Author’s response to reviews

Title: Overnight auto-adjusting Continuous Airway Pressure + Standard Care compared with Standard Care Alone in the Prevention of morbidity in sickle cell disease Phase II (POMS2B): study protocol for a randomised controlled trial

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Reviewer reports:

Howard and colleagues submitted the protocol of a randomized controlled trial evaluating the effect on cognitive functions of auto-adjusting continuous positive airways pressure (APAP) on the top of standard of care, compared to standard of care, in paediatric and adult patients with sickle cell anaemia (SCA). The research question is clinical relevant; the protocol is well written and compliant with methodological standards of conducting and reporting research.

We thank the reviewer for the positive comments

I suggest that the Journal considers the manuscript for publication, after the authors have addressed the following points:

• The rationale for trying to affect the cognitive performance by reducing low daytime and night-time oxygen saturation (SpO2) using a continuous positive airways pressure (CPAP) in SCA patients could be better explained. Obstructive sleep apnoea (OSA) is more frequent in SCA patients, but OSA is not an inclusion criterion.

Response: As there are relatively few data in unselected patients and questionnaire data is not very sensitive to the presence of OSA on polysomnography there is no consensus over the
criteria for diagnosing OSA on polysomnography in SCA. The available data suggests that OSA is prevalent in children and adults with SCA and that exposure to oxygen desaturation, diagnosable on overnight pulse oximetry, may affect clinically relevant outcomes. As sickle haemoglobin polymerises on oxygen desaturation, any reduction might be detrimental but preventable with auto-adjusting continuous positive pressure, which only increases the delivered pressure to 10 cm water during obstruction. The NIHR Research for Patient Benefit scheme, who funded this study, had a maximum funding limit of £350,000 and as polysomnography costs around £1500 per patient, so £90,000 for 60 patients, it was not possible to undertake full polysomnography to diagnose OSA, but we did include documenting minimum oxygen saturation at baseline, which had been abnormal in the majority of patients with SCA in our previous studies. We have modified the text on pages 3-4 as follows:

'Low daytime and night-time oxygen saturation (SpO2), potentially exacerbated by sleep-disordered breathing, including snoring and obstructive sleep apnoea (OSA), are more common in SCA than in the general population.[12] As there is a paucity of population-based normative data for sleep physiology in children and adults, it is difficult to apply cutoffs for intervention in SCA, particularly as the threshold might be lower as acute hypoxic exposure causes sickle haemoglobin to polymerise.[13] When polysomnography is available, over 40% of unselected children with SCA have an obstructive apnoea hypopnoea index (OAHI) >1,[12] and the majority have OAHI above the normal range.[14] As this is an expensive investigation there are few data in unselected populations of adults with or without SCA but in a recent study, all SCA adults with sleepiness or symptoms of sleep-disordered breathing, e.g. snoring, had an apnoea hypopnoea index of >1.[15] Compared with data from the general paediatric population,[16,17] mean and/or minimum oxygen saturation on overnight pulse oximetry are lower in the majority of patients with SCA.[12,15,18] (Howard et al submitted)

In addition to the evidence for an association of oxygen desaturation with endothelial dysfunction,[19,20] cerebrovascular disease[21] and stroke[22,23], cardiac dysfunction[24] and hospital days for pain,[25] there is evidence for links with cognitive difficulties,[26,27] in line with previous experimental and clinical evidence. Animal data show that intermittent hypoxia during sleep is associated with impaired spatial learning and hippocampal vulnerability.[28] In addition to the evidence for a link with cerebrovascular disease,[29] minimum oxygen saturation is associated with cognitive difficulties in OSA[30] in the adult general population and in other conditions, such as multiple sclerosis.[31] Magnetic resonance imaging (MRI) abnormalities have also been reported in relation to oxygen desaturation in SCA.[32]

It is not clear whether there is any effect that is expected on oxygen saturation (or directly on cognitive function) from a CPAP also in patients with SCA but no OSA, and if so, through which mechanisms.

Response: In addition to the text added on pages 3-4 (see above), our previous studies did show increases in overnight and daytime oxygen saturation in patients on APAP which we have now clarified on pages 4-5 as follows:

'In a small randomised trial of standard care versus auto-adjusting continuous positive airways pressure (APAP) in children with SCA, all 12 were compliant for 6 weeks and both daytime and
mean overnight oxygen saturation increased, the latter significantly. [18] A psychologist blind to treatment arm undertook 5 subtests of the Wechsler scales chosen to examine processing speed, attention and working memory.’

AND on page 5:

'Compared to baseline, subjects experienced small increases in daytime oxygen saturation and decreases in haemoglobin and for the week on both APAP and NOT but there was no difference between interventions (Howard et al submitted).'

