Author’s response to reviews

Title: Brazilian Study in Multiple Sclerosis: a cross-sectional study to assess the humanistic and economic impacts of disease.

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Version: 3 Date: 28 August 2015

Author’s response to reviews: see over
Dear Editor,

Thank you for the compliments and suggestions to our work. We have accepted all suggestions as described point-by-point, according with the reviewer, in the list below:

**Referee 1: Amin Torabipour**

# Major Compulsory Revision:
1. Introduction section, Authors should provide a relevant and clear background of epidemiological and economic aspects of disease in Brazil. I would recommend a brief explanation of the Brazilian health care system (how does the Brazilian healthcare system works? Do patients pay everything out of pocket? Does their plan cover anything? The following article provides a good introduction:
   - Höer et al. Multiple sclerosis in Germany: data analysis of administrative prevalence and healthcare delivery in the statutory health system. BMC Health Services Research 2014 14:381. 
   R.: Modified as proposed. Introduction was all rewritten.

2. In method section, it is necessary to define epidemiological approach (prevalence or incidence), type of costs, and study perspective. Subsequently, resource consumption data and unit costs can be gathered, and the results presented and methodically discussed, in conjunction with sensitivity analysis to test their robustness. For better interpretation of unit costs, it is need to use a scientific conceptual model of MS cost categories in order to cost analysis. Please see this reference:
   R.: Modified as proposed. Reference was assessed, cited and the article was rewritten considering these aspects.

3. Please write the method of generalization of costs (inpatients costs, hospital costs and others).
   R.: Costs were analyzed considering who paid for it, healthcare system or patient/family. Methods of cost assessment were better explained.

4. If the authors have studied some demographic variables including residence place (urban or rural), medical insurance, and marital status of patients, please provide the results in table1 because these factors can affect the costs and resources consumption.
   R.: The only variable we have studied and was not described in the article was regarding patients’ living. The information was included in Table 1.

5. Why authors have used from parametric and non-parametric tests (ANOVA and Kruskal-Wallis) Simultaneously?
R.: The respective test was performed by the variable distribution condition. If the variable was normally distributed, ANOVA one-way test was performed, otherwise, Kruskal-Wallis does. This is described on Statistical Analysis section. For the multivariate analysis, ANOVA with partial sum of squares test was employed.

# Minor Essential Revision:
Title:
- The title is not informative about the contents of the paper, it should be noted that the cost of illness study, not necessarily the burden of disease study. Hence, I recommend the following title:
  1- direct and indirect costs of Multiple Sclerosis in Brazil
  2- direct and indirect costs analysis of Multiple Sclerosis patients in Brazil
R.: Title was reviewed considering the study aims.

Abstract:
The abstract should be understood without reading the manuscript and appropriately summarize the manuscript.
R.: Abstract was rewritten.

- This study has been performed based on the patients perspective, hence, the objective of study should be revised in abstract, lines 49-50.
R.: The study was performed considering the perspective of the household and the healthcare system, which allowed to estimate the humanistic and economic impact of MS to the whole society. However the societal perspective includes the indirect cost and this analysis was not possible due to sample size limitations; this was included as a limitation in the discussion section. Study aim, methods and discussion were reviewed so this point could be better understood.

- The method's section needs to be completed. The number of patients and time of study should be added.
R.: Modified as proposed.

- In results' section, lines 58-59, the authors stated there was significant relationship between EDSS and costs (p=0.001). However, in the main text, the author reported that there was significant relationship between EDSS and direct costs (P=0.012). The authors should state the exact rate of significant level both abstract section and main text. ~
R.: The right value is 0.01.

- The conclusion's section should be stated based on the findings of this study. This study has been performed based on the patients' perspective, not according to the health system perspective.
R.: Modified as proposed. The conclusion was all rewritten, however the study was performed considering the household and healthcare system perspective, as stated above.

Introduction:
Reviewer suggest the following comment to improve this section:

-In line 72: authors stated that 2.5 million people are living with MS. Whereas, These data are as to 2005 (approximately ten years ago). Hence, reviewer suggest following reference:

For example:

R.: Modified as proposed. Introduction was all rewritten; the references were assessed and cited.

-It is need to be discussed the role of cost of illness study in the health policy making.
R.: Modified as proposed.

-line 76: please write the short sentence.
R.: We did not understand this statement.

-The authors should provide a rationale for performing the study based on a new review literature. Please focus on the new and relevant literature.
R.: Modified as proposed. Introduction was all rewritten.

-The introduction should be strengthened.
R.: Modified as proposed. Introduction was all rewritten.

Methods:

-The time of study should be provided in method section.
R.: Modified as proposed.

-lines 89-90: please clarify the number of patients and the sampling method.
R.: Modified as proposed.

-The authors should be explained the number of public and private centers separately.
R.: Modified as proposed.

- line 108: the authors have mentioned that patients were asked about the costs of hospital stay. It would be better that hospital cost be computed based on the medical record of patients. Why didn't you use medical record to calculate hospital costs?
R.: Patients were asked only about the resource consumption, the cost of hospital stay was assessed through official price lists considering the type of funding, which was better reported in the manuscript. The only cost reported by the patient was those funded by himself.

-In resources utilization section, lines 105-110: please mention the references to classify resources.
R.: Modified as proposed.

-Did you calculate the travel expenses as unit costs?
R.: No. This information was not collected.

