ResMed Response Comments and Questions:

1. Irrespective of the difference in data inputs between the York model and the RESMED model, the key question regarding the York model is what constitutes "lifetime", as different patients will die at different times for different reasons. Sensitivity analyses could not be found that have addressed this. **Is this not viewed as relevant? Within the York model, how does the cumulative cost per QALY change on a year-by-year basis?**
2. The York model estimated that for all patients, the cost per QALY gained with CPAP compared to dental devices is £3,899 and has an 80% chance of being cost-effective for a threshold of £20,000 per QALY. The York model also estimated the cost per QALY gained with dental devices compared to conservative management to be £2,000 – but it only has a 20% chance of being cost-effective for a threshold of £20,000 per QALY. What the NICE document does not state anywhere is that – according to our calculations - the cost per QALY gained with CPAP compared to conservative management is £2,524. **Can this be explained?**
3. The York model utilises different unit costs to those in the RESMED model. However, the difference in the ongoing cost of stroke (£2,392 per annum in the York model versus £10,140 per annum in the RESMED model – omitted from Table 6.3 in the NICE report) is likely to play a key role in accounting for the fact that the RESMED model estimated treatment with CPAP (£9,086 over 14 years) to be cheaper than conservative management (£10,645 over 14 years), whereas the York model estimated the lifetime cost of CPAP management to be £9,301 compared with £8,140 with conservative management and £8,797 with dental devices. **These costs were sourced from the Department of Health.**
4. In a sub-group analysis, the York model estimated the cost per QALY gained with CPAP compared to conservative management for patients with mild OSAHS to be £20,585, whereas it's £4,413 for patients with severe disease. They also estimated that compared to conservative

management, CPAP has a 43% chance of being cost-effective for a threshold of £20,000 per QALY in mild patients but a 98% chance in severe patients.

5. The York group estimated the risk of patients developing fatal or non-fatal cardiovascular events using data from the Framingham Heart Study (published in 1990) which looked at cardiovascular risk profiles associated with blood pressure among a cohort in the US. (The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CHD by following its development over a long period of time in a large group of participants (over 5,000 men and women between the ages of 30 and 62) who had not yet developed overt symptoms of CHD or suffered a stroke.). **Whether these risks apply to patients with OSAHS is open to question and potentially creates intrinsic uncertainty within the model. Is there any correlation or conclusions that can be drawn from this cohort as there is no OSAHS within this population?**
6. Probabilistic sensitivity analyses could not be found in the NICE report showing the distribution in costs and QALYs within the York model. **Will this be made available.?**
7. Even though the period of the York model is a patient's lifetime, There was no information in the NICE report about the expected clinical outcomes from the York model in terms of:

   The probability of survival at different time points e.g 5 years, 10 years etc

   - The risk of having a cardiovascular event at different time points.
   - The risk of having a stroke at different time points
   - The risk of having an RTA at different time points.
   - The probability of event-free survival at different time points.

   There were no sensitivity analyses showing the impact of all their risk equations and utility estimates being wrong and what would the relative cost-utility of CPAP be if all cardiovascular events and RTAs were excluded from the analysis. **Will this be added?**

8. Also, sensitivity analyses could not be found in the NICE report showing how the cost per QALY would change if:
    - Different unit costs were used.
    - Different utility values were used.
    - The probabilities of clinical events within the model were varied.
    - Different discount rates were used.
    - The shelf-life of CPAP was varied
9. Another area within the York model that appears to be a limitation is: the accuracy of modelling a patient's life-time when (1) the period of RCTs used for modelling range from 4 weeks to 1 year - it appears that the York group has excluded any non-RCT studies to inform their model such as the 12 year observational study by Marin *et al* which informed the RESMED model, (2) non-OSAHS data, such as that derived from the Framingham study, having been used to predict cardiovascular events and (3) changes in clinical outcomes (i.e. ESS, blood pressure and risk of RTA) having been used to predict utilities. **Please see point 5 above.**

Some other Key Differences outlined :

10. The York group assigned utilities to the different health states in their model by constructing separate algorithms to assess the relationship between utilities and three clinical endpoints:
    - Difference in ESS score between treatments.
    - Differential treatment effect on blood pressure.
    - Risk of RTA.
11. Based on clinical trial data, the York group have incorporated the effect of treatment (i.e. CPAP or dental device) on blood pressure within the model, and used risk equations derived from other sources to predict the risk of patients developing CHD or stroke. Hence, within the York model a patient can remain in the initial OSAHS state until death or experience CHD. Patients who survive a CHD move to the OSAHS post-CHD state, which in turn incorporates increased mortality and morbidity associated with having had a first CHD event. They can then remain in this state until death, or experience an RTA or have a

stroke from which they may become disabled. Alternatively, from the initial OSAHS state, they can experience a stroke. Patients who survive a stroke move to the OSAHS post-stroke state, which in turn incorporates increased mortality and morbidity associated with having had a first stroke. Patients who are not disabled remain at risk of having an RTA. Patients who become disabled post-stroke are no longer able to drive and therefore at no further risk of developing an RTA. Once in the OSAHS post-stroke state, patients remain in this state until death, whether directly or as a result of an RTA. One limitation of the model, acknowledged by the York group, is that it does not separately record CHD events following a stroke.

12. The York group built a Markov model depicting the management of OSAHS over a patient's lifetime, whereas the RESMED model spanned a period of 14 years.
13. The York group used their model to estimate the cost-effectiveness of CPAP compared with a dental device and conservative management (which comprises a one-off visit to a GP).
14. The York model assumes the CPAP devices are replaced after 5 years, whereas the RESMED model assumes a shelf-life of 7 years.
15. The York model characterises a patient's prognosis over their lifetime in terms of four health states: (1) OSAHS, (2) OHAHS post-coronary heart disease (CHD), (3) OSAHS post-stroke and (4) death. The model records the ESS score of a hypothetical patient cohort and any change in ESS associated with treatment.

Conclusion

ResMed would respectfully ask for clarification on whether the York model accurately reflects the lifetime course of a hypothetical cohort of patients with OSAHS, compared with data used within the ResMed model, or whether too many assumptions have been made such that it creates greater clinically uncertainty because of:

- The limitations with the RCTs that have been used to inform the model.

- Data from non-OSAHS patients having been used to predict the risk of CHD and stroke among OSAHS patients, based on expected blood pressures.
- Difference in ESS score between treatments, differential treatment effect on blood pressure and risk of RTA having been used to predict utilities.