Including everyone and not only patients with OSA or low SpO2 at baseline might raise ethical concerns, and might dilute the effectiveness of the interventions, if there is no biological plausibility.

Response: We appreciate this point and have considered it very carefully over the past 17 years since we were first funded to look at overnight respiratory support in SCA. The advantage of using APAP rather than CPAP is that the pressure only rises when the patient obstructs. The majority of patients in our previous cohort looking at sleep-disordered breathing (Rosen et al 2014) and pilot overnight respiratory support studies (Marshall et al 2009, Howard et al submitted) had apnoea-hypopnoea indices and overnight oxygen saturations outside the normal range (Scholle et al 2011). Although occasional adverse events related to PAP are reported, we saw none in our previous pilot studies; the main problem with positive airways pressure interventions is non-compliance if the patient does not feel that the nuisance is worth any potential benefit. We have therefore modified the text on pages 3 and 4:

‘Low daytime and night-time oxygen saturation (SpO2), potentially exacerbated by sleep-disordered breathing, including snoring and obstructive sleep apnoea (OSA), are more common in SCA than in the general population.[12] As there is a paucity of population-based normative data for sleep physiology in children and adults, it is difficult to apply cutoffs for intervention in SCA, particularly as the threshold might be lower as acute hypoxic exposure causes sickle haemoglobin to polymerise.[13] When polysomnography is available, over 40% of unselected children with SCA have an obstructive apnoea hypopnoea index (OAHI) >1,[12] and the majority have OAHI above the normal range.[14] As this is an expensive investigation there are few data in unselected populations of adults with or without SCA but in a recent study, all SCA adults with sleepiness or symptoms of sleep-disordered breathing, e.g. snoring, had an apnoea hypopnoea index of >1,[15] Compared with data from the general paediatric population,[16,17] mean and/or minimum oxygen saturation on overnight pulse oximetry are lower in the majority of patients with SCA.[12,15,18] (Howard et al submitted)’

AND on page 4

‘There is therefore a case for exploring whether interventions to improve sleep-disordered breathing, OSA and nocturnal desaturation improve clinically relevant endpoints in SCA. Adenotonsillectomy is an invasive procedure which may not cure OSA.[38] Continuous positive airways pressure is standard treatment for OSA in adults but the potential discomfort of breathing against a continuous pressure of 10 cm water is not easy to justify unless there is
polysomnographic evidence of frequent airway obstruction. For auto-adjusting continuous positive airways pressure, the continuous pressure is set to a more comfortable pressure of around 4 cm water and the pressure only rises to a preset maximum of e.g. 10 cm water when obstruction is detected by the machine, making it more appropriate for patients with only a few episodes of obstruction per night;[39] additional modalities may be effective for causes of sleep-disordered breathing other than OSA.[40] APAP is likely to improve minimum oxygen saturation by preventing desaturation in even minor degrees of airway obstruction. Although occasional adverse events related to APAP are reported, we saw none in our previous pilot studies; the main problem with positive airways pressure interventions is non-compliance if the patient does not feel that the nuisance is worth any potential benefit.

At the end of the discussion the authors write “Based on our previous findings that many patients with sickle cell disease have minimum oxygen saturation overnight lower than the minimum documented in healthy asymptomatic children in the general population, we have elected to recruit both patients with evidence for obstructive sleep apnoea and those with more severe desaturation into this trial. This decision will allow comparisons of the magnitude of benefit across these groups.” The sentence does not provide a satisfactory rationale

Response: We enclose our pilot trial (POMS 2a) manuscript with this resubmission as well as including more background information in the Introduction (see above)

and is also a bit inconsistent with the eligibility criteria, since: i) patients with “severe desaturation” are in fact excluded (at least those with “overnight oximetry showing mean overnight saturation of <90% for <30% of the night”);

Response: Our respiratory physician colleagues felt that this group should be referred for treatment and we have made this clearer in the text on page 6

‘overnight oximetry showing mean overnight saturation of <90% for <30% of the night (i.e. they do not meet current recommended levels of overnight oxygen desaturation for referral for overnight oxygen therapy)’

ii) in case of desaturation or “severe desaturation”, CPAP therapy is not expected to be necessarily more effective than oxygen therapy alone, if there is desaturation but no specific conditions that would respond to a CPAP;