-In costs section, line 112: it is recommended that authors discuss the type of costs according to new references.
R.: Modified as proposed.

-In health-related quality of life section, lines 129: why didn’t you use from World Health Organization-quality of life questionnaire?.
R.: As this study followed a cost-of-illness methodology, the EQ-5D was more appropriate. It is widely used and provides robust measures of utility.

-In line 135: please provide more details about conversion method of EQ-5D to a single index.
R.: Modified as proposed.

-In statistical analysis, please clarify the statistical distribution of the dependent variables (normal or non-normal distribution).
Results:
- Please show the disease modifying drugs in table 2 and 3 (such as interferon).
R.: Modified as proposed.

- In table 3, it is necessary to provide direct and indirect costs separately.
R.: Indirect costs were not calculated as stated in lines 301-302. In table 3 costs regarding direct medical and nonmedical resources are reported.

-Line 177: Change "meanwhile" to "however".
R.: Modified as proposed.

-Line 217 and 219: the word "annual costs" would be a better word choice than the phrase, "yearly costs."
R.: Modified as proposed.

-Page 8, line 230: remove the phrase, "in the sample".(Change "in the sample" to "the.")
R.: Modified as proposed.

-In productivity loss section, line 185: the word "patients" would be a better word choice than the phrase, "total samples."
R.: Modified as proposed.

-Line 223 to 226: this results is not shown in table2. please add "P value" in table
R.: Table 2 is shown in the manuscript just to illustrate the amount of resources used in order to calculate costs. Thus, we included p-values only in table 3, which is the real aim of the study.
Besides, tests would not be conclusive once there are few observations in each category of resource.

-P value be added to table3 as a new column
R.: P value added to table 3.

Discussions:
-Authors should revise better and more the current literature in the field. For example, a good study can be found here:
R.: Modified as proposed. The discussion was all rewritten; references were assessed and cited.

- Line 245: the word "annual costs" would be a better word choice than the phrase, "yearly costs."
R.: Modified as proposed.

Conclusion:
-Conclusion section isn't adequate and relevant.
R.: Modified as proposed. Conclusion was all rewritten.

References:
-Kindly provide the last accessed detail and check the formation of reference 14.
R.: Reviewed.

Referee 1: Fernanda Queiros

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".
R.: As stated above, the study was performed considering the perspective of the household and the healthcare system, which allowed to estimate the humanistic and economic impact of MS to the whole society. However the societal perspective includes the estimation of indirect costs, as this outcome was planned but not performed due to limitations of sample size, the study aim was maintained and this issue was highlighted in the discussion section. Introduction, study aim, methods and discussion were reviewed so this point could be better understood.
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.
R.: Modified as proposed.

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.
R.: Modified as proposed.

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?)
R.: The study objectives were rewritten. The associated factors assessed were those related to costs. Utility measures were also better explained.

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?
R.: The topic in the methodology section regarding utility was rewritten. Quality of life and utility measures are different concepts that are related to each other. Utility derives from the economic theory from Neumann and Morgenstern of decision making, in which a model was developed to represent how people make decisions when face uncertainty conditions, based on individual preferences. So, utility measures that are derived from a judgment of individuals of its health status and summarize concepts related to health and quality of life, are usually used to definition of public health policies, resource allocation and the evaluation of services and programs [31]. Measures usually range from 0 to 1, that conceptually are valued using as a reference the death as the worst health state (equal to 0) and the perfect health as the best health state (equal to 1).

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.
R.: p value added on table 1.

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.
R.: Modified as proposed. Methods of cost analysis were reviewed.
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.
R.: P-values were added to table 3. Data reported in this table are not related to the multivariate model; results from this analysis were described only in the text.

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.
R.: Modified as proposed. Methods and results were rewritten.

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.
R.: The text was modified.

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

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.
R.: Modified as proposed. Statistical methods were reviewed.

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?
R.: Once health system and the individuals compose the society, we call these perspectives as a burden for the whole society. These perspectives were reviewed along the article.
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).

R.: We stated our main outcome as the “burden” of the disease because these three outcomes were assessed. The perspectives of the analysis were rewritten along the article.

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.

R.: As reported above, utility measures are reported as health states that can range from 0 to 1. This concept was better described in the text.

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)?
R.: These limitations were better discussed in the text. As this was not the main objective of the study, this difference could be attributed to sample size.

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.

R.: Modified as proposed. Conclusion was all rewritten.

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.
R.: Modified as proposed.

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.
R.: Modified as proposed.

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.
R.: Modified as proposed.

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.
R.: All of the collected variables with statistical and/or clinical importance were included in the model. The model was reviewed and the variable “presence of any self-reported comorbidity” was included.

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?
R.: All comorbidities were self-reported by patients. Modified in the text.

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?
R.: Only patients with the diagnosis of relapse-remitting and secondary progressive MS were included. Study Design and Patient Assessment section was reviewed.

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).
R.: Modified as proposed.

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).
R.: Modified as proposed.

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".
R.: Modified as proposed.

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.
R.: Modified as proposed.

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.
R.: Modified as proposed.

30. The acronym DMTs was not spelled out in the manuscript. Please, do so before using the acronym for the first time.
R.: Modified as proposed.

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)".
R.: These descriptions were included in the Methods section.

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.
R.: Modified as proposed.

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
R.: Modified as proposed.

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".
R.: Modified as proposed.