Author’s response to reviews

Title: PREVALENCE AND CORRELATES OF NON-ADHERENCE TO IMMUNOSUPPRESSANTS AND TO HEALTH BEHAVIOURS IN PATIENTS AFTER KIDNEY TRANSPLANTATION IN BRAZIL - THE ADHERE BRAZIL MULTICENTRE STUDY: A CROSSSECTIONAL STUDY PROTOCOL

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Author’s response to reviews:

Juiz de Fora, 8th November 2017,

Subject: Revision of MS: BNEP-D-17-00188R1 Manuscript, BMC Nephrology.

BMC Nephrology

Dear Editors,

Thank you for your helpful comments and suggestions to improve the quality of our manuscript. We have carefully reviewed each point raised and the subsequent questions asked. Below you will find a point-by-point response (addressed in italics). We have added a revised manuscript as well as a copy in which the changes are indicated in red. We hope that our revisions and responses are acceptable and that the manuscript now conforms to the standards of BMC Nephrology.
Yours sincerely,

Helady Sanders-Pinheiro

On behalf of my co-authors

To editors

While the paper was under evaluation the project was selected to receive grants from and Astellas Pharma Brazil Ltd. As other funding institutions, this institution had no role in the design of the study and collection, analysis, interpretation of data and in writing the manuscript.

The new grant source was added to the text, Funding, page 21, line 23-24; page 22, line 1-3.

“The study received internal grants from Fundação Instituto Mineiro de Estudos e Pesquisas em Nefrologia (IMEPEN), internal research grants from Libbs Pharmaceutical Ltd. and from Astellas Pharma Brazil Ltd. None of the grants has a Grant number. The institutions had no role in the design of the study and collection, analysis, interpretation of data and in writing the manuscript.”

Concerning the comments from Referee 1:

We thank you for your comments and suggestions to strengthen our paper.

1. The sample size calculation was based off of a non-adherence rate of 50%. While I realize this prevalence of non-adherence was identified in a study previously undertaken by the authors in Brazil, the authors state that the study was single center. Compared to previous literature (which the authors also quote) this prevalence rate seems quite low, and I think the study would be more
robust if it used a more prudent estimate, especially since the authors acknowledge that there is a large amount of regional diversity in Brazil.

The sample size was calculated for population frequency studies, considering the kidney transplant (KT) population under follow-up in Brazil in 2012, according to Brazilian Transplant Register (RBT, http://abto.org.br/abtov03/Upload/file/RBT/2012/RBT-dimensionamento2012.pdf), of 31,241 patients. The hypothetic frequency of non-adherence of 50% was chosen based on the few available studies applying the same diagnostic method and the available Brazilian studies.

The prevalence of Non-adherence varies according to the diagnostic methods used. In the ADHERE BRAZIL study we opted to combine methods in order to increase accuracy, called triangulation method. There are few studies applying this strategy in KT patients:


4. Silva AN et al., Nephrology 2016; 21(11):938-943: 03 methods [self-report (BAASIS), assay and collateral report], a Brazilian KT single centre study – prevalence of 70.5%.

Furthermore, there are only eight Brazilian studies about non-adherence to immunosuppressives in KT. They report a prevalence of non-adherence, evaluated by different methods, varying from to 3.4 to 70.5%, and two of them have already been cited above. Table 1.
Study, year  | Diagnostic method of Non-adherence | Proportion
Bittar et al,  |  |  |
Transplant Proc.  |  |  |
1992;24(6):2720-2721  | Stop of IMS  | 3.4% |
Michelon et al,  |  |  |
Transplant Proc;  |  |  |
2002,34:2768-70  | Stop of IMS  | 5.2% |
Branh et al,  |  |  |
Transplant Proc.  |  |  |
2012;44(8):2391-3.  | IMS Refill  | 58.7% |
Marsicano et al,  |  |  |
BMC Nephrol 2013;14:108.  | Self-report (BAASIS)  | 35.0% |
Garcia et al,  |  |  |
Int Urol Nephrol.  |  |  |
2015;47(11):1899-905.  | Self-report (ITAS)  | 46.4% |
Marsicano et al,  |  |  |
PLoS One. 2015;  |  |  |
10(11):e0138869  | Self-report(BAASIS), IMS level, Collateral report  | 51.0% |
(Already cited above)
So, based on the wide variability we decided to use the hypothetical frequency of 50%.

