Online Supplement

Home Oxygen Therapy for Adults with Chronic Lung Disease

An Official American Thoracic Society Clinical Practice Guideline

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PARTICIPANTS

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Table E1: Conflict of interest grid

Panelist's Name	PICO 1) Should long-term oxygen be prescribed for adults with COPD who have severe chronic resting room air hypoxemia?	PICO 2) Should long-term oxygen be prescribed for adults with COPD who have moderate chronic resting room air hypoxemia?	PICO 3) Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia?	PICO 4) Should long-term oxygen be prescribed for adults with ILD who have severe chronic resting room air hypoxemia?	PICO 5) Should ambulatory oxygen be prescribed for adults with ILD who have severe exertional room air hypoxemia?	PICO 6) Should portable liquid oxygen be provided for adults with chronic lung disease who are prescribed continuous oxygen flow rates of more than 3 L/min during exertion?	All Disclosures
Carlin, Brian, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Drummond, M. Bradley, MD, MHS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Ekström, Magnus, MD, PhD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Garvey, Chris, FNP, MSN, MPA	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Ghazipura, Marya, PhD, MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Graney, Bridget, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Holland, Anne, PT, PhD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Hossain, Tanzib, MD, MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Jackson, Beverly, MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Jacobs, Susan, RN, MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Kallstrom, Thomas, MBA, RRT	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs

Knight, Shandra MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Krishnan, Jerry, MD, PhD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Lederer, David, MD, MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Lindell, Katheleen, PhD, RN	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Prieto-Centurion, Valentin, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Renzoni, Elisabetta, MD, PhD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Ryerson, Christopher, MD, MAS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Schneidmann, Ann, MS, CNS, CHPN	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Swigris, Jeffrey, DO, MS	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Tan, Ai-Yui, MD	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs
Upson, Dona, MD, MA	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs	No relevant COIs

METHODS

Panel Composition, Meetings, and Conflicts of Interest

The ATS Document Development and Implementation Committee selected and approved the chair and co-chairs for the guideline panel. The co-chairs identified an inter-professional group of experts. After the Committee's approval, the composition of the guideline panel consisted of 4 co-chairs with 18 voting members: 11 pulmonary/critical care physicians, 4 nurses, 1 registered respiratory therapist, and 1 physiotherapist. To capture the critical input of an oxygen user, the panel included a patient representative (Figure 1). The guideline panel was assisted by an epidemiologist and biostatistician as the lead methodologist, two pulmonary physician methodologist trainees, and a medical librarian, who were all non-voting members.

Panel meetings were held in person at two full-day sessions approximately 12 months apart, and via teleconference on an *ad hoc* basis to review survey results, evidence profiles, and to discuss recommendations. The panel chair ensured all conflicts of interest (COI) were reviewed and updated at each panel meeting (Table E1).

Formulation of Questions and Prioritization of Outcomes

The co-chairs made a preliminary list of key research questions in PICO (Population, Intervention, Comparator, and Outcome) format. These questions were submitted by members of the panel and then voted upon in a multi-round survey process in order to arrive at the final six questions using a modified Delphi approach (1). During the first round, each panel member completed a survey wherein they gave each question a relative score of 1 (low priority) to 10

(high priority) based on how vital the panel member ranked the importance of the question. To add another dimension and reduce potential skewness of the resulting scores, panel members were also asked to rank their top six questions from among those that they scored 5 or higher. From these results, the average score and the average ranking were calculated across all panel members. The top three questions using each method (average score and average ranking) were selected for inclusion. From the first round, five questions were selected (as there was one question that was in the top three by both methods). The panel was then given the option of suggesting up to two additional questions (not included in the first round) that they felt merited investigation; four additional questions were suggested during this process, which were compiled into one consolidated question. This question, along with the next three highest scoring questions from the first round, were submitted as a second round of surveys. The second survey followed the same scoring and ranking process as the first round, and only the resulting top question was selected, along with the initial five questions, to finalize the list of six questions.

Potential outcomes for each of the six questions were submitted to the panel members as a survey (using the GRADE approach from 1 to 9), and then ranked ordinally [as critical, important, or not important] again based on a modified Delphi approach. The survey was used to gain panel consensus on the importance of each outcome for each question.

Literature Searches, Study Selection, and Data Extraction

For the systematic review we defined severe hypoxemia on the basis of a $SpO_2 < 88\%$ by pulse oximetry and/or $PaO_2 < 55$ mmHg/7.3 kPa by blood gas sampling, and moderate hypoxemia as SpO_2 88 to 93% or PaO_2 56 to 60 mmHg/7.5-8.0 kPa. However, we found substantial variability

in definitions for severe hypoxemia across studies, and the data were not reported in a way that would allow re-analyses of outcomes at different thresholds. Moreover, some studies defined eligibility on the basis of PaO_2, whereas others used SpO_2 values. We recognize that SpO_2 is an indirect measure of arterial oxygenation (compared with direct measurement of partial pressure [PaO_2] or percent saturation [SaO_2] by blood gas sampling) and the SpO_2 that corresponds to different values of PaO_2 can vary across individuals (e.g., due to an individual's hematocrit, oxygen-hemoglobin dissociation curve, carboxyhemoglobin levels), we found it difficult to apply an absolute threshold for both SpO_2 and PaO_2 that would correspond to severe or moderate hypoxemia. Thus, we also considered studies using different thresholds and reported the definitions of severe and moderate hypoxemia used by study authors. We have provided suggested thresholds for hypoxemia in the implementation consideration sections.

Literature searches were conducted with the assistance of a medical librarian who searched Ovid Medline and In-Process and Other Non-Indexed Citations, EMBASE, Cumulative Index to Nursing & Allied Health Literature, and Cochrane Central Register of Controlled Trials using indexing terms and keywords agreed upon by the panel. All databases were searched up to June 2019, with no limit on the start date, but non-English language studies were excluded. All relevant studies, regardless of study design, were assessed, including RCTs and observational studies. Questions were split into three groups by theme and searches were completed for each group (patients with COPD, patients with ILD, and patients with any chronic lung disease prescribed portable liquid oxygen). A separate grey literature search was done to identify any conference proceedings or reports. For details of the literature search methodology, please see the supplementary material.

An initial title and abstract screening was completed by two independent reviewers and conflicts were resolved by a third individual. Full-text screening was completed for each of the remaining studies by two individuals independently, and conflicts were again resolved by a third individual. References of all full text studies were hand searched to identify any additional studies for inclusion. Once the list of studies to include was finalized, data from each study were extracted by hand into a separate spreadsheet by one individual and checked by another for accuracy. Corrections were made by joint decision by the two individuals.

Meta-Analyses

When possible, data from individual studies were pooled to create a meta-analysis, using the generic inverse variance method; R Studio 3.5.2 was used for all calculations. Individual estimates were pooled using random-effects models to account for differences in the treatment effect in each study as well as sampling variability. Relative risk (RR) scores were obtained to report the results for binary outcomes and mean differences to report the results for continuous outcomes, accompanied by a 95% confidence interval (CI). Statistical heterogeneity was assessed using the I^2 test, with I^2 of 50% or higher indicating significant heterogeneity. Certainty of evidence was downgraded for inconsistency in the event of significant heterogeneity. Sensitivity analyses were conducted by study design in the presence of observational or crossover RCTs. Heterogeneity was explored using sensitivity analysis according to study design, to explore whether the effect estimates differed in crossover trials compared to parallel group trials.

Evidence Certainty

The GRADE approach (2) was used to assess the certainty of evidence for each intervention on each outcome of interest. Methodologists assessed risk of bias and created evidence profiles using the GRADE Guideline Development Tool (3) which categorizes evidence into one of four levels (High, Moderate, Low, or Very Low). Each level represents the certainty in the accuracy of the estimated individual or pooled effects for a specific intervention, the details of which are shown in Table 1 in the full text of the guideline. All panelists reviewed the evidence profiles for included studies and meta-analyses and provided input and feedback to reach the final certainty level for each evidence provided.

Recommendations

The panel developed recommendations based on the evidence profiles for each PICO question. The Evidence-to-Decision framework (EtD) (3) was used to guide each recommendation. This framework considers the desirable versus undesirable consequences (i.e. benefits vs. burdens, costs, and/or adverse effects), patient values and preferences (including input from the patient advocate member of the panel), cost, cost effectiveness, feasibility of intervention, equity, and the overall acceptability of the intervention (or lack thereof) in determining the final recommendation. Using the GRADE approach, each recommendation was thereby rated as either "strong" or "conditional", the implications of which are outlined in Table 2. For clinical recommendations regarding oxygen education and safety, for which there was no reasonable alternative course of action, a "best practice statement" was developed that did not utilize the GRADE framework. An 'Implementation Considerations' section was included pertinent to each question that addressed implementation and other considerations such as feasibility, costs,

decision making, and monitoring. To facilitate interpretation of our recommendations, we adopted a published terminology for various types of home oxygen therapy (Table 3) (4). We also define different levels of hypoxemia on the basis of SpO_2 and PaO_2 thresholds. While we recognize that SpO_2 values cannot be used to infer the same corresponding PaO2 value in all patients, experience among members of the guideline panel suggested that providing both values would improve the usability of the guideline report.

Manuscript Preparation

The co-chairs and lead methodologist integrated the evidence from each systematic review, the EtD framework, and the voting results for the clinical recommendations into a preliminary document that was distributed to the panel for additional feedback. All comments were then addressed by the panel chair, co-chairs, and lead methodologist, and revised copies were sent to the full panel for additional review and feedback and were subsequently finalized after any remaining comments were addressed. Once the full-length guideline, executive summary, and online supplement were approved by the entire panel, they were submitted simultaneously for independent peer review under the direction of the ATS Documents Editor.

External Review Process

The documents were reviewed by content and methodology experts from the ATS Document Development and Implementation Committee who did not participate in the preparation of the guidelines.

References

1. Dalkey N, Helmer O. An Experimental Application of the DELPHI Method to the Use of Experts. *Management Science* 1963; 9: 458-467.

2. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, Group GW. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924-926.
3. GRADEpro. Computer program. 2014 [accessed 2018 Jul]. Available from: www.gradepro.org.
4. Lacasse Y, Tan AM, Maltais F, Krishnan JA. Home oxygen in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018; 197: 1254-1264.

