Author's response to reviews

Title: Effects of exercise on kidney function among non-diabetic patients with hypertension and renal disease: randomized controlled trial

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Author's response to reviews:

Reviewer's report
Title: Need for Exercise among Patients with Hypertension and Renal Disease (NEPHROS Trial): Randomized Controlled Trial
Version: 1 Date: 31 October 2011
Reviewer: Kevin C Abbott

Reviewer's report:

1) Barcellos et al present a proposed protocol of a RCT comparing regular exercise among patients with non-diabetic CKD and outcomes, most esp eGFR and quality of life, at 16 weeks. Because the exclusion of diabetic patients, who comprise ~50% of CKD patients, is so important, this should be included in the title and methods section of the abstract.

R: The title of the manuscript was changed to “Effect of exercise on kidney function among non-diabetic patients with Hypertension and Renal Disease: Randomized Controlled Trial”. We now also mention the exclusion of diabetic patients in the abstract.

2) Why did the authors exclude diabetic patients?

R: The first idea was to include CKD patients independent of the etiologic disease, but this would lead to very different prognosis at the inception of the study. (Fletcher, 2005) The aim of the trial is to have two groups of individuals with similar prognosis, differing only due to the intervention.

3) The other mean issue is the choice of change in eGFR as an outcome and the use of their internal population to estimate sample size. Because the authors will be assessing longitudinal changes, use of a cross sectional population to estimate sample size is likely not the best choice.

R: In order to calculate the expected change, baseline data are needed, and
unfortunately, there were no Brazilian data available prior to our study. Therefore, we ran a formal pilot study to obtain the estimates and assumed a change of 10% in eGFR to be clinically relevant. These parameters were used in the sample size calculation and are now mentioned more clearly in the text. In the ideal world, we would have data on longitudinal changes in eGFR, but this information is not available in patients in intermediate stages of kidney disease.

4) The authors cite the MDRD study and use that formula (they need to specify exactly which one since there are several; the four variable formula is most commonly used).

R: We used the four variable formula, and now mention it in the text.

5) Using data from the MDRD study, how many patients would have been required to see a difference of 10% in eGFR at 16 weeks? Is this difference an absolute difference between the two groups or is it a "delta delta", namely the difference in change between baseline and 16 week eGFR, between the two groups?

R: Sample size was calculated to see a difference in eGFR between the two groups in the post-intervention phase. However, the sample size proposed also allows detecting change differences of 10% or more in the intervention and control groups as compared to baseline values. This is now mentioned in more detail.

6) It is possible that at 16 weeks, acute hemodynamic changes might be seen rather than persistent changes in kidney function.

R: We agree with the reviewer, and this is why our team includes experts in exercise physiology. As the reviewer is aware, the ideal duration of exercise to produce a persistent effect over the kidney function is unknown. In the review by Johansen KL, four of the ten studies on exercise in individuals with CKD the intervention lasted 12 weeks. We opted not only to have an evaluation at 16 weeks (end of the intervention), but also another one at 24 weeks, exactly to be able to test whether or not the possible changes due to the interventions will be sustained. This is now mentioned.

7) The authors mention medications as covariates, but will any specific medications be considered causes for exclusion (warfarin, for example, or beta blockers, or digoxin?) If not how will the authors assure random distribution between groups (ie does the sample size analysis account for this?)

R: Type of medication in use was not an exclusion criterion for this study. We are assuming that the random allocation of subjects will produce two groups which are comparable at baseline, not only in terms of kidney function, but also in terms of medication use. If we are unlucky and this is not the case, we can adjust for medication use (different types) in the analysis. This explanation was added to
8) How are the groups to be randomized? By computer random number assignment, or some other scheme? We need to be sure the groups are not alternating, which can introduce bias.

R: Individuals will be allocated to the intervention or control group by simple randomization in blocks of six. We will first prepare a list with the names of all the selected patients. Then, three pieces of paper where the word “Intervention” was written and three with the word “Control” will be put in a dark envelope. So, the pieces of paper will be taken from the envelope one by one and the status intervention or control will be assigned to the patients in the list. This procedure will be repeated for every group of six patients. The researcher in charge of making the random allocation was not involved at the screening process of the participants. The “Random allocation” sub-section was expanded for clarification.

