Pragmatic randomised controlled trial of a personalised intervention for carers of people requiring home oxygen therapy

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Abstract
We used a pragmatic randomised controlled trial to evaluate a behavioural change strategy targeting carers of chronically hypoxaemic patients using long-term home oxygen therapy. Intervention group carers participated in personalised educational sessions focusing on motivating carers to take actions to assist patients. All patients received usual care. Effectiveness was measured through a composite event of patient survival to hospitalisation, residential care admission or death to 12 months. Secondary outcomes at baseline, 3, 6 and 12 months included carer and patient emotional and physical well-being. No difference between intervention (n = 100) and control (n = 97) patients was found for the composite outcome (hazard ratio (HR) 1.22, 95% confidence interval (CI) = 0.89, 1.68; p = 0.22). Improved fatigue, mastery, vitality and general health occurred in intervention group patients (all p values < 0.05). No benefits were seen in carer outcomes. Mortality was significantly higher in intervention patients (HR = 2.01, 95% CI = 1.00, 4.14; p = 0.05; adjusted for Australia-modified Karnofsky Performance Status), with a significant diagnosis–intervention interaction (p = 0.028).

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showing higher mortality in patients with COPD (HR 4.26; 95% CI = 1.60, 11.35) but not those with interstitial lung disease (HR 0.83; 95% CI = 0.28, 2.46). No difference was detected in the primary outcome, but patient mortality was higher when carers had received the intervention, especially in the most disabled patients. Trials examining behavioural change interventions in severe disease should stratify for functionality, and both risks and benefits should be independently monitored. 

**Trial registration:** Australian New Zealand Clinical Trials Registry (ACTRN12607000177459).

**Keywords**
Chronic disease, caregivers, education, behavioural research, oxygen

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**Introduction**
Long-term home oxygen therapy (HOT) may be prescribed in respiratory disease to control chronic hypoxaemia and improve patient survival and health status. Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and asthma account for approximately 8.0% of all deaths in Australia and contribute to substantial worldwide morbidity and mortality. In South Australia, patients with chronic hypoxaemia have long been approved for free HOT supply if they meet criteria outlined in the 2005 Position Statement of the Thoracic Society of Australia and New Zealand. Despite considerable care needs, many patients with severe respiratory disease live in the community requiring frequent medical attention, suffering depression and anxiety and cognitive impairment. Impacts on primary caregivers include psychological strain, loss of social life, boredom and enmeshment between patient and carer.

Carer burden is widely acknowledged in relation to many chronic diseases and disabilities. A review of social support in COPD found variable associations between patient and carer outcomes, such as quality of life, physical functioning and self-rated health. Further, living with others and having a carer were associated with higher levels of physical activity and greater participation in pulmonary rehabilitation programmes than those without these supports. Carer support may contribute to patients’ adherence to treatment protocols, potentially impacting patient morbidity and mortality, although effects of education programmes for carers are unclear from the limited research in the setting of chronic hypoxaemia.

Our theoretically informed carer-centred intervention used a social marketing framework and the principles of academic detailing. Academic detailing was developed for use with health practitioners but has more recently been used with patients. It focused on training carers to support their contribution to the care of their patient requiring long-term HOT, using evidence-based messages and therapeutic actions. Our primary hypothesis was that this personalised behavioural change strategy, by helping these carers gain confidence in patient care, would lead to reduced patient hospitalisations, delayed patient admission to residential care and improved patient survival.

**Methods**
This study was designed as a pragmatic multicentre randomised controlled trial. Patients approved for Government-subsidised long-term HOT were identified as being eligible for enrolment in a carer—patient dyad. While the caregiver was the focus of the training strategy, the primary outcome was patient-oriented.

**Participants and setting**
Carers of patients receiving long-term HOT for chronic hypoxaemia, living in independent accommodation and having at least one primary carer were eligible. Between 2007 and 2009, carer—patient dyads were recruited from three South Australian hospitals which had similar diagnostic and assessment procedures and patient information delivery. Dyads were randomised to intervention or control group stratified by referring hospital and new versus existing HOT prescription. Each intervention dyad was assigned to one of two research nurses who maintained contact with the allocated dyad throughout the
trial's duration. Details are provided in our previous publication\textsuperscript{14} and Online Supplemental Material.