PICO QUESTIONS

1) Should long-term oxygen be prescribed for adults with COPD who have severe chronic resting room air hypoxemia?	
Population	Adults with COPD and severe chronic resting room air hypoxemia ($PaO_2 \leq 55$ mmHg/7.3 kPa or $SpO_2 \leq 88\%$)
Intervention	Prescription of long-term oxygen therapy
Comparator	No prescription of oxygen therapy
Outcomes	**Critical:** Mortality **Important:** Dyspnea, exercise capacity, quality of life, fatigue, physical activity, healthcare resource utilization, safety

2) Should long-term oxygen be prescribed for adults with COPD who have moderate chronic resting room air hypoxemia?	
Population	Adults with COPD and moderate chronic resting room air hypoxemia (PaO_2 56-60 mmHg/7.5-8.0 kPa or SpO_2 89-93%)
Intervention	Prescription of long-term oxygen
Comparator	No prescription of long-term oxygen
Outcomes	**Critical:** Mortality **Important:** Dyspnea, exercise capacity, COPD exacerbation, quality of life, fatigue, physical activity, healthcare resource utilization, safety

3) Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia?	
Population	Adults with COPD and severe exertional room air hypoxemia ($PaO_2 \leq 55$ mmHg/7.3 kPa or $SpO_2 \leq 88\%$)
Intervention	Prescription of ambulatory oxygen
Comparator	No prescription of ambulatory oxygen
Outcomes	**Critical:** Quality of life **Important:** Mortality, dyspnea, exercise capacity, fatigue, physical activity, healthcare resource utilization, safety

4) Should long-term oxygen be prescribed for adults with ILD who have severe chronic resting room air hypoxemia?	
Population	Adults with ILD with severe chronic resting room air hypoxemia ($PaO_2 \leq 55$ mmHg/7.3 kPa or $SpO_2 \leq 88\%$)
Intervention	Prescription of long-term oxygen
Comparator	No prescription of long-term oxygen
Outcomes	**Critical:** Mortality **Important:** Dyspnea, exercise capacity, quality of life, fatigue, physical activity, healthcare resource utilization, safety

5) Should ambulatory oxygen be prescribed for adults with ILD who have severe exertional room air hypoxemia?		
Population	Adults with ILD who have severe exertional room air hypoxemia ($PaO_2 \leq 55$ mmHg/7.3 kPa or $SpO_2 \leq 89\%$)	
Intervention	Prescription of ambulatory oxygen	
Comparator	No prescription of ambulatory oxygen	
Outcomes	**Critical:**	Quality of life
	Important:	Mortality, dyspnea, exercise capacity, quality of life, fatigue, physical activity, healthcare resource utilization, safety

6) Should portable liquid oxygen be provided for adults with chronic lung disease who are prescribed continuous oxygen flow rates of more than 3 L/min during exertion?		
Population	Adults with chronic lung disease who are prescribed continuous oxygen flow rates of more than 3 L/min during exertion	
Intervention	Portable liquid oxygen delivery systems	
Comparator	All other portable oxygen delivery systems	
Outcomes	**Critical:**	Quality of life
	Important:	Oxygen saturation during exertion, dyspnea, exercise capacity, fatigue, physical activity, adherence, safety

SEARCH STRATEGIES

Search strategy for PICOs 1-3

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 13, 2018>

#	Searches	Results
1	lung diseases, obstructive/	18097
2	exp pulmonary disease, chronic obstructive/	48742
3	bronchitis, chronic/	1675
4	pulmonary emphysema/	15335
5	1 or 2 or 3 or 4 [COPD subject headings]	66026
6	(coad or copd).mp.	39473
7	(chronic adj air$ adj obstruct$).mp.	1067
8	((constrict$ or obstruct$) adj3 (air$ or lung$ or pulmonary or bronch$ or respirat$)).mp.	107739
9	emphysema$.mp.	33681
10	(chronic adj3 bronchiti$).mp.	11077
11	lung, hyperlucent/	149
12	(((thorax or lung$) adj2 hyperlucent) or ((macleod or swyer james) adj syndrome)).mp.	383
13	6 or 7 or 8 or 9 or 10 [COPD textwords]	145477
14	5 or 13 [All COPD]	145477
15	exp Oxygen Inhalation Therapy/ or oxygen therapy/	24255
16	(((prescri$ or supplement$ or therap$ or home$ or domicil$ or portable or ultraportable or ultra-portable or ambulat$ or self-fill or liquid or compress$ or light-weight) adj3 (oxygen or O2 or LOX or concentrator$)) or (oxygen adj2 (POC$ or PLOT$)) or SuppO2).mp.	26851
17	15 or 16 [oxygen therapy]	34893
18	14 and 17	4179
19	limit 18 to english language	3220
20	limit 19 to "all adult (19 plus years)"	1557
21	limit 19 to "all child (0 to 18 years)"	336
22	19 not 20 not 21	1425
23	20 or 22	**2982**

Embase <1974 to 2018 June 15>

#	Searches	Results
1	obstructive airway disease/	1932
2	chronic obstructive lung disease/	110144
3	bronchitis, chronic/	8874
4	pulmonary emphysema/	9837
5	1 or 2 or 3 or 4	126198
6	(coad or copd).mp.	73489
7	(chronic adj air$ adj obstruct$).mp.	1361
8	((contrict$ or obstruct$) adj3 (air$ or lung$ or pulmonary or bronch$ or respirat$)).mp.	178632
9	emphysema$.mp.	46161
10	(chronic adj3 bronchiti$).mp.	19086
11	lung, hyperlucent/	483
12	(((thorax or lung$) adj2 hyperlucent) or ((macleod or swyer james) adj syndrome)).mp.	433
13	6 or 7 or 8 or 9 or 10	236942
14	5 or 13	236942
15	exp Oxygen Inhalation Therapy/ or oxygen therapy/	29692
16	(((prescri$ or supplement$ or therap$ or home$ or domicil$ or portable or ultraportable or ultra-portable or ambulat$ or self-fill or liquid or compress$ or light-weight) adj3 (oxygen or O2 or LOX or concentrator$)) or (oxygen adj2 (POC$ or PLOT$)) or SuppO2).mp.	45339
17	15 or 16 [oxygen therapy]	45973
18	14 and 17	8282
19	limit 18 to english language	7075
20	limit 19 to (adult <18 to 64 years> or aged <65+ years>)	2707
21	limit 19 to (child <unspecified age> or adolescent <13 to 17 years>)	390
22	19 not 20 not 21	4086
23	20 or 22	6793
24	limit 23 to (conference abstracts and conference abstract status)	1225
25	23 not 24	**5568**

EBM Reviews - Cochrane Central Register of Controlled Trials <to 2018 June 21>		
#	Searches	Results
1	lung diseases, obstructive/	2431
2	exp pulmonary disease, chronic obstructive/	4408
3	bronchitis, chronic/	138
4	pulmonary emphysema/	259
5	1 or 2 or 3 or 4 [COPD subject headings]	5866
6	(coad or copd).mp.	12164
7	(chronic adj air$ adj obstruct$).mp.	205
8	((constrict$ or obstruct$) adj3 (air$ or lung$ or pulmonary or bronch$ or respirat$)).mp.	14364
9	emphysema$.mp.	1139
10	(chronic adj3 bronchiti$).mp.	1693
11	lung, hyperlucent/	1
12	(((thorax or lung$) adj2 hyperlucent) or ((macleod or swyer james) adj syndrome)).mp.	1
13	6 or 7 or 8 or 9 or 10 [COPD textwords]	20534
14	5 or 13 [All COPD]	20534
15	exp Oxygen Inhalation Therapy/ or oxygen therapy/	1278
16	(((prescri$ or supplement$ or therap$ or home$ or domicil$ or portable or ultraportable or ultra-portable or ambulat$ or self-fill or liquid or compress$ or light-weight) adj3 (oxygen or O2 or LOX or concentrator$)) or (oxygen adj2 (POC$ or PLOT$)) or SuppO2).mp.	4615
17	15 or 16 [oxygen therapy]	4780
18	14 and 17	815
19	limit 18 to english language	567

CINAHL <to 2018 June 26>		
#	**Query**	**Results**
S1	TX (supplement* OR home OR domicil* OR portable OR ultraportable OR ultra-portable OR ambulat* OR self-fill)	769,439
S2	TI (oxygen* OR O2 OR SupplO2)	12,934
S3	S1 AND S2	2,233
S4	(MH "Home Oxygen Therapy")	374
S5	S3 OR S4	2,381
S6	(MH "Pulmonary Disease, Chronic Obstructive+")	15,251
S7	TX (COPD OR COAD)	21,632
S8	TX (chronic obstructive pulmonary)	21,793
S9	TX (chronic obstructive lung)	1,909
S10	TX (hyperlucent lung*)	36
S11	TX (emphysem* OR bronchitis)	13,530
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11	44,995
S13	S5 AND S12	152

Search Strategy for PICOs 4 and 5

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 13, 2018>		
#	**Searches**	**Results**
1	exp Lung Diseases, Interstitial/	54870
2	(interstitial adj lung$).mp.	9067
3	((interstitial or organizing or eosinophil$) adj3 (fibros$ or pneumon$)).mp.	22627
4	(alveoliti$ or (hypersensitiv$ adj pneumoniti$)).mp.	6772
5	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$ or purpura) adj (lung$ or disease$)).mp.	11266
6	(histiocytosis$ or Churg Strauss or ((Wegener$ or polyangiitis or eosinophilic) adj3 granuloma$)).mp.	25489
7	(pneumoconios$ or pneumokonios$).mp.	7910
8	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis or bagassosis).mp.	16524
9	((diffus$ adj parenchymal) or (pleuroparenchymal adj fibroelastos$)).mp.	673
10	exp pulmonary fibrosis/	20248
11	((lung$ or pulmonary) adj3 (fibros$ or sarcoid$)).mp.	35648
12	(bronchiolitis adj (obliterans or follicular)).mp.	4302
13	lymphangioleiomyomatosis.mp.	1600
14	or/1-13 [All ILD]	126192
15	exp Oxygen Inhalation Therapy/ or oxygen therapy/	24255
16	(((prescri$ or supplement$ or therap$ or home$ or domicil$ or portable or ultraportable or ultra-portable or ambulat$ or self-fill or liquid or compress$ or light-weight) adj3 (oxygen or O2 or LOX or concentrator$)) or (oxygen adj2 (POC$ or PLOT$)) or SuppO2).mp.	26851
17	15 or 16 [oxygen therapy]	34893
18	14 and 17	745
19	limit 18 to english language	566
20	limit 19 to "all adult (19 plus years)"	298
21	limit 19 to "all child (0 to 18 years)"	97
22	19 not 20 not 21	204
23	20 or 22	502

Embase <1974 to 2018 June 15>		
#	**Searches**	**Results**
1	exp interstitial lung disease/	68392
2	(interstitial adj lung$).mp.	21907
3	((interstitial or organizing or eosinophil$) adj3 (fibros$ or pneumon$)).mp.	37781
4	(alveoliti$ or ((fibrosing or hypersensitiv$) adj pneumoniti$)).mp.	26994
5	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$ or purpura) adj (lung$ or disease$)).mp.	26995
6	(histiocytosis$ or Churg Strauss or ((Wegener$ or polyangiitis or eosinophilic) adj3 granuloma$)).mp.	35576
7	(pneumoconios$ or pneumokonios$).mp.	8316
8	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis or bagassosis).mp.	17823
9	((diffus$ adj parenchymal) or (pleuroparenchymal adj fibroelastos$)).mp.	1106
10	exp lung fibrosis/	66740
11	((lung$ or pulmonary) adj3 (fibros$ or sarcoid$)).mp.	55923
12	(bronchiolitis adj (constrictive or oblitera$ or follicular)).mp.	8295
13	lymphangioleiomyomatosis.mp.	2577
14	or/1-13	197079
15	exp Oxygen Inhalation Therapy/ or oxygen therapy/	29692
16	(((prescri$ or supplement$ or therap$ or home$ or domicil$ or portable or ultraportable or ultra-portable or ambulat$ or self-fill or liquid or compress$ or light-weight) adj3 (oxygen or O2 or LOX or concentrator$)) or (oxygen adj2 (POC$ or PLOT$)) or SuppO2).mp.	45339
17	15 or 16 [oxygen therapy]	45973
18	14 and 17	2450
19	limit 18 to conference abstracts	641
20	18 not 19	1809
21	limit 20 to english language	1590
22	limit 21 to (adult <18 to 64 years> or aged <65+ years>)	834
23	limit 21 to (child <unspecified age> or adolescent <13 to 17 years>)	157
24	21 not 22 not 23	647
25	**22 or 24**	**1481**

