Author's response to reviews

Title: Understanding Barriers to Optimal Medication Management for Those Requiring Long-term Dialysis: Rationale and Design for an Observational Study, and Quantitative Description of Study Variables and Data

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Author's response to reviews: see over
Tuesday, 27 January 2015

Dear Sir / Madam,

On behalf of my co-authors, I submit for review and possible publication in *BMC Nephrology* a revision of the Study Protocol MS: 1194539862146567.

In keeping with the revision, the paper has been re-titled “Understanding Barriers to Optimal Medication Management for Those Requiring Long-term Dialysis: Rationale and Design for an Observational Study, and Quantitative Description of Study Variables and Data”.

As a general comment, we have decided to embellish the paper considerably, and given the (very appropriate) concerns of Dr Tennankore about how the data will be analysed and handled (normality, regression techniques). In the 6-7 months since inception of this paper, we have actually completed data collection and are now beginning data analysis. This allows us to add in a descriptive analysis of study data, which is necessary to ensure instrument reliability and a (normal) distribution of psychometric scores that is appropriate and suitable for our analytical plan, as stated in the paper. This is what we have done.

We have also decided to provide our case report forms and the entire data collection survey tool as additional files – Appendix 1 and Appendix 2.

We hope the paper will not be viewed as being more substantial, and of more interest to readers.

I will continue to serve as the corresponding author. In advance, thank you for your consideration.

Sincerely,

Mark R Marshall
Associate Professor in Medicine
Reviewer Tennankore

1. Although including all the approximately 650 patients dialyzed would be ideal, I acknowledge that from a cost/resource standpoint, this may not be feasible. However, there should be more detail around how the random sample will be selected. How will random selection occur (computer based, random number etc...)? How will you ensure a reasonable sample of home modality (PD and HHD) and in-center patients will be included? Will there be consideration for equal selection of ethnic groups? (Maori/Pasifika). Will there be any weighting that will occur? To limit bias and ensure the representation is a true cut of your current population, I would include this in the protocol.

Thank you. We have clarified the participant selection process on page 8

“How participant selection was by computer-generated random selection from the service census. Selection was stratified by two factors to generate equally sized groups within 6 classifications, as defined by the following strata: recorded ethnicity from clinical records (NZ Māori versus Pacific Peoples versus “other” ethnicity), and location of dialysis (in a facility [in-centre HD] versus at home [home HD or PD]).”

2. How were the qualitative questions derived? Was there choice from a number of questions after which consensus was achieved? Details around this should ideally be included in the protocol.

Thank you. We have clarified the derivation of these questions on page 11.

“These questions were developed after brainstorming by the research team, and discussions with local patient support groups within the CMDHB programme.”

3. Appreciating that a more detailed statistical analysis is usually present in the manuscript, it would still be ideal to add a few details to the analysis plan.
   a. For the comparisons-what groups will be compared (low adherence vs normal/high, three levels etc...). This will be relevant when considering statistical analysis-ANOVA/Kruskal Wallis might be more appropriate for multiple group comparisons
   b. How will the Likert scale items be treated? Continuous normal, continuous non-normal etc...
   c. For the regression analysis: what will the dependent variable be? Normal/High vs. poor compliance? What variables will be included in the multivariable regression model? If it is unknown at this point-what will be the threshold for statistical significance to include variables in the model?

Thank you. These are of course critical questions, but are usually beyond the scope of a protocol article, when generally the authors have no inkling as to the eventual data distribution. However, we accept that these are crucial issues, and of course the reader
would like to know what we are going to do with the data.

So, there are two separate questions here, one around how we are going to handle the scores from the psychometric constructs (continuous or categorical), and the other around what are we going to develop in terms of models.

To answer the first point, we have included an analysis of distribution of study data on page 12.

To answer the second point, we have included a description of the customary approaches to modeling of these data on page 13.

Of note, we do not plan to use the somewhat blunt generic OLS approach that is favoured by medical researchers. For these data, we will attempt to use a kind of structural equation modeling technique. At this time, it is not appropriate to make a call on what are going we are going to include in the models as significant mediating or instrumental variables, although for your interest only the example that we have included as Figure 1 in the revised manuscript is in fact the subject of our next paper from this study.....see below

![Figure 1](image)

Table 1: Regression Analysis - Predictors of Medication Adherence

<table>
<thead>
<tr>
<th>Predictor</th>
<th>b</th>
<th>SE B</th>
<th>β</th>
<th>p</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necessity</td>
<td>0.15</td>
<td>(0.02, 0.3)</td>
<td>0.06</td>
<td>0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>Concerns</td>
<td>-0.133</td>
<td>(-0.23, -0.04)</td>
<td>0.48</td>
<td>-0.28</td>
<td>0.01</td>
</tr>
<tr>
<td>Medical Knowledge</td>
<td>-0.15</td>
<td>(-0.41, 0.17)</td>
<td>0.14</td>
<td>-0.08</td>
<td>0.42</td>
</tr>
</tbody>
</table>
| R²=0.11

![Figure 2](image)
4. **Consider including details around cause of ESRD, and whether or not patients had a failed kidney transplant.** There may be some information to gather from potentially non-compliant transplant patients that did not adhere to their anti-rejection medications.

