Author’s response to reviews

Title: Prevention of morbidity in sickle cell disease - qualitative outcomes, pain and quality of life in a randomized crossover pilot trial of overnight supplementary oxygen and auto-adjusting continuous positive airways pressure (POMS 2a): study protocol for a randomized controlled trial

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The Editors
Trials

Dear sirs

We were grateful for the suggestions made by the reviewer which we will take into consideration for the design of our Phase 2 trial. Our responses are below:

Major revisions

1) The inclusion exclusion criteria exclude patients with severe disease but do nothing to exclude those with mild disease i.e. no pain. The individuals are not appropriate for study and the authors should consider excluding those. We have used the sickle cell pain burden interview in our studies for this purpose. J Pain. 2013 Sep;14(9):975-82. doi: 10.1016/j.jpain.2013.03.007.

We agree that this question requires careful consideration for the main trial and we have referenced this useful paper for triage of the burden of pain. Pain is not
the endpoint in this feasibility study looking at patient preference but we have added a sentence noting that patients with a significant burden of pain might have a different spread of preferences.

2) The wide age range in the pediatric portion of the trial is problematic. I think it is unlikely that 8 year olds and 17 year olds are similar in their experience especially regarding sleep. This is directly relevant to feasibility and acceptability. I would recommend using a considerably older cutoff (13 or so).

We appreciate that sleep physiology is different across the full age spectrum in children, as well as differing in this age group from adults. For a Phase 3 study we will choose a more limited age group. In fact there may be problems with compliance in adolescence and there is a good case for a trial in children aged 4-12 years whose parents may be able to encourage compliance and who may have the most to gain from an effective intervention cognitively as well as in terms of sickle complications such as pain. However, there are very few data on acceptability of overnight respiratory support, i.e. either CPAP or oxygen, which would allow us to plan an adequately powered Phase III study in patients with sickle cell disease of any age group. This is a feasibility trial to determine patient preference at various ages for one of two interventions so that, in the Phase II study for which we are funded, we can randomize to either standard care or the intervention (APAP or oxygen) preferred by the patients in this feasibility trial.

Discretionary revisions.

3) Though QOL is a secondary endpoint which is unlikely to be impacted by such a brief intervention the lack of re testing post washout period before the 2nd intervention is problematic. How do we know the washout period is appropriate? Unless the QOL not to mention the blood studies are retested to ensure return to baseline.

The available studies of CPAP suggest that the effect does not carry over and that a 1 week crossover period is reasonable (Dungan et al 2011; To et al 2008). We consider that additional quality of life questionnaires and blood tests would unnecessarily increase the burden for this group of patients considering that this is a feasibility study with an endpoint of patient preference.


4) I am not sure the secondary endpoints are relevant for this study. They are unlikely to be impacted by such a brief intervention. They could be removed without impacting the study.

The safety data will be important and we are trialling collection of the pain and adverse event data and the quality of life questionnaires in advance of the Phase
Understanding the mechanism by which APAP might work, i.e. whether there is an increase in lung volume and daytime oxygen saturation after 1 week of treatment compared with 1 week of oxygen, will be a potentially important aspect in terms of deciding which intervention to use for the Phase 2 trial if there is no obvious participant preference.

We hope that the manuscript will be acceptable for publication

Yours sincerely

Fenella Kirkham
On behalf of the co-authors