EBM Reviews - Cochrane Central Register of Controlled Trials <to 2018 June 21>		
#	Searches	Results
1	exp Lung Diseases, Interstitial/	569
2	(interstitial adj lung$).mp.	692
3	((interstitial or organizing or eosinophil$) adj3 (fibros$ or pneumon$)).mp.	647
4	(alveoliti$ or (hypersensitiv$ adj pneumoniti$)).mp.	542
5	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$ or purpura) adj (lung$ or disease$)).mp.	101
6	(histiocytosis$ or Churg Strauss or ((Wegener$ or polyangiitis or eosinophilic) adj3 granuloma$)).mp.	322
7	(pneumoconios$ or pneumokonios$).mp.	52
8	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis or bagassosis).mp.	137
9	((diffus$ adj parenchymal) or (pleuroparenchymal adj fibroelastos$)).mp.	10
10	exp pulmonary fibrosis/	372
11	((lung$ or pulmonary) adj3 (fibros$ or sarcoid$)).mp.	1874
12	(bronchiolitis adj (obliterans or follicular)).mp.	150
13	lymphangioleiomyomatosis.mp.	54
14	or/1-13 [All ILD]	3750
15	exp Oxygen Inhalation Therapy/ or oxygen therapy/	1278
16	(((prescri$ or supplement$ or therap$ or home$ or domicil$ or portable or ultraportable or ultra-portable or ambulat$ or self-fill or liquid or compress$ or light-weight) adj3 (oxygen or O2 or LOX or concentrator$)) or (oxygen adj2 (POC$ or PLOT$)) or SuppO2).mp.	4615
17	15 or 16 [oxygen therapy]	4780
18	14 and 17	106
19	limit 18 to english language	73

CINAHL <to 2018 June 26>		
#	**Query**	**Results**
S1	TX (supplement* OR home OR domicil* OR portable OR ultraportable OR ultra-portable OR ambulat* OR self-fill)	769,439
S2	TI (oxygen* OR O2 OR SupplO2)	12,934
S3	S1 AND S2	2,233
S4	(MH "Home Oxygen Therapy")	374
S5	S3 OR S4	2,381
S6	(MH "Pulmonary Disease, Chronic Obstructive+")	15,251
S7	TX (COPD OR COAD)	21,632
S8	TX (chronic obstructive pulmonary)	21,793
S9	TX (chronic obstructive lung)	1,909
S10	TX (hyperlucent lung*)	36
S11	TX (emphysem* OR bronchitis)	13,530
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11	44,995
S13	S5 AND S12	152
S14	(MH "Lung Diseases, Interstitial+")	2,351
S15	TX (interstitial lung OR pulmonary fibrosis)	2,257
S16	S14 OR S15	3,762
S17	S5 AND S16	35

Search Strategy for PICO 6

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to June 13, 2018>		
#	**Searches**	**Results**
1	((portable or ultraportable or ambulat$ or domicil$ or home$ or prescri$ or supplement$) adj2 (LOX or liquid oxygen)).mp.	37
2	(liquid$ adj3 (O2 or oxygen)).mp.	457
3	(oxygen adj3 (PLOT$ or LOX)).mp.	117
4	1 or 2 or 3 [liquid oxygen]	570
5	lung diseases, obstructive/	18097
6	exp pulmonary disease, chronic obstructive/	48742
7	bronchitis, chronic/	1675
8	pulmonary emphysema/	15335
9	5 or 6 or 7 or 8 [COPD subject headings]	66026
10	(coad or copd).mp.	39473
11	(chronic adj air$ adj obstruct$).mp.	1067
12	((constrict$ or obstruct$) adj3 (air$ or lung$ or pulmonary or bronch$ or respirat$)).mp.	107739
13	emphysema$.mp.	33681
14	(chronic adj3 bronchiti$).mp.	11077
15	lung, hyperlucent/	149
16	(((thorax or lung$) adj2 hyperlucent) or ((macleod or swyer james) adj syndrome)).mp.	383
17	10 or 11 or 12 or 13 or 14 [COPD textwords]	145477
18	9 or 17 [All COPD]	145477
19	exp Lung Diseases, Interstitial/	54870
20	(interstitial adj lung$).mp.	9067
21	((interstitial or organizing or eosinophil$) adj3 (fibros$ or pneumon$)).mp.	22627
22	(alveoliti$ or (hypersensitiv$ adj pneumoniti$)).mp.	6772
23	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$ or purpura) adj (lung$ or disease$)).mp.	11266
24	(histiocytosis$ or Churg Strauss or ((Wegener$ or polyangiitis or eosinophilic) adj3 granuloma$)).mp.	25489
25	(pneumoconios$ or pneumokonios$).mp.	7910

26	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis or bagassosis).mp.	16524
27	((diffus$ adj parenchymal) or (pleuroparenchymal adj fibroelastos$)).mp.	673
28	exp pulmonary fibrosis/	20248
29	((lung$ or pulmonary) adj3 (fibros$ or sarcoid$)).mp.	35648
30	(bronchiolitis adj (obliterans or follicular)).mp.	4302
31	lymphangioleiomyomatosis.mp.	1600
32	or/19-31 [All ILD]	126192
33	18 or 32 [COPD or ILD]	264134
34	exp exercise test/	59421
35	((fitness or stress or step or walk$ or treadmill or ergometry) adj test$).mp.	29633
36	34 or 35	78019
37	walk test/	594
38	("6 minute" adj2 walk).mp.	3581
39	(six adj minute adj2 walk).mp.	1788
40	6MW.mp.	178
41	36 or 40 [walk test]	78106
42	((portable or ultraportable or ambulat$ or domicil$ or home$ or prescri$ or supplement$) adj2 (LOX or liquid oxygen)).mp.	37
43	(liquid$ adj3 (O2 or oxygen)).mp.	457
44	(oxygen adj3 (PLOT$ or LOX)).mp.	117
45	42 or 43 or 44 [liquid oxygen]	570
46	33 and 41 and 45 [COPD/ILD and walk test and liquid oxygen]	13
47	33 and 45 [COPD/ILD and liquid oxygen]	**67**

Embase <1974 to 2018 Week 25>

#	Searches	Results
1	exp exercise test/	76216
2	((fitness or stress or step or walk$ or treadmill or ergometry) adj test$).mp.	50950
3	1 or 2	105573
4	walk test/	1006
5	("6 minute" adj2 walk).mp.	7688

6	(six adj minute adj2 walk).mp.	7169
7	6MW.mp.	506
8	3 or 7 [walk test]	105843
9	((portable or ultraportable or ambulat$ or domicil$ or home$ or prescri$ or supplement$) adj2 (LOX or liquid oxygen)).mp.	48
10	(liquid$ adj3 (O2 or oxygen)).mp.	612
11	(oxygen adj3 (PLOT$ or LOX)).mp.	160
12	9 or 10 or 11 [liquid oxygen]	763
13	exp interstitial lung disease/	68385
14	(interstitial adj lung$).mp.	21903
15	((interstitial or organizing or eosinophil$) adj3 (fibros$ or pneumon$)).mp.	37776
16	(alveoliti$ or ((fibrosing or hypersensitiv$) adj pneumoniti$)).mp.	26991
17	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$ or purpura) adj (lung$ or disease$)).mp.	26995
18	(histiocytosis$ or Churg Strauss or ((Wegener$ or polyangiitis or eosinophilic) adj3 granuloma$)).mp.	35571
19	(pneumoconios$ or pneumokonios$).mp.	8316
20	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis or bagassosis).mp.	17822
21	((diffus$ adj parenchymal) or (pleuroparenchymal adj fibroelastos$)).mp.	1106
22	exp lung fibrosis/	66735
23	((lung$ or pulmonary) adj3 (fibros$ or sarcoid$)).mp.	55919
24	(bronchiolitis adj (constrictive or oblitera$ or follicular)).mp.	8294
25	lymphangioleiomyomatosis.mp.	2577
26	or/13-25	197062
27	obstructive airway disease/	1932
28	chronic obstructive lung disease/	110120
29	bronchitis, chronic/	8874
30	pulmonary emphysema/	9837
31	27 or 28 or 29 or 30	126174
32	(coad or copd).mp.	73467
33	(chronic adj air$ adj obstruct$).mp.	1361
34	((contrict$ or obstruct$) adj3 (air$ or lung$ or pulmonary or bronch$ or respirat$)).mp.	178605
35	emphysema$.mp.	46160
36	(chronic adj3 bronchiti$).mp.	19085

37	lung, hyperlucent/	483
38	(((thorax or lung$) adj2 hyperlucent) or ((macleod or swyer james) adj syndrome)).mp.	433
39	32 or 33 or 34 or 35 or 36	236915
40	31 or 39	236915
41	26 or 40 [ILD or COPD]	418755
42	12 and 41 [ILD/COPD and liquid oxygen]	109
43	limit 42 to English language	**76**

EBM Reviews - Cochrane Central Register of Controlled Trials <to 2018, 26 June>

#	Searches	Results
1	((portable or ultraportable or ambulat$ or domicil$ or home$ or prescri$ or supplement$) adj2 (LOX or liquid oxygen)).mp.	19
2	(liquid$ adj3 (O2 or oxygen)).mp.	56
3	(oxygen adj3 (PLOT$ or LOX)).mp.	5
4	1 or 2 or 3	59
5	lung diseases, obstructive/	2431
6	exp pulmonary disease, chronic obstructive/	4408
7	bronchitis, chronic/	138
8	pulmonary emphysema/	259
9	5 or 6 or 7 or 8 [COPD subject headings]	5866
10	(coad or copd).mp.	12164
11	(chronic adj air$ adj obstruct$).mp.	205
12	((constrict$ or obstruct$) adj3 (air$ or lung$ or pulmonary or bronch$ or respirat$)).mp.	14364
13	emphysema$.mp.	1139
14	(chronic adj3 bronchiti$).mp.	1693
15	lung, hyperlucent/	1
16	(((thorax or lung$) adj2 hyperlucent) or ((macleod or swyer james) adj syndrome)).mp.	1
17	10 or 11 or 12 or 13 or 14 [COPD textwords]	20534
18	9 or 17 [All COPD]	20534
19	exp Lung Diseases, Interstitial/	569

20	(interstitial adj lung$).mp.	692
21	((interstitial or organizing or eosinophil$) adj3 (fibros$ or pneumon$)).mp.	647
22	(alveoliti$ or (hypersensitiv$ adj pneumoniti$)).mp.	542
23	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$ or purpura) adj (lung$ or disease$)).mp.	101
24	(histiocytosis$ or Churg Strauss or ((Wegener$ or polyangiitis or eosinophilic) adj3 granuloma$)).mp.	322
25	(pneumoconios$ or pneumokonios$).mp.	52
26	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis or bagassosis).mp.	137
27	((diffus$ adj parenchymal) or (pleuroparenchymal adj fibroelastos$)).mp.	10
28	exp pulmonary fibrosis/	372
29	((lung$ or pulmonary) adj3 (fibros$ or sarcoid$)).mp.	1874
30	(bronchiolitis adj (obliterans or follicular)).mp.	150
31	lymphangioleiomyomatosis.mp.	54
32	or/19-31 [All ILD]	3750
33	18 or 32 [COPD or ILD]	23988
34	exp exercise test/	7800
35	((fitness or stress or step or walk$ or treadmill or ergometry) adj test$).mp.	7679
36	34 or 35	14067
37	walk test/	100
38	("6 minute" adj2 walk).mp.	1775
39	(six adj minute adj2 walk).mp.	1337
40	6MW.mp.	81
41	36 or 40	14106
42	((portable or ultraportable or ambulat$ or domicil$ or home$ or prescri$ or supplement$) adj2 (LOX or liquid oxygen)).mp.	19
43	(liquid$ adj3 (O2 or oxygen)).mp.	56
44	(oxygen adj3 (PLOT$ or LOX)).mp.	5
45	42 or 43 or 44	59
46	33 and 41 and 45	14
47	33 and 45	27
48	limit 47 to English language	12