**Intervention**

Local experience with academic detailing for patients and carers in the palliative care setting and for general practitioners treating refractory breathlessness\textsuperscript{16,17} informed our carer-centred intervention\textsuperscript{14} (Online Supplemental Material). The intervention took place in the carer's home and comprised two educational visits by research nurses trained in respiratory health and social marketing principles (Online Supplemental Material). Participants were not previously known to these nurses. The intervention visits were directed towards carers, aiming to motivate them to take actions consistent with five key messages developed a priori as important for carer and/or patient care using best available evidence at the time (Figure 1). Up to five messages were delivered, depending upon the nurses' expert assessment of carer needs at the time of each visit. Although the intervention was designed for and delivered to carers, patients were permitted to attend sessions. Patients in both study arms continued to receive usual care, which included information about disease management and HOT use.

**Ethics and privacy considerations**

This trial was approved by the Flinders Clinical Research Ethics Committee, Repatriation General Hospital Research and Ethics Committee, Royal Adelaide Hospital Research Ethics Committee, and Australian Government Department of Veterans’ Affairs Human Research Ethics Committee.

**Outcome measures**

The primary outcome was a composite of patients' survival time to hospitalisation, residential care admission or death over the course of 12 months. Secondary outcome measures were perceived carer burden\textsuperscript{18}, level of expected and received social support, social activities and provide service to others\textsuperscript{19}, perceived level of mastery\textsuperscript{20}, self-esteem\textsuperscript{21}, health-related quality of life (HRQoL)\textsuperscript{22}, fatigue\textsuperscript{23,24} and respiratory-related health status\textsuperscript{24} (Table 1), were collected at baseline, 3, 6 and 12 months after the first visit.

**Descriptive data**

Demographic data were collected at baseline (Table 2). Spirometry was not included in qualifying criteria, as several respiratory diseases were included, some with little relationship to baseline lung function, and spirometry was considered potentially unreliable and a cause of undue discomfort in patients with advanced disease.

**Statistical analyses**

Survival to hospitalisation, residential care admission or death was measured as a composite; (post hoc this

**Figure 1.** Academic detailing key messages.

<table>
<thead>
<tr>
<th>Plan</th>
<th>Understand</th>
<th>Review</th>
<th>Partners</th>
<th>Carers</th>
</tr>
</thead>
<tbody>
<tr>
<td>To ensure the person has an action plan for exacerbations and knows how to get one if necessary.</td>
<td>To ensure each person has an overall understanding of the (medical) treatment and skills and techniques to participate in their own care.</td>
<td>Establish a process where the plan is regularly reviewed.</td>
<td>Take a partnership approach where communication is around the roles and opportunities for both the patient and the carer.</td>
<td>The carer’s health and well-being is important.</td>
</tr>
</tbody>
</table>

**Table 1.** Secondary outcome measures.

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>Tool used</th>
<th>Who completed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived caregiver burden</td>
<td>Overload scale\textsuperscript{18}</td>
<td>Carer</td>
</tr>
<tr>
<td>Level of expected and received social support, social activities and provide service to others</td>
<td>Anticipated and received social support (ARSS) scale\textsuperscript{19}</td>
<td>Carer</td>
</tr>
<tr>
<td>Perceived level of mastery</td>
<td>Mastery Scale\textsuperscript{20}</td>
<td>Carer</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>Self-esteem scale\textsuperscript{21}</td>
<td>Carer</td>
</tr>
<tr>
<td>Health-related quality of life (HRQoL) and disability</td>
<td>SF36\textsuperscript{22}</td>
<td>Carer and patient</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Identity – consequence fatigue scale (ICFS)\textsuperscript{23}</td>
<td>Carer</td>
</tr>
<tr>
<td>Dyspnoea, fatigue, emotional function and mastery</td>
<td>Chronic respiratory questionnaire (CRQ)\textsuperscript{24}</td>
<td>Patient</td>
</tr>
</tbody>
</table>
composite outcome was decomposed and survival analysis for each of the three components was undertaken) Power calculations based on the composite outcome suggested a recruitment sample of 300 would provide 80% power to detect a 16% absolute risk reduction, assuming a 10% dropout rate to 135 dyads per arm.

