Author's response to reviews

Title: Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution

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Version: 3 Date: 25 July 2003

Author's response to reviews: see over
To the Editor

Please consider our revised manuscript, “Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution”. We have considered all discretionary and compulsory revisions from both reviewers and have either responded to each point below and/or have incorporated their suggestions into the text. We found Dr Afari’s comments to be both thoughtful and constructive criticism. All of Dr. Afari’s recommendations were incorporated into the text and have made this manuscript a much stronger one. We did not agree with most of Ms. Merz’s compulsory revisions and have responded below. We believe the manuscript is now better and suited for publication in BMC Health Services Research.

We have checked the format of this manuscript against the BMC checklist. Thank you for your consideration of our revised manuscript.

Sincerely,

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Reviewer Niloofar Afari
The authors would like to thank Dr. Afari for such an insightful, constructive and useful review.

Compulsory revision 1
Dr. Afari recommends a more detailed discussion of the rationale for using either the CIDI or the SCID. We agree with this recommendation and have done so on page 5.

Compulsory revision 2
Dr. Afari questions the utility of the SPHERE as a screening tool for CFS primarily because it is not clear that the SPHERE would identify those with somatization disorder. In fact, the SPHERE has a subscale (formerly referred to and published as SOFA, now referred to as SOMA) that does identify somatization. However, as Dr. Afari requested, we have added more detail into this section of the paper (page 7-8) and hope that it is satisfactory.

The second part of his comment requests a detailed discussion of the rationale for recommending the SPHERE to screen for the 8 case defining symptoms. There is no rationale as Dr Afari is correct that the SPHERE does not screen all symptoms and accordingly, this language has been removed from the text. We have added further details on what approach can be taken to assess the CFS symptom complex (page 7-8).

Reviewer Susanne Merz

Compulsory revision 3a
Ms. Merz stated that our terminology was not consistent. She noted that the term CFS was used rather than chronic fatigue (CF). This manuscript is about chronic fatigue
syndrome (CFS), not chronic fatigue. We have gone through the document and made sure that we used the appropriate terminology.

She noted that references 11-13, 18-19, and 23 did not use the then current (CDC 1994) CFS criteria. We included references 11-13 as documentation for scales that measure fatigue. It is irrelevant that the studies in the articles did not use the same CFS definition because the intent was to measure fatigue severity irrespective of the disease in question. Similarly, we included references 18 and 19 to document studies establishing normative values for the SF-36 as a measure of disability. Again, the illness in question is irrelevant to such normative data. Finally, reference 23 was included as documentation of use of actigraphy to measure physical activity.

She suggests that the background be rewritten so that the reader is made aware that references 2-5 do not describe identical patient groups. We do not agree because references 2-5 chronicle the history of CFS case definitions. There is considerable overlap in all of the case definitions. Readers who are interested in the evolution of our concept of CFS over time can consult the references. The intent of the article is not to belabor this point, but rather to identify ambiguities in the 1994 CFS case definition and suggest ways that the case definition can be more uniformly applied.

Compulsory revision 3b
Ms. Merz notes that our list of differential diagnoses is far from complete and suggested additional citations that would broaden our list. We intentionally generalized so as to provide examples of the sorts of conditions that should be exclusionary and open it up to good clinical judgment. In our Group discussions over the past 3 years, we quickly concluded that it is impossible to produce a shopping-list of all possible conditions in the differential diagnosis of CFS.

She questioned whether a lifelong disease like diabetes should be viewed as a temporary medical exclusion. The authors spent considerable time discussing this and similar conditions. We do not agree with her and our recommendation must stand as the recommendation of an expert panel.

She questioned our wording of BMI > 40 and we have changed the wording. She questioned our wording of illnesses that may resolve with little or no likelihood of recurrence and we have changed the wording.

Compulsory revision 3c
Ms. Merz notes that a revised version of the manuscript should summarize new recommendations for CFS work up in a more easily surveyed fashion. We did not make recommendations concerning the work-up of patients with CFS and do not understand her comment.

She questioned our wording of BMI > 40 and we have changed the wording. She questioned our wording of illnesses that may resolve with little or no likelihood of recurrence and we have changed the wording.

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Ms. Merz notes that a revised version of the manuscript should summarize new recommendations for CFS work up in a more easily surveyed fashion. We did not make recommendations concerning the work-up of patients with CFS and do not understand her comment.

Ms. Merz also noted that the paragraph on investigation of sleep disturbance (page 10) should be complemented with recent understanding about clinically indicated tests and then suggests that microscopy of blood can give diagnostic hints and that the group take a position on the significance of a positive 2-5A test. The paragraph on sleep disturbance that she references has nothing to do with microscopy of blood, a 2-5A test, or other laboratory tests and to the best of the knowledge of the expert panel, non of these tests are
known to be clinically indicated tests for CFS.

Compulsory revision 3d
Ms. Merz suggests that we prepare a separate article reviewing the various instruments that measure the symptom domains of CFS. We note in the introduction that the objective of this article is to identify ambiguities in the current CFS case definition and to recommend revisions for improving the precision of case ascertainment for research studies. The entire reason we reviewed and discussed the various scales was to recommend standardized and validated instruments to improve precision of case ascertainment. The standardized, validated, internationally accepted instruments we suggested address each of the major symptom domains of CFS (fatigue, sleep, cognition, and pain) and also address the disability associated with CFS. To follow her recommendation would obviate our reason for preparing the article. She also suggested that we include mention of a FibroFatigue Scale, which is neither standardized, validated, or internationally recognized and does not address the multidimensional nature of CFS in sufficient detail.

Compulsory revision 4a
Ms. Merz suggested we add a summary similar to a diagnostic fill-in form that would provide clinicians throughout the world with an easily surveyed and easily accessible common instrument for their work-up and diagnosis. Dr. Merz apparently neither understood the reason for writing the article nor the difficulties of evaluating or diagnosing CFS. We note in the Background that the objective is to improve the precision of CFS case ascertainment in research studies. We further note that although we primarily intended our recommendations to apply to the research settings that many suggestions may be useful for practitioners because the recommend instruments to record and measure symptom domains and disability. We stressed the difference between research and clinical studies throughout the article. Finally, in our conclusions we noted that CFS has not been empirically defined and that we recommend an international trial using the instruments recommended in the article. In short, a “fill-in-form” as she suggested is not currently possible to construct.

Compulsory revision 4b
This article does not provide revised criteria for CFS. We suggest that if our article is accepted it be cited as Reeves WC, Lloyd A, Vernon SD, Klimas N, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Services Research 2003; Volume: page.

Compulsory revision 5a
We cannot conceive of a more easily surveyed fashion in which to present the discussion and conclusions

Compulsory revision 5b
We do not completely understand what Ms. Merz is saying. It appears that she wants us to abandon the requirement that CFS be a diagnosis of exclusion. As Ms. Merz noted the concept of exclusionary conditions makes sense only in research settings. This article was written specifically for research settings. She suggests dividing patients into one group of unexplained CFS and another of explained CFS. This is the concept of stratification that we discussed in several sections of the manuscript.

Compulsory revision 5c
Ms. Merz states that it is essential for the Study Group to suggest ONE common rating scale (for example the *FibroFatigue Scale*). As I discussed above (3d) this is impossible. She also suggested that we define additional stratification subgroups. We believe our discussion of stratification and the reasons for stratification are preferable to a shopping list.

**Compulsory revision 6**
As discussed in detail above (3d) we cannot agree to write a separate article dealing with instrumentation.
We incorporated Ms. Merz’s revisions to the abstract

**Compulsory revision 7**
We rectified the typographical errors she noted