CINAHL <to 2018 June 26>		
#	Query	Results
S1	TX (supplement* OR home OR domicil* OR portable OR ultraportable OR ultra-portable OR ambulat* OR self-fill)	769,439
S2	TI (oxygen* OR O2 OR SupplO2)	12,934
S3	S1 AND S2	2,233
S4	(MH "Home Oxygen Therapy")	374
S5	S3 OR S4	2,381
S6	(MH "Pulmonary Disease, Chronic Obstructive+")	15,251
S7	TX (COPD OR COAD)	21,632
S8	TX (chronic obstructive pulmonary)	21,793
S9	TX (chronic obstructive lung)	1,909
S10	TX (hyperlucent lung*)	36
S11	TX (emphysem* OR bronchitis)	13,530
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11	44,995
S13	S5 AND S12	152
S14	(MH "Lung Diseases, Interstitial+")	2,351
S15	TX (interstitial lung OR pulmonary fibrosis)	2,257
S16	S14 OR S15	3,762
S17	S5 AND S16	35
S18	S12 OR S16	48,109
S19	TX liquid	44,708
S20	TX (liquid (oxygen OR O2 SupplO2 OR SuppO2))	162
S21	S18 AND S20	90

PRISMA FLOW DIAGRAMS

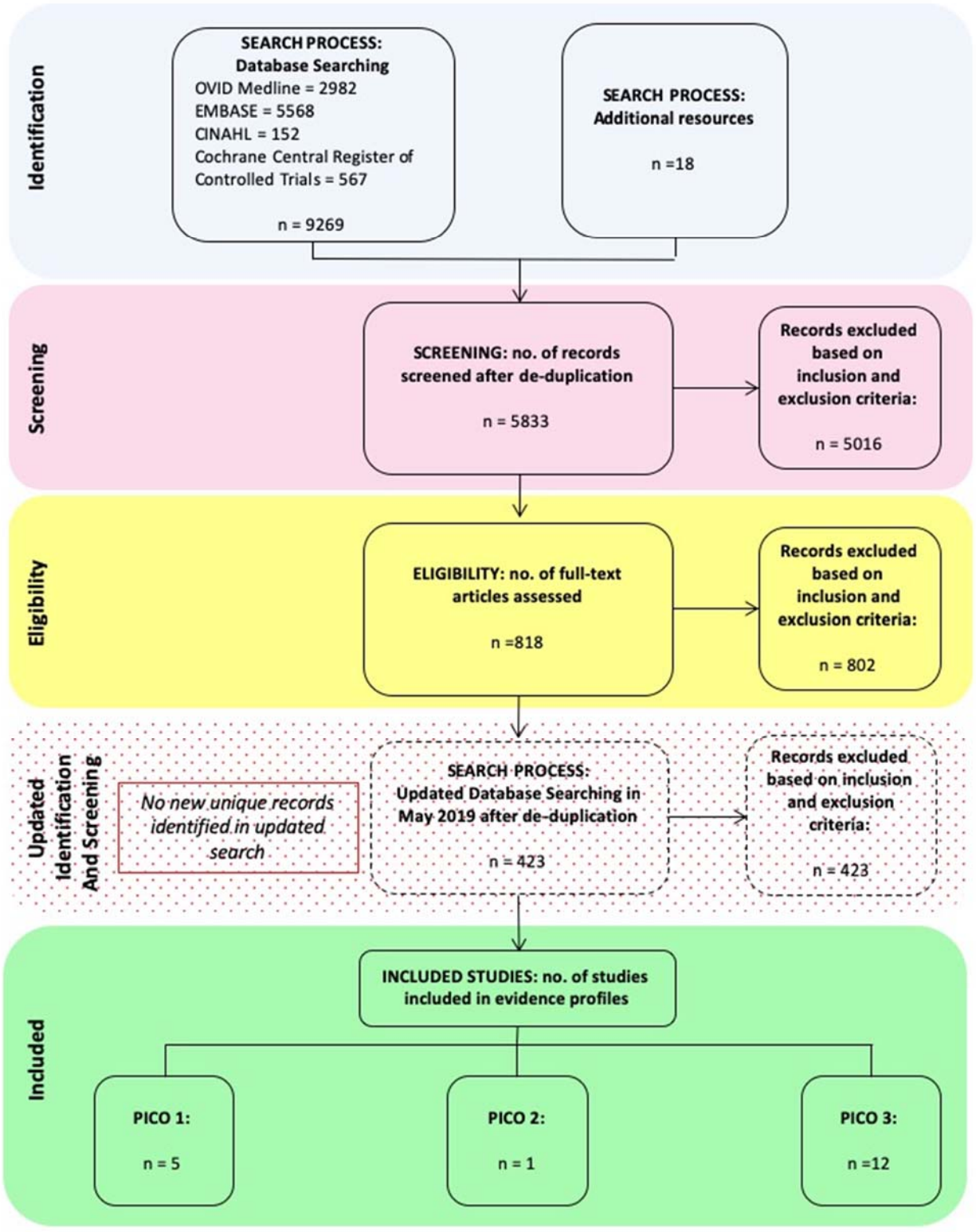

Figure E1: PRISMA (1) diagram for the process of inclusion of studies for PICOs 1 through 3

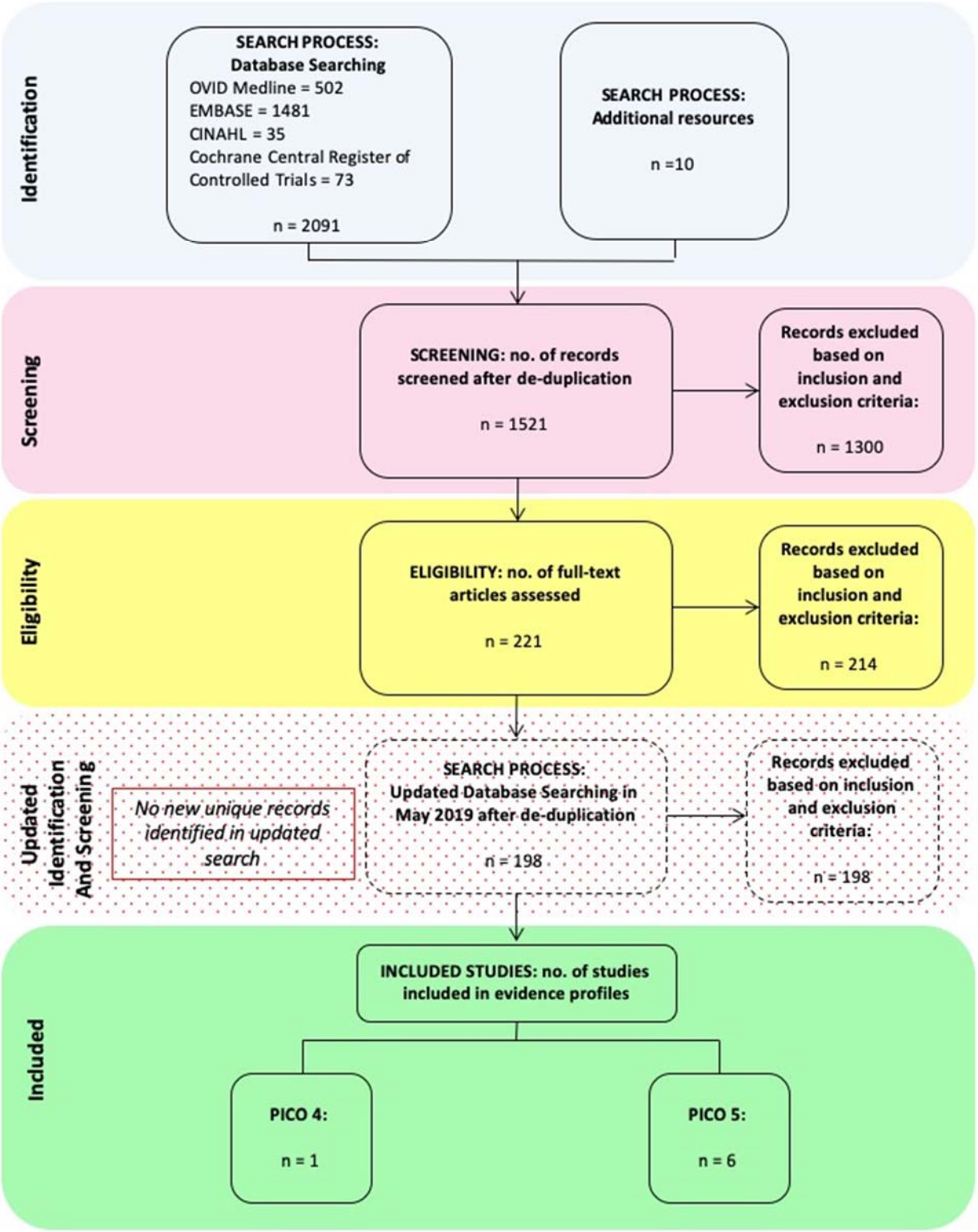

Figure E2: PRISMA (1) diagram for the process of inclusion of studies for PICOs 4 and 5