9) In addition to the exclusionary criteria, are there criteria for assessing that exercise would not be safe for patients, since it is assumed most patients have been sedentary? Will there be an "acclimation period" to allow patients to work up to a reasonable exercise schedule?

R: All patients from the intervention group will be submitted to an acclimation period, in which risk assessment will be evaluated, as well as light and moderate-intensity activities will be prioritized. The whole exercise protocol was revised in order to make this step clearer.

10) How will patients be contacted in their homes? Might this be considered intrusive?

R: In the Brazilian Unified Health System, community health agents usually visit households. Therefore, this will not be considered intrusive. With the approval of the City Secretariat of Health and of the heads of the health centers, the research team will invite eligible patients to take part. This was done before in several Brazilian studies and worked satisfactorily in all cases.
Disease (NEPHROS Trial): Randomized Controlled Trial" may not consistent with the study design. Need for exercise.....may be answered by using descriptive design to explain the need for exercise... I suggest to modify it to be "Effect of exercise on increasing kidney function among Patients with Hypertension and Renal Disease: Randomized Controlled Trial".

R: We have changed the title to “Effect of exercise on kidney function among non-diabetic patients with Hypertension and Renal Disease: Randomized Controlled Trial" in order to comply with the suggestions from both reviewers.

2) Sequence of the methodology should be modified in a proper way of RCT design. Suggestion is a) Design and setting, b) Recruitment and eligibility including inclusion and exclusion criteria (with sample size calculation, this can be add to the analysis subheading), c) Random allocation, including how to generate list random numbers and allocation concealment, d) intervention and procedure, e) outcomes (primary and others) with description of their measurements f) data collection and g) data analysis.

R: The structure of the Methodology section was revised and changed according to the CONSORT statement for randomized trials of nonpharmacologic treatment.

3) The author calculated 63 subjects for each treatment group and expanded to be 100 each. Even the reasons are presented, it is unclear whether the increase number is appropriate. The author should provide more concrete information, e.g. expected % of loss to follow-up, etc.

R: Sample size was expanded to prevent the effect of losses of follow-up estimated by 20%. This subsection was expanded for clarification. We actually opted to stick with 75 subjects per group instead of 100.

4) Sample size was calculated by using the estimate of primary outcome, glomeruler filtration rate measured at the end of 16 weeks. This is not consistent with the interest repeated measures of the outcome at before, 8 and 16 weeks after starting interventions and 8 weeks after the end of intervention. The estimate sample size may be inappropriate to answer research question.

R: The evaluation at 8 weeks does not aim to test the main hypothesis of the study. It is actually a process evaluation. The 24 weeks evaluation is aimed to test a different research question: Are the benefits achieved (if any) sustained after some weeks (this issue is actually highlighted by reviewer 1)? Because we calculated our sample size to test the main hypothesis of the study (at 16 weeks), we now mention the issue raised by the reviewer in the text.

5) In the random allocation on page 8-9, the authors present detail of baseline characteristics and how data will be collected. This is not the stage to present the information. However, it is unclear whether random allocation will be concealed before providing intervention.
R: This sub-section was re-written and explanations on random procedures and allocation were included. See answer to Comment #6 below.

6) The author present block of six will be generated for balancing sample size between the two groups. I wonder whether it can be apply for the 100 sample size of each.
R: Now clarified.

7) Duration of intervention should be clearly presented.
R: The intervention will last 16 weeks. This information was added to the Methodology section of the new version of the manuscript.

8) Quality of life is mentioned as one of the primary outcomes but it is not information in the primary and secondary outcomes.
R: The “Outcomes” subsection was expanded to contain information on quality of life as recommended by the Reviewer.

9) Statistical analysis is unclear which outcomes will be analyzed by which statistic for intervention comparison. In the RCT we don’t need to do the comparison analysis of baseline characteristics between the groups. It is not the research objective.
R: Baseline characteristics will be compared to identify covariates to which we will have to adjust the effect of the intervention assuming that the randomization may not be perfect to prevent any relevant difference in terms of prognosis of the disease between the two groups. (Lang TA, 2006) Assuming the two groups will be comparable, no need to adjust for covariates will be needed. The “Data analysis” sub-section was expanded to attend the criticism of the Reviewer with regard to statistic methods that will be used for each outcome.