Reviewer's report

Title: Brazilian Study in Multiple Sclerosis: a cross-sectional study to assess burden of disease and unmet needs

Version: 2  Date: 25 June 2015

Reviewer: Fernanda Queirós

Reviewer's report:

Major Compulsory Revisions

1. I did not understand your main objective: "the primary aim of the study was to determine the burden of MS under the perspective of both Brazilian society and the healthcare system". What do you mean by "perspective of Brazilian society" and perspective of "healthcare system"? These terms need to be clarified at the Background section and, therefore, make clear why would be important to compare these two "perspectives".

2. Your title talks about "burden of disease" and "unmet needs". However, your Table 1 does not present the mean annual income or any other proxy of economic classes for your sample. I assume that this variable plays a major role in a discussion about unmet needs. Please, include this information or soundly justify why it was not included in your manuscript.

3. Although the authors state that the Expanded Disability Status Scale (EDSS) is "the most frequently used disability scale employed in MS studies", it is necessary to briefly describe in the body of the manuscript how it is scored and the cut-off points used to create each disability category. That is important because the results are presented by these categories.

4. You secondary objectives are also not clear. What do you mean by "utility of specific MS-related health states and fatigue? I could not find how you investigated "possible factors associated with those health outcomes”? (which health outcomes?)

5. I also had a hard time to understand the meaning of the Health-related Quality of Life utility score. You explain it ranged from 0 to 1, with 0 representing "death". How is that possible? What does this extreme in the scale represent?

6. Table 1: The authors stated that "The frequency of early retirement due to MS was also increased by disability severity (mild 191 = 11%, moderate = 53%, and severe = 64%). Time from diagnosis to retirement and age of retirement were not markedly different across severity groups as shown on Table 1. " To make such claims that there was no difference among groups, one should present the result of a statistical test. Please, include a column to report p-values in order to support your claims regarding differences among the three severity groups. Make the adjustment on the manuscript text, including the specific p-values in the fragment commented here.

7. In Table 3 you present three partial costs (A, B, and C), which are not
described in the manuscript. At the Costs section, please describe the criteria used to create the three groups, so readers will understand why they are important to be presented separately.

8. Table 3: Instead of reporting p-values as a note, include a column to report all of them, not only the significant ones. Are these p-values for the between-subjects effect of the ANOVA, right?! You need to report F-values and degree of freedoms.

9. At the end of the subpart Costs, at the Results section, you state " In the multivariate analysis, only EDSS level was associated with higher direct costs (p=0.012). The other variables in the model were gender (p=0.210), education (p=0.134), impact of fatigue (p=0.83), episode of recurrence (p=0.075), having osteoporosis (p=0.168), MS type (p=0.227) and current activity (p=0.591), which were not associated with direct costs." In Table 3, at the notes, it is implied that you used both Kruskal-Wallis and ANOVA tests. However, in your Statistical Analysis you state that "ANOVA with partial sums of squares (Partial SS) test was employed to analyze the association between MS-related direct costs and the following variables: EDSS level, gender, educational level, fatigue level (MFIS 1 scale), MS relapse, osteoporosis disease, type of MS, and occupation." These are contradictory. Please, revise your analysis to properly describe the methodology and the results in accordance to what you explain that was done.

10. In the body of the manuscript, in the Results section (subpart Costs), you need to properly describe the results of the ANOVA test. Did you include any interaction terms in your model? What was the dependent variable used in your ANOVA model? At your Methodology, in the Costs section, the authors say that "Direct costs related to MS management were estimated by multiplying the amount of resources used by the corresponding unit cost." However, you do not specify that your analysis would look at medical and non-medical costs - as reported in the Results. As you present averages for all direct costs (medical and non-medical) and medical only, it is not clear which variables were used in the ANOVA.

11. You need to include descriptive of Health-related Quality of life and Fatigue (in your Table 1, for instance) before Figure 1.

12. Which statistical test did you use to perform the analysis for the results presented at Figure 1 and 2? The tests used for each of your results need to be better described in the Statistical section.

13. At your methods, results and discussion, I can only identify the cost of MS treatment for the health system and the individuals, as presented in your Table 3. I could not understand your inference of the cost observed and its negative impact on the Brazilian society. What are you calling "burden to the Brazilian society", as stated at the end of the first paragraph at the Discussion section?

