Author's response to reviews

Title: The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers

Authors:

Luis Nacul (luis.nacul@lshtm.ac.uk)
Eliana M Lacerda (eliiana.lacerda@lshtm.ac.uk)
Peter D Campion (p.d.campion@hull.ac.uk)
Derek F Pheby (derekpheby@btinternet.com)
Maria L Drachler (jcdc.leite@googlemail.com)
Jose C Leite (jcdc.leite@googlemail.com)
Fiona Poland (F.Poland@uea.ac.uk)
Amanda Howe (Amanda.Howe@uea.ac.uk)
Shagufta Fayyaz (Shagufta.Fayyaz@lshtm.ac.uk)
Mariam Molokhia (Mariam.Molokhia@kcl.ac.uk)

Version: 3 Date: 7 February 2011

Author's response to reviews:

Dear Dr Reeve,

We are very grateful for the constructive comments from your reviewer and editorial team. We are pleased to submit a new version of our manuscript with significant improvements to reflect the comments received. These are explained below and the related amendments were entered in the text as track changes. We trust this will meet your satisfaction and we look forward to hearing from you.

Yours sincerely,
Dr Luis Nacul

Response to comments from editors

We have added the definition of ME/CFS to the title and abstract and fully reviewed the text for English language use.

Response to reviewers report

1. No comments needed

2. This has been addressed as part of the first request for compulsory review (see below)

3. The following information was added to the Results in text format, to avoid excessive use of Tables.
Mean SD(years) Median Interquartile range (years)

Age at onset 39.5 11.5 41.5 30.4 – 48.3

Fatigue duration 9.5 6.9 8 4.25 - 15

We added to Table 1 the breakdown of diagnosis by the 3 definitions, as suggested.

4. This important point is now addressed in the text. We refer to statistical significance as well as to minimum important difference (MID).

5. We have addressed this comment by reviewing the various sections of the paper.

6. We have created a sub-section in the text with Strengths and Limitations.

7. We have included additional information on our work on setting up a Disease Register for the study of ME/CFS and how this links with our preparatory work to set-up a biobank and a post-mortem tissue bank for the study of ME/CFS. We have also submitted a paper on the epidemiology of ME/CFS, which is under review, thus not referenced, and which contains further information on the study methods.

8. We have changed the text accordingly, and avoid use of terms such as ‘on average’.

9. We have re-structured and simplified the Discussion section to improve readability.

Major compulsory reviews

1. Request – To clarify the operation of case confirmation by the three case definitions

Action – We have added to the text further information on the operation of case definitions. In summary, patients were identified and invited to participate in the study by their GPs, who had already established they were cases of ME/CFS, based on their experience and on guidance on diagnosis of ME/CFS provided by the research team to them. After this first stage, consenting patients completed a research questionnaire with information on the presence of a range of symptoms and other clinical information that enabled case confirmation and classification according to one or more of the diagnostic criteria used in the study. Finally an electronic algorithm based on clinical presentation and built into the database enabled establishment of conformity according to diagnostic criteria.

R – Describe the caveat about the feasibility of Canadian CLINICAL working case definition and 1994 CDC REARCH case definition; especially the difference by the measure procedure in the samples from primary care setting or
community dwellings

A – The authors consider that both definitions are clinical case definitions, as Fukuda et al stated: “Our guidelines include recommendations for the clinical evaluation of fatigued persons, a revised case definition of the chronic fatigue syndrome, and a strategy for subgrouping fatigued persons in formal investigations.” (Ann Intern Med. 1994; 121:953-959. Clinical Working Case Definition of ME/CFS). These definitions have been widely used in both clinical and research settings and have also been compared (Jason, ----). As the participant patients were previously assessed by their GPs, and other possible explaining medical conditions for their symptoms were excluded, their clinical manifestations (signs and symptoms) were asserted by an algorithm to conform to the clinical case definitions used. This is now explained in the text.

R – It is bothersome that the authors had discussed the specificity in several places in the Discussion section

A – The authors agree that the terminology used can be misinterpreted and made changes in the text ensuring avoidance of repetitions.

2. R – The authors should be careful with scientific wording about “compare” as more statistically appropriate.

A – It is changed in the text accordingly, e.g. “Data processing and analysis” paragraph, p. 7..

3. R - In Table 5, the SF-36 scale scores were compared between subjects meeting Canadian criteria and 1994 CDC criteria. However, the two subgroups were not exclusive. That is, some subjects could be confirmed cases by both Canadian and CDC criteria. In this case, the statistics reported in the table might not be robust.

A – We reviewed Table 5 and the text in results and discussions were rectified accordingly.

Discretionary revisions

1. R –... replace “compares” with “describes”. Second paragraph in the Results section.

A – The text has been changed accordingly.

2. R - Could this association be accounted by their co-morbid conditions? If the existing data allows, the authors should describe as part of case characteristics.

A – We believe this in unlikely to be the case. The authors were strict in applying
the case definitions, and all patients with co-morbid conditions that could explain their symptoms were excluded.