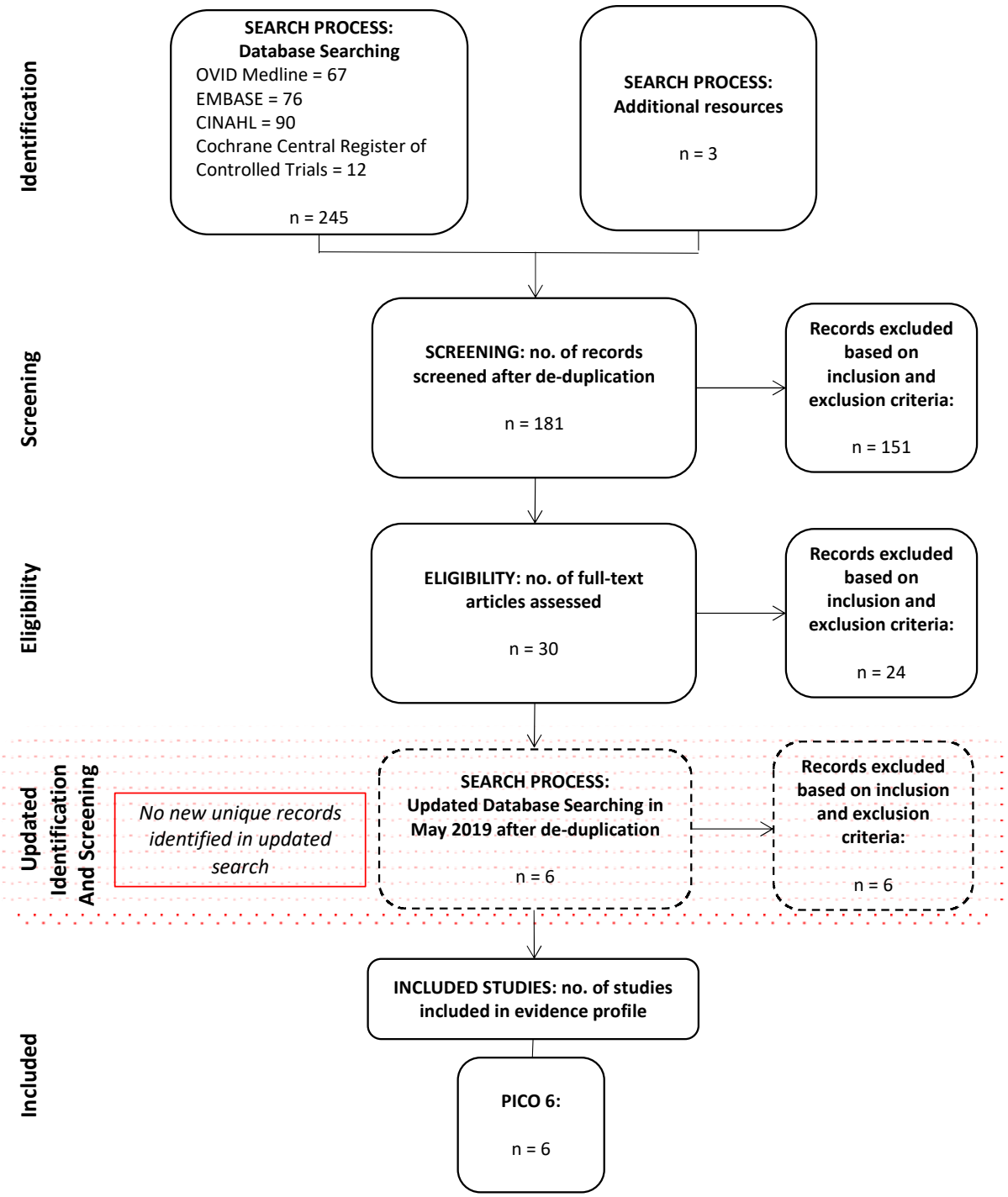

Figure E3: PRISMA (1) diagram for the process of inclusion of studies for PICO 6

References

1) Moher, D. L., A; Tetzlaff, J; Altman, DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* **6**, e10000097.

SUMMARY OF STUDIES

Summary of Studies for PICO 1

Question: Should long-term oxygen be prescribed for adults with COPD who have severe chronic resting room air hypoxemia?

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Levine et al, 1967 (1) (Pre-post study)	3	While the study presented its results only in figure-form, thereby preventing us from calculating mean differences and statistical significance, a clear trend was observed where all 3 patients experienced an improvement in exercise tolerance (increased distance walked on treadmill at 0.75 mph) at all grades. More significant increases in exercise tolerance were observed at milder grades (i.e. lower elevation).		The study included six patients with long-standing COPD with severe hypoxemia, cor pulmonale, and secondary erythrocythemia. All were markedly disabled. Patients were followed for up to 18 months and 3 of the 6 patients were tested for exercise capacity using a treadmill at 0.75 mph at different grades (elevation) before oxygen therapy (control period) and after beginning oxygen therapy. O_2 was administered via nasal prongs at 4 l/min during exercise and **2-3 l/min during rest for 24 hrs/day**.
NOTT et al, 1980 (2) (RCT)	203 (101 LTOT; 78 male, 23 female; 102 control; 82 male, 20 female)	1-year mortality risk for LTOT prescribed 24 hours/day vs. nocturnal oxygen therapy:	**OR: 0.53** (0.25 to 1.11)	Patients from 6 North American centers were screened for inclusion in the NOTT trial. All of the patients had severe hypoxemia (PaO_2 < 55 mmHg/7.3 kPa) and the majority were male. O_2 administered at **1–4 L/min continuously (prescribed 24 hours/day) or nocturnal oxygen only. Goal was to achieve a PaO_2 60 to 80 mmHg/8.0-11.0 kPa.** Oxygen was delivered by a stationary concentrator for an average of 17.7 h/day (SD = 4.8) in the LTOT group prescribed continuously, plus use via liquid or compressed gas. The group assigned nocturnal oxygen therapy used oxygen by a stationary concentrator for an average 12.0 h/day (SD= 2.5), plus use via liquid or compressed gas. Both groups had close follow-up care, including home visits and outpatient clinic visits.
		2-year mortality risk for LTOT prescribed 24 hours/day vs. nocturnal oxygen therapy:	**OR: 0.45** (0.25 to 0.81)*	
		1-year mortality risk for LTOT prescribed 24 hours/day vs. nocturnal oxygen therapy:	**-11.9%** (-5.63% to -18.17%)	
		2-year mortality risk for LTOT prescribed 24 hours/day vs. nocturnal oxygen therapy:	**-22.4%** (-13.38% to -31.42%)	
		Mortality rate in LTOT group with high POMS (high depression/anxiety, POMS >/=43):	**21.7%**	
		Mortality rate in control group (nocturnal oxygen therapy) with high POMS (high depression/anxiety, POMS<43):	**52.2%**	
MRC et al, 1981 (3) (RCT)	87 (66 male, 27 female; 42 LTOT, 45 control)	5-year mortality risk for LTOT prescribed at least 15 hours/day vs. control (room air):	**RR 0.41** (0.17 to 0.98)*	RCT of LTOT has been carried out in three UK centers. Everyone was under 70 years of age and had either bronchitis or emphysema, with irreversible airway obstruction, severe arterial hypoxemia, carbon dioxide retention, and a history of congestive heart failure. Patients were randomized to either OT or no OT. Oxygen was administered through nasal prongs prescribed for at least **15 hrs/day** at 2 l/min or higher to achieve a PaO2>60 mmHg/8.0 kPa**.** The LTOT group also received home visits by registrars and technicians to assess oxygen usage and obtain arterial blood gas measurements. Both groups received close follow-up in the outpatient clinic. The groups were matched clinically and in terms of lung function and labs.
		5-year mortality risk for LTOT prescribed at least 15 hours/day vs. control (room air):	**-45.2%** (-30.11% to -60.29%)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Crocket et al, 1993 (4) (Observational)	26	1-year mortality rate: (all received LTOT)	**23.1%**	All patients with a diagnosis of chronic obstructive airflow disease, referred to the respiratory unit of Flinders Medical Centre in Adelaide for home oxygen therapy assessment in 1990, were entered into the study. LTOT was prescribed only where the Thoracic Society of Australia and New Zealand guidelines were met, PaO_2 < 55 mmHg/7.3kPa and cessation of smoking for at least 1 month. LTOT was administered for **at least 15 hrs/day** via a concentrator plus small portable "C" size cylinders (440l).
		Risk of admissions for LTOT vs. pre-LTOT:	**RR: 0.70** (0.15 to 3.30)	
		Risk of increased bed days per patient-year of follow-up (LTOT vs. pre-LTOT):	**RR: 0.65** (0.40, 1.05)	
		Mean survival time for males: (years)	**MD: 3.0** (1.34 to 4.66)*	
		Mean survival time for females: (years)	**MD: 2.0** (0.44 to 3.56)	
		Mean difference in survival time between males and females (years):	**MD: 1.0** (-1.26 to 3.26)	
Bao et al, 2017 (5) (RCT)	54 (28 LTOT; 15 male, 13 female; 26 control; 14 male, 12 female)	MD in BODE score for LTOT vs. conventional therapy:	**MD: -0.85** (-1.53 to 1.41)	Study looked at patients with Stage IV COPD from Pudong, Shanghai, China. None of the patients suffered coronary artery disease with congestive heart failure, acute exacerbation of COPD, bronchial asthma, cancer, bronchiectasis, interstitial lung diseases, or pulmonary tuberculosis. Patients were randomly divided into two groups: the LTOT group and the control group, which received conventional therapy. LTOT was administered for **at least 15 hrs/day** at 2 l/min.
		MD in BODE for LTOT group before vs. after beginning oxygen therapy:	**MD: -0.84** (-0.27 to -1.41)*	
		MD in number of hospitalizations for LTOT vs. conventional therapy:	**MD: -1.17** (-1.73 to -0.59)*	

Abbreviations: 6MWT, six-minute walking test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; hrs, hours; l, liters; l/min, liters per minute; kPa, kilopascal; LOX, liquid oxygen; LTOT, long-term oxygen therapy; mmHg, millimeters of mercury; mph, miles per hour; MR, mortality rate; MVV, maximum voluntary ventilation; OR, odds ratio; O_2, oxygen; OT, oxygen therapy; PaO_2, pulmonary partial pressure of oxygen; POMS, profile of moods index; RR, relative risk; SD, standard deviation; SE, standard error; vs, versus
*indicates statistical significance at p<0.05

References

1. Levine BE, Bigelow DB, Hamstra RD, Beckwitt HJ, Mitchell RS, Nett LM, Stephen TA, Petty TL. The role of long-term continuous oxygen administration in patients with chronic airway obstruction with hypoxemia. *Annals of Internal Medicine* 1967; 66: 639-650.
2. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Annals of Internal Medicine* 1980; 93: 391-398.
3. Stuart-Harris C, Bishop JM, Clark TJH. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981; 1: 681-686.
4. Crockett AJ, Moss JR, Cranston JM, Alpers JH. The effects of home oxygen therapy on hospital admission rates in chronic obstructive airways disease. *Monaldi Archives for Chest Disease* 1993; 48: 445-446.
5. Bao H, Wang J, Zhou D, Han Z, Zhang Y, Su L, Ye X, Xu C, Fu M, Li Q. Community Physician-Guided Long-Term Domiciliary Oxygen Therapy Combined With Conventional Therapy in Stage IV COPD Patients. *Rehabilitation Nursing Journal* 2017; 42: 268-273.

Summary of Studies for PICO 2

Question: Should long-term oxygen be prescribed for adults with COPD who have moderate chronic resting room air hypoxemia?

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
LOTT et al, 2016 (1) (RCT)	419 (220 LTOT, 199 no LTOT)	Hazard Ratio, Time to all-cause Death or First Hospitalization, patients with moderate resting hypoxemia only (LTOT vs. no LTOT):	**HR: 0.96** (0.63 to 1.47)	A total of 14 regional clinical centers and their associated sites (a total of 47 centers) screened patients who had stable COPD and moderate resting room air hypoxemia (SpO_2, 89 to 93%) or moderate exercise-induced desaturation (during the 6-minute walk test, SpO_2 ≥80% for ≥5 minutes and < 90% for ≥ 10 seconds). All the patients signed a contract in which they agreed not to smoke while using oxygen. In the supplemental-oxygen group, patients with resting desaturation were prescribed 24-hour oxygen, and those with desaturation only during exercise were prescribed oxygen during exercise and sleep at 2 l/min. The control group had no supplemental oxygen.
		Hazard Ratio, Time to all-cause Death or First Hospitalization, patients with moderate resting plus moderate exertional hypoxemia (LTOT vs. no LTOT):	**HR: 0.95** (0.72 to 1.27)	
		Hazard Ratio, Time to all-cause Death or First Hospitalization, patients with moderate resting hypoxemia or moderate resting plus moderate exertional hypoxemia (LTOT vs. control):	**HR: 0.95** (0.75 to 1.21)	

Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; l/min, liters per minute; LTOT, long-term oxygen therapy; SpO_2, peripheral capillary oxygen saturation
*indicates statistical significance at p<0.05

References

1. Long-Term Oxygen Treatment Trial Research G, Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA, Jr., Criner GJ, Diaz P, Fuhlbrigge AL, Gay SE, Kanner RE, MacIntyre N, Martinez FJ, Panos RJ, Piantadosi S, Sciurba F, Shade D, Stibolt T, Stoller JK, Wise R, Yusen RD, Tonascia J, Sternberg AL, Bailey W. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. *New England Journal of Medicine* 2016; 375: 1617-1627.