Response: The proposal submitted to the NIHR Research for Patient Benefit scheme was originally for a 3-arm trial: standard treatment vs APAP vs oxygen but the feedback was that we should run a 2-arm trial. We therefore ran a pilot (POMS 2a; submitted simultaneously with this resubmission), in which there was a patient preference for APAP over oxygen therapy. APAP is likely to improve minimum oxygen saturation, which has been linked to cognitive function in other conditions as we have clarified in the text, by preventing desaturation in even minor degrees of airway obstruction. We have made this clearer in the text on page 3

‘In addition to the evidence for an association of oxygen desaturation with endothelial dysfunction,[19,20] cerebrovascular disease[21] and stroke[22,23], cardiac dysfunction[24] and
hospital days for pain,[25] there is evidence for links with cognitive difficulties,[26,27] in line
with previous experimental and clinical evidence. Animal data show that intermittent hypoxia
during sleep is associated with impaired spatial learning and hippocampal vulnerability.[28] In
addition to the evidence for a link with cerebrovascular disease,[29] minimum oxygen saturation
is associated with cognitive difficulties in OSA [30] in the adult general population and in other
conditions, such as multiple sclerosis.[31] Magnetic resonance imaging (MRI) abnormalities
have also been reported in relation to oxygen desaturation in SCA.[32]

And on page 4

‘APAP is likely to improve minimum oxygen saturation by preventing desaturation in even
minor degrees of airway obstruction.’

iii) in fact, based on its eligibility criteria, the study will include also patients with no
desaturation, neither mild nor severe.

Response: In our experience, compared with the normative data in German children, very few
patients with SCA have no desaturation at all as we have clarified in the text on page 3 and in the
enclosed manuscript from our POMS2a pilot trial.

‘As there is a paucity of population-based normative data for sleep physiology in children and
adults, it is difficult to apply cutoffs for intervention in SCA, particularly as the threshold might
be lower as acute hypoxic exposure causes sickle haemoglobin to polymerise.[13] When
polysomnography is available, over 40% of unselected children with SCA have an obstructive
apnoea hypopnoea index (OAHI) >1,[12] and the majority have OAHI above the normal
range.[14] As this is an expensive investigation there are few data in unselected populations of
adults with or without SCA but in a recent study, all SCA adults with sleepiness or symptoms of
sleep-disordered breathing, e.g. snoring, had an apnoea hypopnoea index of >1.[15] Compared
with data from the general paediatric population,[16,17] mean and/or minimum oxygen
saturation on overnight pulse oximetry are lower in the majority of patients with SCA.[12,15,18]
(Howard et al submitted)’

In case of the inclusion of patients for whom there is no known or expected plausibility for the
interventions to work might be justified by practical reasons.

Response: as clarified above we were unable to undertake polysomnography because of financial
constraints and feel that we have justified the use of APAP in the text of this manuscript and the
enclosed manuscript on the results from the pilot 2A.

‘In addition, in a pilot study (POMS 2a) (Howard et al submitted) for this phase II study (POMS
2b), we compared safety and tolerability in children and adults for two alternative interventions:
APAP and Nocturnal Oxygen Therapy (NOT). In a crossover design, after a week’s baseline,
each intervention was used for 1 week, with a week-long washout between phases. Compared to
baseline, subjects experienced small increases in daytime oxygen saturation and decreases in
haemoglobin and for the week on both APAP and NOT but there was no difference between
interventions (Howard et al submitted). Ten of 16 (62.5% [95% confidence intervals 38.6, 81.5])
who completed qualitative interviews reported a preference for APAP (Howard et al submitted). Practical advantages of APAP include the cost, size and portability of the APAP machine, an optional humidifier attachment to treat dry throat, an adjustable mask, optional addition of oxygen if required and capacity for remote compliance monitoring.

In any case, the authors are invited to make the rationale for the study intervention and for the eligibility criteria clearer.

Response: We thank the reviewer for their insights into this difficult problem and hope that we have explained the rationale for the study intervention and the eligibility criteria clearer.

• Primary outcome and expected effect size.

Authors are invited to:

- provide a rationale for using the Wechsler scale as the instrument to measure cancellation (related to visual attention and processing speed). Please, provide details for the test and the psychometric characteristics of the scale

We agree that more information regarding choice of cognitive test-battery was needed. We have revised the cognitive outcomes section on page 10-11, to read:

‘Cognitive Outcomes’

Several studies have shown an association of nocturnal hypoxia and sleep disordered breathing with cognitive impairment, including deficits in processing speed, visual attention, executive function, and memory. Moreover, improvement in processing speed has been demonstrated in the general population with OSA following adenotonsillectomy[52] as well as in patients with SCA treated with APAP.[18] In light of these findings, a battery of cognitive tests will be used to track cognitive outcomes in the current study.