3. R – Please cite the reference for the source on SF-36 diseases-specific norms. It would be useful to list the sample size for each disease-specific norms in Table 4. Eg. Back pain/sciatica (n=2635), cancer (except skin) (n=253), etc. Another caveat is that the sample means from selected disease-specific studies are not quite comparable in the age inclusion to the current ME/CFS study.

A – The source is referenced in the discussion (ref. 12 - Ware Jr. JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME: User's manual for the SF-36v2TM health survey. Lincoln: QualityMetric Incorporated; 2007), and we have now incorporated sample sizes to Table 4. Age is indeed associated with functional status, with higher scores usually associated with increasing age. While our study was restricted to individuals up to 65 years old, the population survey included individuals over this age. Unfortunately we do not have access to data for diseased population groups by age. However, as we would expect the population values to be even higher by the exclusion of elderly individuals, the comparison of those under 65 only would if anything tend to show a more dramatic contrast between those with ME/CFS and other diseased population groups. We added this point to the discussion to reflect that.

4. R – Page 10. The authors stated that “unlike disease specific measures, it can be adequately used for comparisons between people with ME/CFS and healthy individuals and those with a range of other diseases.” Is this authors’ personal statement or it could be backed-up by literature? SF-36 has been used in various studies to compare the changes over time or treatment, across illness groups or case-control. It might not be disease- or illness-specific, but it can certainly pick up certain level difference in term of health-related quality of life (or functioning status).

A – The ability to make comparisons between groups of patients with different conditions is one of the characteristics of the SF-36. We have added the appropriate reference to the text.

5. R – Page 12. The authors indicated that “The ‘role physical’ scale was the most affected of all, suggesting this could be a suitable outcome measure in ME/CFS.” What is the data evidence leading to the statement? The norm-based scores in ME/CFS cases for Role Physical, Physical Functioning, General Health, Vitality, and Social functioning were 25.4 (SD=8.2), 27.7 (10.6), 28.3 (8.0), 28.4 (7.1), and 25.7 (9.8), respectively. There is no significant difference when comparing the mean scores.

A – Role Physical presented the lowest mean value. However, we appreciate the lack of statistical significance when comparing this with some of the other indicators. We changed the text, adding the word ‘observed’, and also noted this
was ‘one of the lowest scores’, to avoid any misunderstanding.

Minor essential revisions

1. R – The 3rd paragraph in the Background section, please provide references to adjust the importance of examining caregivers’ health.
   A – References inserted

2. R – Sample size/power calculation
   A – We now made it clear in the text the comparisons we were referring to.

3. R – Throughout the Results section, the authors used the wording such as “on average”, “consistently”, “much”, “slightly”, “even”, and “actually” lower. Alternatively, the authors could determine the statistical significance using the sample mean, standard deviation, and sample size to calculate the t-statistics and p-value between the group mean from the current ME/CFS and that from selected disease-specific mean.
   A – We have revised the text accordingly.

4. R – Last sentence, Data collection paragraph, the authors stated that “The SF-36 has been used and validated in patients with ME/CFS in different settings [12-25].” Use of the SF-36 in ME/CFS is not equivalent to validation of the SF-36. The references that the authors listed were using the SF-36 instrument rather than validating the SF-36 in ME/CFS population.
   A – We changed the text accordingly, to reflect use rather than validation.

5. R – Please briefly describe what was measured for the 8 SF-36 scales in the line along with “eight health domain scales”. For example, Physical Functioning measures the functioning in running, caring groceries, climbing flight of stairs, bend, walking, bathing, etc; Role Physical includes measures on time reduction on work or activity, limitation to work or other activities, etc.
   A – Descriptions were added to the text

6. R – The authors presented the correlation results on the SF-36 scales of cases and their caregivers in addition to unmatched analysis on the group mean difference. Will the finding differs from that using matched analysis on 44 matched pairs.
   A – In fact we conducted a paired analysis. We have also adjusted to age difference between cases and controls and this has not changed the results in any significant way.

7. R – From Table 7 and Figure 2, it was not clear if the authors presented the correlation or linear regression slope coefficient. If it’s linear regression,
include the adjusted R-square in Table 7 and Figure 2.

A – Linear regression was used and the R-squared inserted in Table 7 and Figure 2.

8. R – “The fact that the scores of cases meeting the Canadian criteria were consistently lower than those with the CDC-1994 criteria further suggests that diagnosis specificity is related to disease severity, and that specific diagnoses such as the Canadian may be more appropriate for research studies investigating risk factors and disease biomarkers.” As mentioned in the comment of Major Compulsory Revisions, the group comparison in Table 5 was not statistically sound due to the overlapping subjects in both groups. In addition to the questionable statistical significance presented in the table, the lower mean scores are necessarily indicating higher specificity or higher sensitivity. One should not try to draw this conclusion based on the group mean comparison on non-exclusive groups. It requires some statistical approaches such as Kappa agreement, concordant, discordant, specificity, sensitivity, etc, given there is no gold standard classification definition.

A – We have replaced Table 5 and there is no overlap of groups. This is reflected in the statistics and interpretation of findings, which were changed in light of the ‘correct’ results.