Author’s response to reviews

Title: Auto-titrating Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnoea after Acute Quadriplegia (COSAQ): study protocol for a randomized controlled trial

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Author’s response to reviews: see over
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Dear Editorial Staff,

Thank you for the opportunity to respond to the reviewers comments on our paper entitled “Auto-titrating Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnoea after Acute Quadriplegia (COSAQ): study protocol for a randomized controlled trial”. We are pleased to note that the reviewer considered the paper of “outstanding merit and interest to the field” and that there are no mandatory revisions required for the paper. I have outlined our point-by-point response to the Discretionary Revisions below

Discretionary Revisions:
1. The investigators estimate that approximately 820 admissions with quadriplegia will be required across the ten participating centers to ensure recruitment and randomization of 150 subjects. The length of the study is projected to be six years. Given the inherent difficulty in accruing subjects for study after suffering an acute spinal cord injury, an overview of the number of annual admissions for acute SCI to these centers would be of value in determining feasibility of recruitment.

During the protocol development and initiation of the trial, site visits were made to each of the participating sites, acute admission records audited and feasibility assessed. As noted in the power calculations and feasibility section of the protocol, these assessments were initially made based on the experience of the previous feasibility trial. As the reviewer notes, recruitment in acute SCI is challenging and the initial estimates of likely participant accrual to each individual unit/site have been as projected. However, the rate of participant consent observed in the uncontrolled feasibility study has not been replicated thus far during the RCT. Attention has been paid to maximizing participation at each site and as at end-April 2013, we have randomized 82 participants. Based on these actual accrual rates, the study remains on-track to recruit and randomize the required 150 participants within the allotted time.

2. The psychological and physical trauma associated with an acute SCI is of course highly significant. How do you intend to control for changes in neurocognition that might be a consequence more of time since injury rather than that associated with CPAP treatment? For instance, if the mean time since injury to randomization for the cohort receiving CPAP treatment turns out to be 1 month, and that for usual care alone 4 months, might not cognitive testing differ substantially between the two groups regardless of CPAP treatment, and yet both groups be considered “acute” injury. Will randomization be matched for time since injury?

The reviewer raises an important consideration. The neurocognitive and other variables will be analysed as “change within subject over time” and as such, subjects will act as their own control, but this may not account for substantial baseline between-group differences. Our statistical advice was that with a sample of 150 participants, this risk (and the similar one in point 3 below) are unlikely as “time since injury” should be randomly assigned across the groups and any mean difference would arise solely from chance. Notwithstanding this, “time since injury” is recorded and can be tested for significance and included (e.g. in mixed model analyses) if indicated.
3. Along the same lines, it might be difficult to assess the effects of CPAP on spirometric function, which is known to improve significantly with time during the first year post-injury.

See above

4. Is there any reason to assess the quality of life instrument, given that the investigators found so much variability in this assessment during the feasibility study?

During study trial development, the question of AQoL validity/usefulness was considered and discussed, particularly in light of the feasibility data. Despite the variability observed, it was considered an important secondary outcome and thus included.

5. There are minor spelling/punctuation errors, as follows:
   a. Background. Line 7: suspect “quipmnet” is meant to be equipment
      Thankyou. Modified
   
   b. Background. Paragraph 7, Line 8: “enrolment” should be enrolment
      That spelling is correct for Australian English; happy for the Editorial staff to alter this if required
   
   c. Methods/Designs: “Post-Enrolment data collection”; should be Enrollment
      As above
   
   d. Methods/Designs: Baseline Measures, line 9: should read “All these tests..”
      Thankyou. Modified
   
   e. Estimated Subject Numbers, 2nd paragraph, line 4: should be “admissions...”
      Thankyou. Modified