Primary outcome analysis was conducted using Kaplan–Meier survival curves and multivariate Cox regression. Multilevel models with measures at baseline, 3, 6 and 12 months were used to assess differences between the study arms for HRQoL and other secondary outcomes. No imputation was conducted for missing data for secondary outcomes and relied instead upon mixed effects models in which missing data were assumed missing at random. All main analyses were performed on an intention to treat basis with all randomised subjects included in the analysis. Subjects experiencing any of the three events were followed until the date of the event and subjects not experiencing an event were censored at 12 months follow-up. Analysis was performed using STATA version 13.0. Two-sided z values ($p < 0.05$) determined statistically significant differences between groups for each outcome.

Post hoc analyses explored associations between baseline characteristics and mortality using a nested case-control design in which each ‘death’ was frequency-matched with two ‘survivors’ based on patient age, gender, intervention group, respiratory diagnosis and carer relationship with the patient and performed with SPSS v 22.0. Baseline information on variables considered likely to be associated with patient mortality was retrospectively collected. Univariate and multivariate binary logistic regression were used to determine independent predictors of death. Examining for collinearity, variables with probability value <0.15 in univariate analyses were determined statistically significant differences between groups for each outcome.

### Results

One hundred ninety-seven patients with their primary carer were included as ‘dyads’. Patients had COPD (78%), asthma, ILD, pulmonary hypertension and bronchiectasis (Table 2). Dyads were randomised to intervention ($n = 100$) and control ($n = 97$) arms and were mostly in permanent partnerships (intervention, 73%; control, 78%) (Table 2). Baseline characteristics were comparable between groups, with the exception of Australia-modified Karnofsky Performance Status (AKPS) for which control patients had significantly higher scores ($p < 0.001$) indicating better performance status. More intervention dyads failed to complete 12-month assessments (patients $n = 40/100$; carers $n = 20/100$) when compared to the control group (patients $n = 19/97$; carers $n = 10/97$) (Figure 2).

There was no significant difference between the two study arms for the composite survival primary outcome (all 197 patients included; hazard ratio (HR) = 1.22, 95% confidence interval (CI) = 0.89, 1.68; $p = 0.22$; Figure 3). Decomposition of the

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**Table 2. Baseline characteristics patients and carers.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention, $n = 100$</th>
<th>Control, $n = 97$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD; years)</td>
<td>75.3 ± 8.8</td>
<td>73.6 ± 9.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65.0</td>
<td>58.8</td>
</tr>
<tr>
<td>Ever smoked (%)</td>
<td>92.0</td>
<td>85.6</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>BMI (mean ± SD; kg/m²)</td>
<td>26.1 ± 6.5</td>
<td>26.3 ± 6.1</td>
</tr>
<tr>
<td>Respiratory diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>78.0</td>
<td>79.4</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>ILD</td>
<td>18.0</td>
<td>14.4</td>
</tr>
<tr>
<td>Other</td>
<td>3.0</td>
<td>5.2</td>
</tr>
<tr>
<td>AKPS ($^c$) (mean ± SD)</td>
<td>61.8 ± 11.1</td>
<td>67.9 ± 12.2</td>
</tr>
<tr>
<td><strong>Carers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD; years)</td>
<td>66.7 ± 11.5</td>
<td>66.7 ± 13.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>28.0</td>
<td>35.1</td>
</tr>
<tr>
<td>Relationship with patient (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent partner</td>
<td>73.0</td>
<td>78.3</td>
</tr>
<tr>
<td>Son/daughter</td>
<td>23.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Friend</td>
<td>2.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Other</td>
<td>2.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Self-esteem ($^c$) (median (IQR))</td>
<td>44 (40–48)</td>
<td>44 (39–48)</td>
</tr>
<tr>
<td>Caregiver burden ($^d$)</td>
<td>8 (6–9)</td>
<td>7 (6–9)</td>
</tr>
<tr>
<td>Mastery ($^e$) (mean ± SD)</td>
<td>25.1 ± 4.7</td>
<td>25.6 ± 5.1</td>
</tr>
<tr>
<td>Social support ($^f$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticipated (median (IQR))</td>
<td>9 (8–11)</td>
<td>9 (8–12)</td>
</tr>
<tr>
<td>Received (median (IQR))</td>
<td>25 (21–30)</td>
<td>27 (23–32)</td>
</tr>
</tbody>
</table>

