baseline measurements as repeated measures, incorporated clustering effects and included the following pre-specified covariates, baseline measurements for other primary outcomes, age, gender, marital status, education level, type of MS, time since diagnosis, level of disability, and centre.

Using this approach, the mean difference at 1 year for GFS was almost unchanged (-0.28 (-0.58, 0.02), p=0.07), for fatigue self-efficacy was slightly higher (7 (1, 13), p=0.02), and for the MSIS-29 slightly lower (-3.90 (-8.08, 0.28), p=0.07).

4. The figure shows a very high proportion of MS patients who declined to participate: some information on the reasons would be useful. It is not clear why 80/80 cases allocated to CLP received the treatment vs 72/84 in the FACETS, or why at 1 yr follow-up there were 15/81 non responders in the experimental vs 8/77 in the control group: was the ?traditional? treatment more well-accepted by patients?

Have added the following paragraph to the discussion:

Only some of those who declined participation in the FACETS trial provided reasons for doing so.

When reasons were provided, they were predominantly related to lack of time or existing work,
holiday or childcare commitments. A small minority of individuals felt that a group approach was not for them or did not wish to take part in a research trial. However, we acknowledge it is possible that there might have been a recruitment bias towards those more amenable to a non-pharmacological approach.

We are sorry for the confusion related to the term ‘non-responder in Figure 1. It was a poor choice of wording on our part and is misleading. We have changed it in the flow diagram to ‘did not return outcome measures’. This refers to the number of participants who did not return the postally administered outcome measures at one year and does not relate to treatment response. There is no statistically significant difference in the numbers who did not return their questionnaires in the two arms (chi-squared = 2.1, p = 0.15). Given that this was at 1 year follow up several months after any contact had been made with the participants we felt that this was a reasonable response rate.

5. Major revision

The ITT analyses show a modest improvement in some primary outcome measures of borderline statistical significance: given the importance to find even small effects on fatigue induced by low cost non pharmacological treatment a power analysis should be added"

We have added a short summary of the power calculation from the protocol.

Sample size considerations

The sample size requirement was 146 participants with follow-up data based on having 85% power to detect a medium standardised effect size of 0.5 for the primary outcome measures, using a two-sided 5% significance level (see protocol for justification for this medium effect size). As a variety of fatigue measures have been used in other trials, we used standardised effect sizes to enable comparisons between them.

We have added the following to the discussion section

While attrition was relatively low at one year there was a diminution of sample size to 131 (the original sample size calculation requirement was n=146). Statistical power would have been reduced
slightly to 80% (NQuery Advisor) and while still a reasonable level of power this is lower than that at
follow-ups 1 and 2 and might account in part for the slightly lower p-values obtained at 1 year follow-
up. However, we note that the limits of the 95% confidence interval for the between group treatment
effect size for fatigue severity at 1 year (-0.61, 0.01) do include the value (-0.5) of the SES specified in
the original sample size calculation.

In addition to significant improvements in fatigue severity and self-efficacy there were statistically
significant improvements in MS-specific quality of life that had not been present at 4 months follow-
up. The delayed appearance of this latter impact might be because the changes to lifestyle encouraged
by FACETS may take some time to implement effectively.

Additional point

I have now added a table of baseline characteristics to the manuscript to address point 3 and so that
readers have a better sense of the study sample.