14. The burden of MS is not solely represented by the yearly mean cost for treatment of it. Therefore, your main objective, it seems to me, should be the economic yearly cost of MS. Also, you could re-organize the summary of your three results at the beginning of the Results section, listing your economic, Health-related Quality of life and Impact of Fatigue results (these appear to your
three main outcomes that would help you to re-state your three objectives).

15. What do you mean by "health state" in the sentence: "worsening in health state evaluation following increasing in disability level could be observed."? This sentence is not clear. Also, the importance of these findings were not discussed. The authors, conversely, highlights possible limitations of their findings.

16. What does the lack of association between impact of fatigue and severity of disease means? Why do you think you did not find an association (limitations of your data)?

17. Your conclusion is not aligned with your objectives (probably because your objectives are not well and clearly described). In your methods and results, you do not describe "disease-modifying therapy", you do not specifically discuss this outcome and it is not described what the healthcare system covers.

Minor Essential Revisions

18. What do you mean by "price list consultation"? Please, find a clearer term and give the reference of the source where you got the exchange rate from.

19. I would suggest to move the description of the questionnaire MFIS-BR (Fatigue) to appear before the description of Costs. The questionnaire acronym is mentioned in the section Costs, without being described before.

20. The term "Fatigue" in your manuscript should be changed by "Impact of Fatigue in Quality of Life", or something similar. The term "Fatigue" got me confused, made me thinking about level of fatigue, which is not what you are measuring with the MFIS-BR.

21. Why the described covariates were chosen? It seems that the authors collected much more data ("comorbidities", as listed at the end of the Study Design and Patient Assessment section) and it is not clear if the selection of the covariates was based on statistical or theoretical reasons. Please, describe the criteria used to pick the covariates.

22. Osteoporosis was used as a covariate (as described at the end of the Statistical Analysis section), but was not described before in the Methodology. Was it assessed by a study's physician (following which criteria) or self-reported based on an existing diagnosis?

23. The authors state that used in the analysis " type of MS" and describe two of them in Table 1. However, there are four disease forms, right? Why did you list only two?

24. Still regarding " type of MS", probably most readers of this paper will have a solid background on MS. Nonetheless, some may be novice to the field and, because of that, it would be more informative to list, at least, these types (either a couple lines at the introduction or in the Methods section, when listing the covariates).

25. Table 1: This table also present labor force characteristics. Include such information in the title (and in the Results section, when referring to reader to this table).
26. Table 1: Anything that is abbreviated in a table should be described at the table's notes, so the table can stand alone from the main manuscript. Thus, as you spelled out "EDDS" and "n.a.", do the same for "SD", "MS" and "Y/N".
27. Table 1: Fix the headers of the columns with the four disability categories to include the name of each of them above the score’s range.
28. Table 2 is cut off in the document reviewed, which does not allow the visualization of the SD values in the last column. Be sure to fix this.
29. Table 2 and Table 3: As already mentioned about table 1, anything that is abbreviated in a table should be described at the table’s notes.
30. The acronym DMTs was not spelled out in the manuscript. Please, do so before using the acronym for the first time.
31. Figure 1 and 2: Same rationale - spell out any abbreviations. You should also improve the description of the Figures. At Figure 1, briefly describe the meaning of the Utility index. At Figure 2 improve the description by stating, for example, "MFIS scores varies from 0 to 84, with the following categories: absent (0 - 38), low (39 - 58), and high (59 - 84)".
32. You need to give some background on the Brazilian health care system. Are you presenting results for the public Unified Health System (SUS), private healthcare system or both? If you are discussing only the outcomes for patients treated by the "SUS", you need to clarify which costs are covered for the treatment of MS. You did that at the beginning of the Discussion, but I judge necessary to do it before presenting results, which will help readers to understand them.
33. You state "Currently, in Brazil, MS treatment is provided by the Ministry of Health through a Specialized Pharmaceutical Assistance Program and according with its criteria DMTs are provided for individuals with MS, following revised McDonald criteria [12,18]. Considering the 2007 year, this program had spent approximately BR$1.4 billion, and 13% of this total was related to MS treatment [19]. " This percentage, alone, does not tell the reader if this is a significant amount of the total Specialized Pharmaceutical Assistance Program expenditures. Moreover, what is the relationship between your sample’s mean costs and the total expenditure on MS treatment by this program? I would suggest you to move this role part to the introduction, to early in the paper inform the reader about the program.

Discretionary Revisions
34. I would recommend not using "etc" at the description of item "iv" in the Resources Utilization section. Instead, use "for example" or "among others".

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.