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**Cost-effectiveness of Ambulatory Oxygen in improving quality of life in fibrotic lung disease: Preliminary evidence from the AmbOx Trial**

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## **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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## **Take-home message**

Ambulatory Oxygen may be cost-effective in improving quality of life in fibrotic lung disease. To be more conclusive, we need to understand societal willingness to pay for quality of life improvements and whether improvements are sustained.

## **Plain language summary**

Interstitial lung disease (ILD) is an umbrella term used to describe a range of lung conditions that cause scarring (fibrosis) of the lungs. The conditions are long-term and usually get worse with time, with very few treatment options to improve symptoms. ILD can have a big impact on quality of life for patients, making them short of breath and affecting their ability to carry out usual activities. A recent clinical study carried out in the UK found that using “ambulatory” oxygen treatment given to help people with ILD when they go about their day-to-day activities for a two-week period improved their quality of life. Using data from this study, we find that ambulatory oxygen may be good value for money for the National Health Service (NHS). However, before we can be certain about this, we need to understand whether the improvement seen in patients’ quality of life lasts for longer than two weeks.

## TO THE EDITOR

Fibrotic Interstitial Lung Diseases (ILDs) are chronic and often progressive conditions resulting in substantial impact on morbidity, health-related quality of life (HRQoL), and health system costs. Ambulatory oxygen (AO) used during routine daily activities could lead to improved exercise performance, reduced symptoms and improved mobility in daily life. A UK prospective, multicentre, mixed method, randomised controlled crossover trial in patients with fibrotic ILD (AmbOx trial: NCT02286063), the first study on AO effects in daily life, reported improved HRQoL after two weeks of AO compared to no intervention, when measured by the King's Brief ILD (K-BILD) questionnaire[1-3]. Although AO is used in ILD, evidence supporting its health-economic impact is absent. Here, we evaluate the cost-effectiveness of AO in patients with ILD, using data collected alongside the AmbOx Trial.

AmbOx included adults with fibrotic ILD with isolated exertional hypoxia[1, 2]. Participants (mean age 67.9years; 31% female) were randomised to receive either AO during routine activities of daily living (n=41) or no intervention (n=43) first. After a two-week period, the groups were crossed over to the alternative. AO for two weeks was associated with a significant improvement in total K-BILD score compared to no oxygen (mean difference adjusted for treatment order 3.7, 95%CI 1.8 to 5.6).

For this economic evaluation, data were analysed on a complete case basis (n=74; of the 76 participants completing AmbOx, 2 had missing K-BILD scores). We estimated resource use and costs incurred from a National Health Service (NHS) perspective. Costs of AO were based on the number of cylinders used (median 2.75 cylinders per week, range 0-14) [1, 2] and assumed use of one nasal cannula per participant [4, 5]. Rental prices for oxygen cylinders (£0.25/day), refills (£10.56/refill) and delivery (£16.90/delivery) were not available from UK suppliers (commercial in confidence) and so were assumed based on online information for an Australian medical gas cylinder company[6]. As AO was not anticipated to have any effect on disease progression in the short-term, costs related to any unplanned health professional visits or hospital admissions were not included. The mean cost for AO for two weeks was estimated to be £91.02 (95%CI £77.83 to £104.21) per participant [costs expressed in GBP 2017 (£), after conversion using 1AUD=0.608 GBP).

We estimated the incremental cost per unit improvement in total K-BILD score, the primary trial outcome [1]. A one-point improvement in K-BILD score over a two-week period was estimated to cost an additional £25.21 (bootstrapped 95%CI £15.21 to £69.48). Sensitivity analyses using the intention to treat cohort (with multiple imputation to adjust for missing values) gave a similar incremental cost of £27.38 (95%CI £15.68 to £86.77). Likewise, the estimated cost-effectiveness was not substantially impacted if the costs of the intervention were changed by up to +/-80% of that assumed in the primary analysis (mean estimated cost per unit improvement in K-BILD £14.42 to £46.72 over a two-week period).