In the 2 weeks between recruitment and randomisation, and again at the end of the study, a psychologist blind to treatment arm will administer standardised tests applicable and comparable in children and adults, with demonstrated validity and reliability, to examine cognitive domains which may improve if overnight desaturation is relieved and sleep improves.

The baseline cognitive assessment will measure general cognitive ability using the Wechsler Abbreviated Scale of Intelligence (WASI), and processing speed, working memory, and cancellation using the Wechsler Intelligence Scale for Children-IV ([WISC-IV], <16 years) or Wechsler Adult Intelligence Scale-IV ([WAIS-IV] >16 years). The Wechsler scales were chosen as they have normative scores validated in a representative sample, including ethnic minorities, in the United Kingdom, show strong reliability and validity, are widely used in the literature and are frequently used measure of cognitive function in sleep apnoea as well as SCA, with demonstrated sensitivity to dysfunction in SCA as well as to change following APAP.[18]
Moreover, the Wechsler scales have an extensive empirical database, rigorous standardisation procedures, and robust psychometric properties, including well-replicated validity, stability, and reliability. The cancellation subtest can be administered across a wide age range with age-adjusted scaled scores that range from 1 to 19. A scaled score within 8 and 12 is considered to be within the average range.

In addition, on the basis of previous research suggesting sensitivity to dysfunction in SCA, executive function will be assessed using the Tower and Sorting subtests of the Delis-Kaplan tests of Executive Function [D-KEFS], and via parent- (<16 years) or self- (>16 years) report using the BRIEF questionnaire...’

- explain what the BRIEF questionnaire consists in

Response: We have added the following text on page 11:

‘...and via parent- (<16 years) or self- (>16 years) report using the BRIEF questionnaire. The BRIEF-questionnaire is sensitive to atypical variations in EF development[53] and is the most commonly used screener questionnaire for executive dysfunction. It is either used as self-report for adults (i.e., 18 and 90 years) or given to the child’s parents (i.e., care giver) to answer questions about either their own or their child’s executive functioning or self-regulation on their everyday behaviour. It is considered an ecologically-valid alternative to lab-based assessments,[54] and consists of 86 (parent) or 75 (self) questions related to everyday behaviours associated with executive function. It is comprised of eight subscales (Inhibit, Shift, Working memory, Plan/Organize, and Emotional Control, Initiate, Monitor, Organisation of Materials and Inhibitory Self-Control) that create an overall summary score (General Executive Composite). Higher scores indicate poorer EF.’

- provide the rationale for sizing the study on an expected effect size of 2.3 points (or 2.4?) as difference in cancellation performance. This is close to the effect size found in a pilot study in children. Is there any evidence about the clinical relevance of this effect size and on whether the same clinical relevance is expected in children and adults? Does the limited study duration represent a reason not to expect any greater effect?

Response: We agree that the description of the sample size calculation and target effect size was confusing. We have revised the text on page 7 to read:

In the previous pilot study in children, the results of the cancellation task within each subject group were normally distributed with standard deviation 2, resulting in a mean score difference between APAP treatment and standard care at six weeks of 2.6. Based on this finding, 24 evaluable subjects (in each cohort) will provide 90% power to detect a difference in the primary outcome of 2.6 while preserving a significance level of 0.05 (2-sided). This calculation assumes that there is a moderate correlation of 0.5 between the baseline and follow-up measures, and accounts for model adjustment for baseline score. Allowing for 20% withdrawal/loss-to-follow-up, a sample size of 30 subjects randomised 1:1 into two groups will have > 90% power to detect a difference of 2.6 points in cancellation using an Analysis of Covariance (ANCOVA) model to adjust for the baseline cancellation measure and minimisation factors. The same design
characteristics will be used for the adult cohort and the child cohort. Though the values used in
the sample size calculation were derived from a cohort of children, no pilot data for adults are
available, and the mechanisms by which the treatment effect may be different for adults and
children are currently unknown.'

• Blinding. Please provide information on blindness of other study personnel (e.g.
statistician).

We thank the reviewer for pointing out this oversight. We have revised the description of the
blinding procedures on page 6 to read:

'The outcomes will be assessed by study personnel blind to treatment arm so that although the
family and some professionals involved in data collection know the treatment allocation, the
assessors of endpoints, including cognitive function, imaging, pain frequency and quality of life
will not know the treatment assignment. All study personnel not directly involved in treatment
administration and compliance will be blinded to randomisation assignment until the blind is
broken for each cohort. Blinded study personnel include data managers and the trial statistician,
as well as assessors of endpoints.'

• References. Please, conform all references and the ways they are cited in the text to the
journal requirements

We have done our best with this and will correct any errors that emerge when your system has
rechecked