Summary of Studies for PICO 3

Question: Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia?

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Studies where patients are on or eligible for LTOT				
Leggett et al, 1977 (1) (RCT, acute effects during exercise)	26 (19 male, 7 female)	MD in distance walked, Group 1: (2L O_2/min vs. RA, meters)	**MD: 51.6** (25.92 to 72.28)*	As part of the assessment for treatment with a long-term domiciliary oxygen supply, 26 patients [Mean age 59 (1.5) years] who suffered from chronic hypoxemic cor pulmonale with pulmonary hypertension as a result of their chronic obstructive lung disease were studied. All were in a stable clinical state at the time of assessment, without peripheral edema or chest infection, and had no progressive change in body weight, FEV_1, or arterial blood gas tensions (PaO_2, $PaCO_2$) during the previous 3 weeks. All performed either a treadmill or a progressive bicycle exercise when breathing air, and 15 patients also repeated the exercise when breathing 30% oxygen, the order of the air or oxygen studies being randomized. Each patient walked twice when breathing each gas mixture, with a rest of at least 30 minutes between each walk and no more than 4 walks on the same day. The different gas mixtures were given in random order. Three subgroups were studied, some patients being common to each group: group 1 included eight patients who walked when breathing air or 2 L of O_2/min with and without the oxygen walker. Group 2 comprised 8 patients studied when breathing air or 4 L of O_2/min without carrying the walker, and also 2 or 4 L of oxygen/min when carrying the oxygen walker. Group 3 consisted of 9 patients who underwent the same procedures as those in group 2 but they wheeled the oxygen walker on a modified shopping trolley.
		MD in distance walked, Group 2: (4L O_2/min alone vs. RA, meters):	**MD: 53.0** (28.11 to 77.89)*	
		MD in distance walked, Group 2: (2L O_2/min with walker vs. RA, meters):	**MD: -25.0** (-49.89 to -0.11)*	
		MD in distance walked, Group 2: (4L O_2/min with walker vs. RA, meters):	**MD: 13.0** (-11.89 to 37.89)	
		MD in distance walked, Group 3: (4L O_2/min alone vs. RA, meters):	**MD: 75.0** (35.21 to 114.79)*	
		MD in distance walked, Group 3: (2L O_2/min with trolley vs. RA, meters):	**MD: 34.0** (-5.79 to 73.79)	
		MD in distance walked, Group 3: (4L O_2/min with trolley vs. RA, meters):	**MD: 59.0** (19.21 to 98.79)*	
McKeon et al, 1988 (2) (RCT, acute effects during exercise)	21 (11 male, 10 female)	MD in distance walked (max), portable O_2 vs. RA, meters:	**MD: 88.0** (-23.15 to 199.15)	Study of 21 patients, all of whom were attending the Princess Alexandra Hospital for treatment of COPD and had significant disability with exertional dyspnea despite treatment with inhaled and oral bronchodilators. Patients were in a stable condition at the time of the study. All were using inhaled salbutamol; 18 were taking oral theophylline or inhaled ipratropium bromide; 18 were using inhaled beclomethasone and 13 were receiving oral prednisone. No patient demonstrated any clinical features of right heart failure. 2 showed ECG evidence of right axis deviation and 2 had evidence of right ventricular hypertrophy. 6 were receiving diuretics, and 1 digoxin. 3 were currently smoking cigarettes and 18 were ex-smokers. 6 patients were using LTOT > 15 hrs/day. All patients receiving LTOT, eligible for LTOT, and not eligible for LTOT were included in this study, and results were not presented separately. Tests were performed at least 30 minutes apart in random order. Mean age of the patients was 62 (SD = 9) years. Portable O_2 was administered via cylinder at 4 l/min during exercise. 75%: distance equal to 75% of maximum distance walked on room air VAS: visual analog scale score of breathlessness; patients pointed to scale between 0-300 mm to indicate severity of exertion (300 indicating extreme breathlessness)
		MD in distance walked (max), portable O_2 vs. CA, meters:	**MD: 82.0** (-27.56 to 191.56)	
		MD in distance walked (75%), portable O_2 vs. RA, meters:	**MD: 77.0** (-13.51 to 167.51)	
		MD in distance walked (75%), portable O_2 vs. CA, meters:	**MD: 57.0** (-31.34 to 145.34)	
		MD in VAS (max), portable O_2 vs. RA, mm:	**MD: -8.0** (-38.01 to 22.01)	
		MD in VAS (max), portable O_2 vs. CA, mm:	**MD: -7.0** (-37.30 to 23.30)	
		MD in VAS (75*), portable O_2 vs. RA, mm:	**MD: -62.0** (-94.38 to -29.62)*	
		MD in VAS (75*), portable O_2 vs. CA, mm:	**MD: -63.0** (-99.75 to -26.25)*	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Vergeret et al, 1989 (3) (RCT)	159 (51 Gaseous O_2; 45 male, 6 female; 33 Liquid O_2; 31 male, 2 female; 75 oxygen concentrators; 63 male, 12 female)	1-year mortality rate for fixed O_2 patients:	**12.0%**	Study to determine whether the availability of ambulatory oxygen to LTOT patients (in addition to fixed O_2) improved physical activity. Patients included were aged 40-75 years (mean 63 (7.4) years for the Fixed O_2 group, 61 (8.1) years for the Portable O_2 group), with severe COPD, defined by the following criteria: FEV_1 /FVC < 60%, TLC > 80% of reference values, FEV_1 < 1L, and with stable chronic respiratory insufficiency: PaO_2 < 8 kPa/60 mmHg and > 5.3 kPa/40 mmHg; $PaCO_2$ < 8.2 kPa/62 mmHg. Patients had not suffered from any episodes of respiratory decompensation for at least 6 weeks. Patients should already have LTOT by a fixed oxygen source. Only those able to walk more than 200 meters with portable oxygen equipment during a 12 min walking test with gasometrical supervision were retained for the survey. Patients excluded already had portable oxygen, had been hospitalized more than 3 times in the previous year for respiratory failure, or had suffered left heart failure or an associated pathology influencing functional and/or vital prognosis. The study duration was 1 year. O_2 was administered either by oxygen concentrators plus gaseous oxygen in 0.4 m^3 cylinders or LO in the form of a stroller and liberator, at a mean flow rate of 2.2 (SD = 0.7) l/min during exercise.
		1-year mortality rate for portable O_2 patients:	**17.9%**	
		MD in hrs/day spent outside for patients on < 15 hrs/day O_2, portable O_2 [n=14] vs. fixed O_2 [n=34]:	**MD: -0.3** (95% CI not reported/calculable)	
		MD in distance walked (meters/day) for patients on < 15 hrs/day O_2, portable O_2 [n=14] vs. fixed O_2 [n=34]:	**MD: -226.0** (95% CI not reported/calculable)	
		MD in hrs/day of rest for patients on > 18 hrs/day O_2, portable O_2 [n=14] vs. fixed O_2 [n=34]:	**MD: -1.1** (95% CI not reported/calculable)	
		MD in hrs/day spent outside for patients on > 18 hrs/day O_2, portable O_2 [n=14] vs. fixed O_2 [n=34]:	**MD: 1.9** (95% CI not reported/calculable)	
		MD in distance walked (meters/day) for patients on > 18 hrs/day O_2, portable O_2 [n=14] vs. fixed O_2 [n=34]:	**MD: 365.0** (95% CI not reported/calculable)	
Garrod et al, 2000 (4) (RCT)	25 [22 completed] (19 male, 6 female; 11 OT, 11 air)	MD in ISWT distance, O_2 vs. air cylinder at baseline (meters):	**MD: 27.3** (14.7 to 39.8)*	26 patients with stable severe COPD (median age 70 years, range 52–84) were recruited from the outpatient clinics of the London Chest Hospital. Patients had had no exacerbations in the previous 6 weeks. Of the 26 patients approached, one declined, one was admitted to hospital after the initial assessment, and two were unable to attend follow up due to admission to hospital with exacerbation of COPD; therefore, 22 patients completed the study. All patients had limited exercise tolerance due to dyspnea and all had a fall in arterial saturation of at least 4% from baseline to 90% or below on exercise testing. Patients were excluded from the study if they had unstable angina, intermittent claudication, or other mobility limiting conditions. 11 of the 25 patients were receiving long term oxygen therapy at home. The duration of follow-up was 6 weeks from recruitment to reassessment. Patients in the OT group performed physical training whilst breathing supplemental oxygen at 4 l/min and patients in the AT group attended an identical exercise program whilst breathing compressed air at 4 l/min. *Note*: The results reported here are baseline results before exercise training.
		MD in Borg dyspnea after room-air SWT at baseline, O_2 vs. air:	**MD: -0.68** (-1.05 to -0.31)*	
O'Donnell et al, 2001 (5) (Crossover RCT, acute effects of exercise)	11 (4 male, 7 female)	MD in endurance time at symptom-limited peak exercise, O_2 vs. room air (minutes):	**MD: 4.7** (3.76 to 5.64)*	11 clinically stable patients with advanced COPD and who met the criteria for ambulatory O_2 were studied in Ontario. The study was a double blind, placebo-controlled crossover RCT. After giving written informed consent, patients were familiarized with all testing procedures and completed a symptom-limited incremental exercise test. In a separate visit, subjects then performed two constant-load exercise tests at approximately 50% of their previously determined maximal work rate while breathing either 60% O_2 or room air (RA, 21% O_2), with a 60- to 90-min washout or recovery period between tests. The mean age of patients was 68 (SD = 2) years.
		MD in Borg dyspnea score at symptom-limited peak exercise, O_2 vs. RA:	**MD: -0.20** (-0.83 to 0.43)	