SD: standard deviation; IQR: interquartile range; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; AKPS: Australia-modified Karnofsky Performance Status.

$^a$ AKPS – Lower scores indicate greater functional impairment with score range 0–100.

$^b$ Difference between study groups: $p < 0.001$.

$^c$ Measured with the self-esteem Scale.

$^d$ Measured with the overload Scale.

$^e$ Measured with the mastery Scale.

$^f$ Measured with the anticipated and received social support Scale.
primary outcome revealed no differences between arms for hospitalisation (intervention, \(n = 76\); control, \(n = 66\); HR = 1.23, 95% CI = 0.89, 1.72; \(p = 0.21\); Figure 4) or residential care admission (intervention, \(n = 6\); control, \(n = 7\); HR = 0.91, 95% CI = 0.31, 2.71; \(p = 0.86\); Figure 5), but a between-group significant difference in the number of patient deaths (intervention, \(n = 29\); control, \(n = 11\); HR = 2.73; 95% CI = 1.36, 5.46; \(p < 0.005\); Figure 6). This difference remained borderline-significant after adjusting for baseline AKPS (HR = 2.01; 95% CI = 1.00, 4.14; \(p = 0.05\); Figure 6). Adjustment for diagnosis did not significantly change the effect on death (HR = 2.58; 95% CI = 1.28, 5.19), although a significant
interaction between diagnosis and intervention ($p = 0.028$) demonstrated a higher risk of death in the intervention group compared to control for COPD patients (HR = 4.26; 95% CI = 1.60, 11.35; $p = 0.004$) although not for ILD patients (HR = 0.83; 0.28, 2.46; $p = 0.73$).

Secondary outcome measure results (Online Supplemental Material) over 12 months showed the intervention was associated with significant improvements in patients’ generic HRQoL (SF36 Vitality ($p = 0.013$) and General Health ($p = 0.021$); Online Supplemental Table 1S) and in two Chronic Respiratory Questionnaire (CRQ) domains: Mastery ($p = 0.003$) and Fatigue ($p = 0.015$; Online Supplemental Table 2S). For carers, there were no statistically significant differences between randomised groups for any secondary outcomes (Online Supplemental Table 3S).

**Post hoc analyses**

Characteristics of the 40 patients who died and 80 frequency-matched surviving patients showed baseline dyspnoea (CRQ), AKPS and partial pressure of oxygen were significantly worse in those who died during the 12 months after the intervention compared to survivors (Online Supplemental Table 4S). Death certificate access was not permitted by Ethics Committees, but utilisation data showed that 34 of the 40 patients had died during or immediately after a hospital admission, and the main hospital discharge diagnoses were listed as COPD ($n = 10$), ILD ($n = 4$), respiratory failure ($n = 4$) and lower respiratory tract infections ($n = 6$), with 10 non-respiratory discharge codes. Overload and social functioning were worse in the carers of patients who died (Online supplemental Table 4S). AKPS was the only significant contributor to predict death (odds ratio 0.95; 95% CI 0.92–0.99; Online supplemental Table 5S).