We also undertook post-hoc analyses to estimate the cost-effectiveness of AO in providing a benefit based on the number of participants who reported a minimum of an 8 or 4 unit improvement in total K-BILD score (these values have been reported as the minimal clinically important difference, MCID[3, 7]), or an improvement in the patient-reported global assessment of change in breathlessness and walking ability at the end of each two-week treatment period, one of the pre-defined major secondary trial outcomes [2]. A 8-unit improvement in K-BILD score was reported for 13 (17.6%, NNT 5.85) and a 4-unit improvement for 27 (36.5%, NNT 2.81) of participants [2]. Given an incremental cost of £91.02 (95%CI £77.83 to £104.21) per person treated for two weeks, it is estimated to cost an additional £532.47 (£455.31 to £609.63) to achieve one additional 'responder' of at least 8-units or £255.77 (£218.70 to £292.83) to achieve one additional 'responder' of at least 4 units on the K-BILD, over a two-week period.

Data on global assessment of change was available for 76 participants. More participants perceived an improvement in their walking ability (51, 67.1%) or breathlessness (52, 68.4%) after receiving oxygen as compared to no oxygen (1, 1.3% in each case). This corresponds to a number needed to treat of 0.02 for one additional patient to perceive an improvement in walking ability or breathlessness, and an estimated incremental cost of £1.82 (£1.56 to £2.08) over two weeks to achieve one additional person perceiving an improvement.

This economic evaluation is the first to examine the cost-effectiveness of AO in fibrotic ILD, often a devastating and progressive group of diseases with substantial impact on patients' HRQoL and limited treatment options. Whether or not AO is considered to be of acceptable cost-effectiveness depends on society's (unknown) willingness to pay for an improvement in K-BILD score or the global assessment measures. The analysis suggests a much lower number needed to treat (and therefore cost for one additional responder) to obtain a perceived

improvement in breathlessness or walking ability according to the global assessment measures, than to achieve an improvement in HRQoL according to the K-BILD. This apparent responsiveness for the global assessment of change might be related to the comparative bluntness of the single item measure and the possible impact of non-blinding on the participants' self-reported perception of improvement.

There are limitations associated with our study. Costs for oxygen cylinders were assumed, although sensitivity analysis suggests this assumption did not substantially impact findings. The AmbOx trial was open label, had a relatively small sample size and a short duration of oxygen use (2 weeks) making it challenging to extrapolate the costs or benefits to ILD patients in the longer term. It is possible that people using AO would be more likely to access long-term oxygen therapy as they become accustomed to the idea of using oxygen, with yet unknown benefits and drawbacks. This analysis should be considered as indicative only, until data from a larger study with longer follow-up is available to support more conclusive assertions. Finally, light weight oxygen cylinders were used for all patients to standardise the intervention and to allow for higher oxygen flow rates in patients with more severe exertional hypoxia [2], but further studies are needed to assess whether portable oxygen concentrators may be more beneficial for the subset with milder ILD.

We had intended to evaluate cost per quality-adjusted life year (QALY) by deriving QALYs using utility values from the existing medical literature for health states described by the K-BILD or the St George's Respiratory Questionnaire (SGRQ), another secondary outcome measure [1]. However, appropriate HRQoL data in ILD patients on which to base an estimate of QALY gain are not available. Further research to derive a preference-based utility index for the K-BILD instrument is required to support accurate assessment of the benefits of treatment targeting HRQoL in ILD. Moreover, future trials should consider collecting a preference-based measure of health (such as the EQ-5D-5L) as an outcome[8, 9].

Nevertheless, despite these limitations, this study is the first to provide an indication of the cost-effectiveness of AO for improving HRQoL outcomes in ILD. Further evidence for the long-term effectiveness of AO, conversion of HRQoL outcomes in ILD to QALYs, and societal willingness to pay for HRQoL improvements are required to ensure the benefits of AO are accurately captured in economic evaluation and can be interpreted in resource allocation decisions.



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