Thank you, done

5. **In addition to the NZDep score, I would also present the sub-components (income, employment etc...) separately as there may be interesting information to derive from this.**

Thank you. Where we can, we have done this. Unfortunately, the Ministry of Health provides the NZDep score to us only as an aggregated score. However, we have collected some of these data independently.

6. **Consider adding the Morisky Scale as a figure to the manuscript. As it is the primary outcome, it would be a valuable piece of information for readers.**

We have also decided to provide all our case report forms and the entire data collection survey tool (including the MMAS-8 tool) as additional files – Appendix 1 and Appendix 2

**Reviewer Griva**

1. **My main reservation relates to low power that may threaten the generalisability of findings and their potential contribution to the current literature.** The proposed sample size is too small and target population too heterogenous to draw any meaningful conclusions to guide future interventions. The target sample of 100 patients is purposeful very diverse including patients on different modalities (Home HD and PD and HD that ) and from different ethnic background. The resulting subgroups would therefore be far too small to allow tailoring of programs of support. I would hence like to suggest increasing sample
size or perhaps limiting to one modality so that more meaningful conclusions can potentially be drawn.

Thank you. For conventional regression analysis, we agree. However, for other regression techniques (including those which we are planning to use), this is not necessarily the case. For instance, the use of structural equation modeling would generally require random sampling of only <100 cases for modeling, if the dataset were larger than this. Our decision to limit the sample size to 100 was a considered one, somewhat based on a cost/resource standpoint, but more so from a standpoint that the techniques we are using generally require much smaller sample sizes than the somewhat blunt OLS approach that is favoured by medical researchers (see example above) comparative to mediation analysis (implemented by PROCESS in SAS).

2. The authors claim that determinants of non adherence are not well understood –which is only partly true as there are several studies documenting associations between cognitions/beliefs and non adherence in hemodialysis yet the proposed investigation lacks power to ascertain relationships more confidently.

Thank you. We feel that our statement is true and supported by the literature (as reviewed in the manuscript). Most non-adherence data is in HD, and centered upon adherence to dialysis schedule, which is a totally different kettle of fish from medication non-adherence.

3. Would parental consent be sought for patients under the age of 18 (or is 16 considered adequate for consent); related to this are questionnaires validated to use for patients below age of 18.

Thank you. In New Zealand, 16 is an adult…at this age, legal parental consent is not ought nor sufficient. There literature on the various instruments in the 16-18 year range is patchy – there is abundant literature using the MMAS-8 to assess adherence in young adolescents, but fewer data on the other constructs. Of note, the youngest patient in the eventual 100 patients was 17, and the next youngest 24. We feel that the sampling frame is still valid.

Reviewer Raynor

1. The study design appears to be based upon interviewing each patient about one medication that they are taking. These can vary considerably, for example from a subcutaneous erythropoietin stimulating agent to a dietary phosphate binder. The choice of agent discussed is left to the patient. One could propose that problems with adherence differ between different types of medication. It is not clear how the issues of adherence that differ between types of medication will be studied independently of the other demographic factors that are being studied when the choice of medication being discussed is not chosen at random.

Thanks you. We agree, but this was a pragmatic decision. So many of our home HD patients are not on phosphate binders or antihypertensive medication, and with the
changing practice patterns around Hb targets, ESA use is very varied as well. Our pragmatic approach must be regarded as a limitation of the study, however, and we have added this to the discussion on page 14.

2. The interviews are not being recorded but are being conducted by a pair of interviewers. It is not clear why they are not being recorded for future qualitative or thematic analysis.

Thank you. Our decision to not record was a considered one, based on a cost/resource standpoint. In addition, as you will see from Appendix 2, the qualitative portion of the overall study is rather small, and supplementary rather than a core feature. As it is, we have ample written notes that will be analyzed later. However, this compromise can be expected to reduce the strength and number of insights from the qualitative portion of the study, and this has been noted on page 14.