**Discussion**

This was a pragmatic trial conducted to evaluate a novel training intervention designed for carers involving carer–patient dyads prescribed Government-subsidised long-term HOT for chronic hypoxaemia associated with a range of severe respiratory diseases. While the target of the intervention was the carer, the primary outcome was patient-focused. Results did not support our primary hypothesis related to improved
patient healthcare utilisation, as no difference between study arms was found for the primary outcome – the composite of patients’ survival to hospital or residential care admission or to death over the course of 12 months. In fact, a significantly higher mortality rate was detected in patients whose carers received the intervention, despite beneficial changes in some secondary outcomes such as patients’ self-reported overall health status. Whereas risk of death was increased for intervention patients with COPD, it was not for those with ILD. Post hoc analyses showed that AKPS was a significant contributor to predicting death. These important and unexpected findings warrant careful evaluation and discussion.

The intervention was directed towards carers in anticipation of improved patient support. Links between carer support and patient treatment adherence have been shown, and lack of social support has been found to be a barrier to patient self-management. We hypothesised that the intervention would reduce healthcare utilisation by enhancing the carer’s competence and confidence in everyday patient support, thereby optimising patient adherence to treatment paradigms existing at that time. However, promoting the carer’s input may have inadvertently contributed to a perceived role conflict regarding the patients managing themselves. Positioning patients in a less operational role could have negatively influenced their coping strategy and reduced their active self-management, ultimately leading to an increase of deaths. Whereas we anticipated that the intervention would improve carers’ confidence in managing care, there were no positive outcomes detected in carers’ mastery or quality of life accompanying the patients’ improvements in mastery, generic HRQoL and General Health.

Several questions arise from these findings.

1. Was the intervention a driver for carers and/or patients to feel empowered to control deteriorating disease status without seeking outside help? At first glance, the number of deaths arising during or post-hospitalisation (34/40) suggests that their choice to escalate care was correct. We have no supportive evidence of better decision-making since self-efficacy – a person’s belief in their ability to perform relevant strategies – was not measured directly and we did not monitor patient self-management activities or their action plan use.

2. Was the balance between ‘oxygen as panacea’, ‘oxygen as a burden’ and ‘antecedents to beliefs’ disturbed by the intervention? Patients and carers often assume that oxygen reduces dyspnoea or enables better functioning, but when they learnt that these were not the purpose of the treatment, the perceived positive association with oxygen provision could have been unsettled. With greater knowledge, patients and their carers might also see HOT as a hindrance to their activities and social interactions, and become aware of potential dangers, so negative perceptions of HOT could have been enhanced following the intervention.

3. Did dyads actively consider end of life care as part of what they perceived as better disease...
management? Another non-pharmacological disease management modality with strong evidence for improved patient outcomes – pulmonary rehabilitation – is strongly associated with effective social support, better self-management, self-efficacy, and changes in HRQoL, which can predict adaptive alterations in illness perceptions.\(^{30}\) Our intervention, which involved primarily the carer, could have enhanced patient awareness of their severe disease status and the burden placed on their carer, or a realisation that death was an imminent outcome, resulting in the patient ‘letting go’. At the time this study commenced, discussions with patients about directing their advanced care were not routine, and it was not actively addressed at any time by the research nurses.

At least one other large study targeting behavioural change in respiratory patients conducted around the time of our trial found unexplained increased mortality,\(^{31}\) and the independent Data and Safety Monitoring Board (DSMB) stopped that trial before completion. It should not be assumed that behavioural modification interventions are entirely safe, and we agree that DSMBs should be routinely instituted in such trials,\(^{31}\) while considering the value of best supportive care alongside the value of trial information.\(^{31}\)

Post hoc analyses revealed that three factors did show statistically significant univariate associations with poor survival: patients’ resting arterial blood oxygenation, their level of perceived dyspnoea and their performance status. Taken together, these are consistent with more severe functional impairment, but AKPS was the sole contributor to the multifactorial prediction model. AKPS is used in palliative care settings to assess performance status and provides a guide to prognosis,\(^{33}\) although patients enrolled in this study were not receiving formal palliative care. The mortality differential between study arms was smaller after adjustment for AKPS but did remain significant.