For the sample size calculation for frequency studies, we need also to choose the sample error and the design effect. We applied, for all simulations, a sample error of 5% (confidence interval of 95%). The design effect is an adjustment made to find a survey sample size, due to a sampling method, resulting in larger sample sizes, than you would expect with simple random sampling (in this case it is equal to 1.0) (Heo M et al. Statistics in Medicine. 29 (3): 382–390). We chose participating centers by convenience but aiming to ensure an adequate representativeness. However, patients were randomized. So, as it was not possible to apply a design effect of 1.0, and based on the characteristics of the sampling strategy, we judged that a design effect greater/equal to 2.0 would be adequate. We used a design effect of 3.0 (we assume that the stratified and clustered sample would have a threefold increase relative to the usual variance estimator for independent samples) and obtained a sample size of 1,139 individuals. We expect a participation rate of 70%. If we consider a hypothetical frequency of non-adherence of 60% or 70%, applying a design effect of 2.0, we obtain 729 and 1094 patients respectively. Simulations of sample size are summarized in Table 2. Furthermore, the sample size for prevalence is based on the Binomial distribution, and as can be seen in Table 1, the 50% prevalence is the estimate that maximizes the theoretical variance, given by p (1-p), where p is the hypothesized prevalence, providing bigger sample sizes.

Table 2. Simulations of sample size for frequency studies
(http://www.openepi.com/SampleSize/SSPropor.htm)
<table>
<thead>
<tr>
<th>N</th>
<th>Sample error</th>
<th>Design effect</th>
<th>Non-adherence</th>
<th>Sample size</th>
<th>Prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.241 5%</td>
<td>2.0</td>
<td>50%</td>
<td>759</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.241 5%</td>
<td>3.0</td>
<td>50%</td>
<td>1139</td>
<td></td>
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</tr>
<tr>
<td>31.241 5%</td>
<td>2.0</td>
<td>51%</td>
<td>759</td>
<td></td>
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<tr>
<td>31.241 5%</td>
<td>2.0</td>
<td>60%</td>
<td>729</td>
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</tr>
<tr>
<td>31.241 5%</td>
<td>3.0</td>
<td>60%</td>
<td>1094</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.241 5%</td>
<td>2.0</td>
<td>70%</td>
<td>639</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.241 5%</td>
<td>3.0</td>
<td>70%</td>
<td>959</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.241 5%</td>
<td>2.0</td>
<td>70.5%</td>
<td>633</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.241 5%</td>
<td>3.0</td>
<td>70.5%</td>
<td>950</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were three typing mistakes regarding the Sampling design and setting section: total KT population - 57815 (instead of 59001), Methods section, page 11, line 7; KT population under follow-up – 31241 (instead of 20504), Methods section, page 11, line 8; and sample size 1139 (instead of 1130), Methods section, page 11, line 11.

2. The multilevel correlates of non-adherence to immunosuppressants are collected by investigator-developed self-report questionnaire. Is it possible to obtain some of this data from chart review rather than patient recall? (ex: Number of treated acute rejection episodes, creatinine, estimated glomerular filtration rate, re-hospitalizations may be difficult for patients to answer).

Clinical data is retrieved from medical files and not from patient self-report.

This information is cited in Methods section, page 13, lines 5-14.

Patient level: Demographic (age, sex, race, education, employment status, marital status, family income), disease related (aetiology of kidney disease, treatment modality prior to transplant, pre-
emptive transplant, time on dialysis, donor type, post-transplant time, comorbidity, height, weight), and therapy related data (drugs of immunosuppressive schema, number of immunosuppressive medications, daily number of doses of immunosuppressants) are collected through structured interview and review of charts [20,26,58-61]. The following post-transplantation clinical data is collected from medical charts: number of treated acute rejection episodes, creatinine level, estimated glomerular filtration rate, and re-hospitalizations [52,61-63] (Additional Table 2).”

We have clarified the text in the introduction of Methods section, page 12, lines 7-9.

Variables are measured using established instruments, investigator-developed measures specific for this study or collected from medical records.

3. The exclusion criteria states that patients will be excluded if the immunosuppression is based on drugs that the blood monitoring is not available or not covered by Brazil’s health system (e.g. Mycophenolates). Just to clarify, does mean that any patient on mycophenolate will be excluded or does this mean that patients only on mycophenolate will be excluded? (I assume it is the later, but I think this should be clarified in the paper).

Patients will be excluded only if they exclusively take immunosuppressives that blood dosages are not covered by Brazilian Public Health System, e.g. mycophenolates without calcineurin or proliferating signal inhibitors. We modified the text to make this information clearer.

Methods section, page 10, lines 22-24; page 11, line 1.

"Patients are excluded if the immunosuppressive regimen is only based on drugs for which blood monitoring is not available or not covered by Brazil’s health care system, e.g. mycophenolates without calcineurin or proliferation signal inhibitors."