		MD in Borg leg discomfort score at symptom-limited peak exercise, O_2 vs RA:	**MD: -0.40** (-1.07 to 0.27)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Nasilowski et al, 2008 (6) (RCT, acute effects during exercise)	13 (7 male, 6 female)	MD in distance walked (6MWT), LOX vs. CA (meters):	**MD: 33.0** (-31.19 to 97.19)	Fifteen patients with COPD undergoing LTOT were included in the study (13 completed). COPD was diagnosed using GOLD criteria. Eligibility for LTOT was based on the ATS/ERS guidelines: PaO_2 <= 55 mmHg or PaO_2 56–60 mmHg and the ECG or radiographic evidence of pulmonary hypertension or polycythemia with haematocrit >= 55%. Exclusion criteria included: refusal to participate in the study, important comorbidities (e.g. limiting angina, musculoskeletal disability and malignancy), recent (within 8 weeks) exacerbation of COPD. Mean age of patients was 66 (SD = 11) years. Oxygen supplementation was 3 L/min for LOX and an equivalent to 3 L/min for POC during exercise vs. 3 L/min flow of cylinder air as a control.
		MD in distance walked (6MWT), portable O_2 vs. CA (meters):	**MD: 25.0** (-44.34 to 94.34)	
		MD in distance walked (6MWT), LOX vs. portable O_2 (meters):	**MD: 8.0** (-60.99 to 76.99)	
		MD in Borg dyspnea score, LOX vs. CA (meters):	**MD: -1.3** (-2.69 to 0.09)	
		MD in Borg dyspnea score, portable O_2 vs. CA (meters):	**MD: -1.2** (-1.34 to 1.10)	
		MD in Borg dyspnea score, LOX vs. portable O_2 (meters):	**MD: 0.1** (-1.04 to 1.24)	
		MD in SIFT function score, O_2 vs. RA:	**MD: 0.6** (-0.3 to 1.5)	
		MD in SIFT content score, O_2 vs. RA:	**MD: 0.3** (-1.1 to 1.7)	
Studies where patients are not eligible for LTOT (patients with isolated exercise-induced hypoxemia, isolated EIH)				
Light et al, 1989 (7) (Crossover RCT, acute effects on exercise)	17 (16 male, 1 female)	MD in work at maximal exercise, O_2 vs. RA (watts):	**MD: 7.6** (-6.83 to 22.03)	17 patients with CAO underwent identical maximal cycle ergometry exercise tests on two occasions 45 minutes apart while breathing either air or 30% oxygen in a randomized, single-blind fashion. To be included in the study, patients were required to have a FEV_1 less than 2.5 L and to have a FEV/FVC less than 60%. In addition, their exercise tolerance had to be limited by shortness of breath. Patients with a wide range of severity of airflow obstruction were evaluated. Patients who were taking oral theophylline and inhaled beta-adrenergic agents continued taking these medications during the study. All patients had at least one maximal exercise test on the bicycle ergometer prior to the study day. Individuals with left ventricular disease, musculoskeletal disorders, or other systemic diseases which would interfere with exercise testing were excluded. Mean age of patients was 62 (5.3) years, with a range of 57 - 77 years. O_2 was supplied during exercise via two-way breathing valve.
		MD in V_E at maximal exercise, O_2 vs. RA (l/min):	**MD: -0.3** (-7.90 to 7.30)	
		MD in V_T at maximal exercise, O_2 vs. RA (l):	**MD: 0.05** (-0.15 to 0.25)	
		MD in V_D/V_T at maximal exercise, O_2 vs. RA:	**MD: -0.02** (-0.10 to 0.06)	
		MD in V_E at highest equivalent workload, O_2 vs. RA (l/min):	**MD: -2.8** (-9.90 to 4.30)	
		MD in V_T at highest equivalent workload, O_2 vs. RA (l):	**MD: 0.05** (-0.15 to 0.25)	
		MD in V_CO_2 at highest equivalent workload, O_2 vs. RA (l/min):	**MD: 0.0** (-0.25 to 0.25)	
		MD in V_D/V_T at highest equivalent workload, O_2 vs. RA:	**MD: -0.02** (-0.10 to 0.06)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Mitlehner et al, 1994 (8) (crossover RCT, acute effects on exercise)	14	MD in peak workload, FiO_2 35% vs. RA (watts):	**MD: 17.9** (8.10 to 27.70)*	The study population consisted of 14 patients with stable COPD and known activity intolerance as well as exercise hypoxemia. The patients were recruited from an ambulatory population, sent for evaluation of OT or by previously discharged patients with known exercise hypoxemia. The stability of measurement results was proven for more than 4 weeks in every case. Patients continued to take their regular medication at the time of evaluation. All patients were on oral corticosteroids, oral or inhaled beta-2-agonists and theophylline. Mean age of patients was 62.7 (SD = 8.1) years. Patients breathed 35% inspiratory oxygen during exercise and room air as the control.
		MD in exercise time, FiO_2 35% vs. RA (seconds):	**MD: 90.0** (31.47 to 148.53)*	
		MD in VO_2, FiO_2 35% vs. RA (ml/min/kg):	**MD: 3.2** (1.22 to 5.18)*	
		MD in VCO_2, FiO_2 35% vs. RA (ml/min/kg):	**MD: 1.3** (-0.52 to 3.12)	
		MD in V_E, FiO_2 35% vs. RA (l/min):	**MD: 1.2** (-2.23 to 4.63)	
		MD in V_E/VO_2, FiO_2 35% vs. RA:	**MD: -5.2** (-8.24 to -2.16)*	
Eaton et al, 2002 (9) (Crossover RCT)	41 (29 male, 12 female)	MD in 6MWT, O_2 vs. RA (meters):	**MD: 19.0** (-21.47 to 59.47)	Patients were recruited from a New Zealand Clinic. They had severe COPD (defined by ATS criteria), did not fulfil for LTOT and demonstrated significant exertional desaturation and dyspnea. Patients were randomly assigned in a double blinded manner to cylinder air or O_2 at 4 l/min and were crossed over after 6 weeks, for a total of 12 weeks of follow-up. There were 9 withdrawals (comorbidities n=3, personal reasons n=6); results from the remaining 41 patients are reported. Mean age of the 41 patients was 67.1 (SD = 9.3) years.
		MD in 6MWT, O_2 vs. CA (meters):	**MD: 40.0** (-5.00 to 85.00)	
		MD in Borg dyspnea score, O_2 vs. RA:	**MD: -0.6** (-1.34 to 0.14)	
		MD in Borg dyspnea score, O_2 vs. CA:	**MD: -0.7** (-1.43 to 0.03)	
		MD in CRQ dyspnea-related QoL score, O_2 vs. CA:	**MD: 2.0** (0.24 to 3.76)*	
		MD in CRQ fatigue score, O_2 vs. CA:	**MD: 1.8** (0.43 to 3.17)*	
		MD in CRQ emotional function score, O_2 vs. CA:	**MD: 3.3** (0.95 to 5.65)*	
		MD in CRQ mastery score, O_2 vs. CA:	**MD: 1.8** (0.43 to 3.17)*	
		MD in total CRQ score, O_2 vs. CA:	**MD: 8.8** (3.31 to 14.29)*	
		MD in SF-36 physical functioning score, O_2 vs. CA:	**MD: 1.6** (-5.26 to 8.46)	
		MD in SF-36 role physical score, O_2 vs. CA:	**MD: 16.8** (6.02 to 27.58)*	
		MD in SF-36 bodily pain score, O_2 vs. CA:	**MD: 5.3** (-4.50 to 15.10)	
		MD in SF-36 general health score, O_2 vs. CA:	**MD: 6.1** (0.42 to 11.78)*	
		MD in SF-36 vitality score, O_2 vs. CA:	**MD: 2.9** (-2.98 to 8.78)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
		MD in SF-36 social functioning score, O_2 vs CA:	**MD: 10.5** (0.31 to 20.69)*	
		MD in SF-36 role emotional score, O_2 vs CA:	**MD: 18.3** (3.21 to 33.39)*	
		MD in SF-36 mental health score, O_2 vs. CA:	**MD: 4.0** (-1.29 to 9.29)	
Nonoyama et al, 2007 (10) (Crossover RCT)	27 (17 male, 10 female)	MD in 5MWT distance, O_2 vs. CA (steps):	**MD: 14.9**(0.85 to 28.94)*	Study of multiple N-of-1 RCTs of oxygen versus ambient air. Included patients with a diagnosis of COPD with dyspnea limiting daily activities, and with desaturation of 88% or less for 2 continuous minutes during a room-air 6MWT. We excluded patients 18 years or younger, those who met criteria for mortality reduction with LTOT, those who received oxygen for palliative care or isolated nocturnal hypoxemia, and those unable to complete the questionnaires or provide informed consent. Follow-up consisted of 3 two-week treatment periods, for a total of 6 weeks. Mean age of patients completing the study was 69 (SD = 10) years. Oxygen was administered at 2 L/minute (range, 1–3 L/min) O_2 via cylinder during exercise as the intervention vs. 24% O_2, diluted with ambient air to produce FiO_2 of 21.2% as the control.
		MD in 5MWT endurance time, O_2 vs. CA (minutes):	**MD: 2.4** (0.58 to 4.22)*	
		MD in CRQ dyspnea-related QoL score, O_2 vs. CA:	**MD: 0.22** (-0.03 to 0.47)	
		MD in CRQ fatigue score, O_2 vs. CA:	**MD: 0.14** (-0.02 to 0.31)	
		MD in CRQ emotion score, O_2 vs. CA:	**MD: -0.01** (-0.20 to 0.18)	
		MD in CRQ mastery score, O_2 vs. CA:	**MD: -0.10** (-0.40 to 0.19)	
		MD in SGRQ symptoms score, O_2 vs. CA:	**MD: -0.17** (-2.63 to 2.29)	
		MD in SGRQ activity score, O_2 vs. CA:	**MD: 0.42** (-1.59 to 2.43)	
		MD in SGRQ impacts score, O_2 vs. CA:	**MD: -0.79** (-2.75 to 1.17)	
		MD in SGRQ total score, O_2 vs. CA:	**MD: -0.32** (-1.71 to 1.06)	
Moore et al, 2011 (11) (RCT, subgroup with EIH)	143 (138 with desaturation; 99 male, 44 female; 68 O_2, 75 Air)	MD in CRQ dyspnea-related QoL score, O_2 vs. CA:	**MD: 0.74** (-0.78 to 2.27)	143 (139 completed) ex-smoker patients (mean age 71.8 (SD = 9.8) years) with severe COPD were randomized to cylinder air or cylinder oxygen, both at 4L/min. 50 of the included patients had exertional desaturation to ≤ 88%. Verbal and written instructions required patients to use cylinders inside and outside the home during exertional activities that induced breathlessness. No recommendations were provided regarding duration of use, activity or exercise. The study duration was 12 weeks total, with an initial follow-up at 4 weeks.
		MD in time to limit of exercise tolerance, O_2 cannula vs. RA (minutes):	**MD: 5.8** (2.23 to 9.37)*	
		MD in Borg dyspnea score at isotime, O_2 cannula vs. RA:	**MD: -2.1** (-3.43 to -0.77)*	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Jarosch et al, 2017 (12) (crossover RCT, acute effects during exercise, included data are subgroup with EIH only)	43 (24 male, 19 female)	MD in 6MWT distance, O_2 vs. CA (meters):	**MD: 28.0** (14.0 to 41.0)*	Patients with severe to very severe COPD entering an inpatient pulmonary rehabilitation program at the Schoen Klinik Berchtesgadener Land were asked to participate. Exclusion criteria were a COPD exacerbation within the last 4 weeks prior to enrollment, acute coronary syndrome, and/or any disability that inhibited patients from performing a 6MWT. Patients were grouped by their level of oxygenation. Mean age of patients with severe exertional hypoxemia was 63 years (SD = 8 years). LOX was administered at a constant flow of 2 l/min via common nasal prongs. Cylinder air at 3 l/min was used as a control.
		MD in 6MWT stop length, O_2 vs. CA (seconds):	**MD: -5.0** (0.0 to -9.0)	
		MD in Borg leg fatigue score, O_2 vs. CA:	**MD: -0.2** (-0.8 to 0.4)	
		MD in Borg dyspnea score, O_2 vs. CA:	**MD: -1.1** (-1.6 to -0.5)*	