This study had several strengths. The sample size and 12-month follow-up allowed time to detect meaningful differences in the primary composite outcome, which was chosen for relevancy to both clinical outcomes and potentially healthcare utilisation. We had reasoned that the latter could inform health policy if savings through reduced healthcare utilisation were demonstrated. Importantly, composite scores were deconstructed for interpretation and generalisability\(^{34}\) and this uncovered the significant imbalance in mortality. Finally, index patients with a variety of lung diseases were recruited, with the explicit aim of enhancing generalisability to typical HOT patients. Messages were delivered based on carers’ needs, so not all possible messages were delivered to all carers. The message ‘to ensure the patient has an action plan for COPD exacerbations or knows how to get one if necessary’ was inherently restricted to carers of COPD patients (78% of the intervention group). Seeking support earlier by contacting a healthcare provider (in person or by telephone) or seeking emergency care are important behaviours that could be influenced by the presence of a carer. Intermediate outcomes, including action plan use and dyad’s relationship dynamics, would have been helpful in unravelling the unexpected ‘death’ results. Unfortunately, this information was not collected, and thus it remains unclear whether this factor may have contributed to differences between study arms. Additionally, we had no lung function data at baseline, given the various diagnostic groups and patient severity. The variable we used to assess functional severity imposed by the primary disease was the AKPS,\(^{33}\) developed as a measure of functional status of patients with terminal illnesses. We chose this as a descriptive characteristic for patients but did not use it for patient stratification. We assumed that any difference between intervention and control groups was due to random variance among the multiple descriptive and outcome measures collected. If we had only enrolled patients with COPD prescribed long-term HOT, we could have explored associations between spirometry and performance status or included other performance criteria, such as 6-min walk distance. However, our study population was non-diagnosis-specific, so these measurements were not available for association analysis.

Because the patient participants generally had severe respiratory disease, deaths were not unexpected, although the extent of imbalance in mortality between groups was. In a 10-year survival analysis of a HOT database in South Australia, the 12-month life expectancy for COPD patients was 78.1% for COPD patients. A systematic review of HOT in ILD showed similar 12-month survival rates.\(^{35}\) In the present study, control group patients had a better 12-month survival (89%), whereas the 1-year survival in our intervention group patients was slightly worse (71%).

This research was planned 15 years ago and was completed 10 years ago. Despite the delay in
providing the findings, the results remain relevant today, since the criteria for treating hypoxaemic patients with long-term HOT are unchanged and patients needing this treatment are even more plentiful. In fact, further research with such patient groups is now warranted with an aim to provide insights into the effects of actively involving primary carers in the support of patients. For future research we recommend:

- Assessing complexities of patient–carer relationship dynamics with both qualitatively and quantitatively;
- Considering patient self-management strategies and behaviour, carer perceptions, and use of advance care plans to understand the development of end-of-life decision-making in a partnership;
- Including larger numbers of patients with non-COPD diagnoses to allow differentiating treatment effects between HOT-patient diagnosis groups;
- Stratifying patients by functional status, lung function, activity and/or exercise capacity;
- Structuring behaviour change interventions for carers in active partnership with the patient to enable engagement of both, especially in late-stage disease;
- Appointing a DSMB.

**Conclusion**

The primary outcome of this pragmatic trial in which carers of patients using HOT received carer-centred training was negative – there was no reduction in the composite of patients’ survival to hospital or residential care admission or death over 12 months. However, there were significantly more deaths in the intervention arm. Post hoc analyses showed the increased risk of death was confined to intervention patients with COPD, and between-group difference in baseline performance status was a major contributor to mortality imbalance. Future research evaluating behaviour change interventions for carers of patients with chronic hypoxaemia should take into account complexities of patient–carer relationship dynamics and stratify for patients’ functional status and diagnosis. We must also accept that behavioural change interventions are not necessarily benign, and in recognising the possibility of consequences beyond hypothesised benefits, an independent DSMB should monitor both benefits and adverse events.

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**Data sharing statement**

De-identified participant data will not be shared as included participants have not consented to this. All available relevant information can be found in the clinical trial registry and/or the online repository. No further information will be publicly available.

**Declaration of conflicting interests**

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**Supplemental material**

Supplemental material for this article is available online.

**References**