Abbreviations: 5MWT, five-minute walking test; 6MWT, six-minute walking test; CA, cylinder air; CAO, chronic airflow obstruction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory [disease] questionnaire; ESWT, endurance shuttle walk test; FEV_1, forced expiratory volume in 1 second; FiO_2, fraction of inspiratory oxygen; FVC, forced vital capacity; hrs, hours; ISWT, incremental shuttle walk test; K-BILD, King's brief interstitial lung disease questionnaire; kg, kilogram; kPa, kilopascal; l, liters; l/min, liters per minute; LCADL, London chest activity of daily living scale; LOX, liquid oxygen; LTOT, long-term oxygen therapy; MD, mean difference; min, minute; ml, milliliter; mm, millimeters; mmHg, millimeters of mercury; mph, miles per hour; MVV, maximum voluntary ventilation; NIOV, non-invasive open ventilation; OR, odds ratio; O_2, oxygen; OT, oxygen therapy; PaO_2, pulmonary partial pressure of oxygen; $PaCO_2$, pulmonary partial pressure of carbon dioxide; POC, portable oxygen canister/cylinder; POMS, profile of moods index; PR, pulmonary rehabilitation; RA, room air; RR, relative risk; SD, standard deviation; SE, standard error; SF-36, 36-item short form health survey; SGRQ, St. George's respiratory questionnaire; SIFT, Surrey information on function tool; SWT, shuttle walk test; TLC, total lung capacity; UCSDSOBQ, University of California San Diego shortness of breath questionnaire; V_CO_2, carbon dioxide production per minute; V_D, physiologic dead space ventilation/min; V_E, exhaled volume/breath; VO_2, oxygen consumption per minute; vs, versus; V_T, tidal volume
*indicates statistical significance at $p<0.05$

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Summary of Studies for PICO 4

Question: Should long-term oxygen be prescribed for adults with ILD who have severe chronic resting room air hypoxemia?

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Braghiroli et al, 2000 (Unpublished RCT) (5)	62	Mortality at 12 Months, O_2 vs RA:	**OR: 0.50** (0.15 to 1.61)	62 patients less than 79 years of age with interstitial pulmonary fibrosis were studied. Inclusion criteria entailed a total lung capacity (TLC) < 80% predicted and an arterial oxygen tension (PaO_2) of 45-60 mmHg/6.0-8.0 kPa (this range is slightly above the cut off for severe resting hypoxemia, $PaO_2 \leq 55$ mmHg/7.3 kPa). This study was based on a systematic review and uses unpublished data.
		Mortality at 24 Months, O_2 vs RA:	**OR: 1.76** (0.64 to 4.86)	
		Mortality at 36 Months, O_2 vs RA:	**OR: 0.99** (0.16 to 6.26)	

Abbreviations: mmHg, millimeters of mercury; O_2, oxygen; OR, odds ratio; RA, room air; RCT, randomized controlled trial.

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Summary of Studies for PICO 5

Question: Should ambulatory oxygen be prescribed for adults with ILD who have severe exertional room air hypoxemia?

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Studies where patients are not eligible for LTOT (patients with isolated exertional desaturation)				
Harris-Eze et al, 1996 (1) (crossover RCT)	7 (6 male, 1 female)	Mean difference in work rate at maximal exercise, O2 vs. RA (watts):	**MD: 10.00** (-4.23 to 24.23)	Subjects with ILD and arterial oxygen desaturation during exercise were recruited from the Division of Pulmonary Medicine at the Royal University Hospital, Saskatoon, Saskatchewan, Canada. Subjects were excluded from participating in the study if they demonstrated any disease of the pleura or chest wall, respiratory muscle weakness (as assessed by maximal inspiratory pressures), cardiac disease, and/or any other disease (apart from ILD) that could impair exercise tolerance. Subjects were also excluded from the study if they presently smoked cigarettes. Tests were separated by at least 3 days and performed at the same time of day for each subject. Mean subject age was 50 (15) years.
		Mean difference in exercise duration, O2 vs. RA (seconds):	**MD: 43.00** (-30.95 to 116.95)	
		Mean difference in Borg dyspnea score at maximal exercise, O2 vs. RA:	**MD: 1.00** (-1.67 to 3.67)	
Troy et al, 2014 (2) (crossover RCT)	6	Mean difference in CPET endurance time, O2 vs. RA (seconds):	**MD: 80.00** (-11.25 to 171.25)	6 IPF subjects displaying oxygen desaturation at 6MWT but without resting hypoxemia were included in the study (mean age 64.5 (6.0) years). Subjects completed both two cardiopulmonary exercise tests (CPET) and two endurance shuttle walk tests (ESWT). *Note: This data is from an abstract only*
		Mean difference in CPET maximal workload, O2 vs. RA (watts):	**MD: 18.00** (-49.93 to 85.93)	
		Mean difference in ESWT distance, O2 vs. RA (meters):	**MD: 265.00** (-297.88 to 827.88)	
Nishiyama et al, 2013 (3) (crossover RCT)	20 (16 male, 4 female)	Mean difference in 6MWT distance, O2 vs. CA (meters):	**MD: 13.00** (-36.58 to 62.58)	Patients with IPF were recruited from the Department of Respiratory Medicine and Allergology, Kinki University Faculty of Medicine in Osaka-sayama, Japan. Patients were 20 years or older, not hypoxemic at rest, but experiencing desaturation to 88% or lower during the 6MWT on room air. Patients already receiving LTOT for mortality reduction, > 10mg/day corticosteroids, or those who could not perform the required tests were excluded. The study was a double-blind, placebo-controlled, randomized crossover trial using ambulatory oxygen and ambulatory air. The mean age of included patients was 73.5 (4.1) years. Patients underwent 2 different types of 6-min walk tests on the first day under either ambulatory intranasal oxygen or air: one was an ordinary standardized test with an enthusiastic walk (6MWT) and the other was a free walk test with a comfortable pace (6MFWT).
		Mean difference in Borg dyspnea, immediately post-6MWT, O2 vs. CA:	**MD: -0.40** (-1.76 to 0.96)	
		Mean difference in Borg dyspnea, 1-minute post-6MWT, O2 vs. CA:	**MD: -0.30** (-1.73 to 1.13)	
		Mean difference in Borg dyspnea, 2-minute post-6MWT, O2 vs. CA:	**MD: -0.50** (-1.71 to 0.71)	
		Mean difference 6MFWT distance, O2 vs. CA (meters):	**MD: 6.00** (-33.56 to 45.56)	
		Mean difference in Borg dyspnea, immediately post-6MFWT, O2 vs. CA:	**MD: -0.60** (-2.15 to 0.95)	
		Mean difference in Borg dyspnea, 1-minute post-6MFWT, O2 vs. CA:	**MD: 0.20** (-1.23 to 1.63)	
		Mean difference in Borg dyspnea, 2-minute post-6MFWT, O2 vs. CA:	**MD: -0.20** (-1.26 to 0.86)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Arizono et al, 2015 (4) (crossover RCT)	72	Mean difference in 6MWT endurance time, O2 vs. RA (seconds):	**MD: 118.70** (24.71 to 212.69)	72 patients (Mean age 66.5 (8.6) years) were included in the study, out of 106 consecutive IPF patients who were assessed for eligibility using the room-air 6MWT. *Note: This data is from an abstract only*
Visca et al, 2018 (5) (crossover RCT)	84 (76 completed) (58 male, 26 female)	Mean difference in 6MWT distance, O2 vs. CA (meters):	**MD: 18.50** (10.90 to 26.10)	AmbOx was a prospective, open-label, mixed-method, crossover randomised controlled trial done at three interstitial lung disease centres (Royal Brompton Hospital, Aintree University Hospital, and North Bristol NHS Trust) in the UK. Eligible patients were aged 18 years or older, had fibrotic interstitial lung disease, were not hypoxemic at rest (transcutaneous arterial oxygen saturation ≥ 94% on room air) but had a fall in transcutaneous arterial oxygen saturation to 88% or less on a screening visit 6-min walk test (6MWT), and had self-reported stable respiratory symptoms in the previous 2 weeks. Patients were excluded if expected to change treatment during the study. The mean age of all patients was 67.9 (SD = 10.4) years. Study duration was two weeks on oxygen and two weeks with no oxygen, for a total of one month.
		Mean difference in Borg dyspnea post-6MWT, O2 vs. CA:	**MD: -1.60** (-1.77 to -1.43)	
		Mean difference in Borg score recovery time, O2 vs. CA (seconds):	**MD: -49.00** (-65.32 to -32.68)	
		Mean difference in Borg fatigue score post-6MWT, O2 vs. CA:	**MD: -0.40** (-0.58 to -0.22)	
		Mean difference in Borg fatigue score recovery time, O2 vs. CA (seconds):	**MD: -14.00** (-24.58 to -3.42)	
		Mean difference in K-BILD Breathlessness and Activities score, O2 vs CA:	**MD: 3.7** (1.8 to 5.6)	
		Mean difference in K-BILD Chest Symptoms score, O2 vs. CA:	**MD: 8.6** (4.7 to 12.5)	
		Mean difference in K-BILD Psychological Symptoms score, O2 vs. CA:	**MD: 7.6** (1.9 to 13.2)	
		Mean difference in UCSDSOBQ total score, O2 vs. CA:	**MD: 2.4** (–0.6 to 5.5)	
		Mean difference in SGRQ total score, O2 vs. CA:	**MD: -8.0** (-12.4 to -3.6)	
		Mean difference in SGRQ Activity score, O2 vs. CA:	**MD: -3.6** (-6.7 to -0.6)	
		Mean difference in Borg dyspnea post-6MWT, O2 vs. CA:	**MD: -1.60** (-1.77 to -1.43)	
		Mean difference in SGRQ Symptoms score, O2 vs. CA:	**MD: -1.7** (-6.6 to 3.3)	
		Mean difference in SGRQ Impact score, O2 vs. CA:	**MD: -2.1** (-5.6 to 1.3)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome (95% CI)		Study Design and Population Characteristics
Studies where patients are eligible for LTOT				
Vieira et al, 2011 (6) (Observational)	17 (11 male, 6 female)	Mean difference in 6MWT distance, O2 vs. RA (meters):	**MD: 76.60** (-26.01 to 179.21)	17 ILD patients, selected from adults undergoing AO by liquid oxygen for at least 3 months (for use during exercise/effort) exhibiting hypoxemia during 6MWT and had significant daily activity (autonomous patients), from a central hospital in Porto, Portugal. The mean age of ILD patients was 55.9 (16.4) years. Patients had been prescribed AO for a mean of 11.1 months, ranging from 3 - 39 months.
		Mean difference in Borg dyspnea post-6MWT, O2 vs. RA:	**MD: -2.00** (-4.04 to 0.04)	
Khor et al, 2017 (5) (Crossover RCT)	20 (16 male, 4 female)	[Trial 1] Mean difference in 6MWT distance, O2 vs. RA (meters):	**MD: 10.00** (-67.38 to 87.38)	Patients were recruited for two trials from two tertiary hospitals, Austin Health and Alfred Health, aged over 18 years with a confirmed diagnosis of ILD of any aetiology and exertional desaturation (defined as desaturation < 90% on room air during the 6MWT). Exclusion criteria included significant communication or locomotor difficulty, primary diagnosis of a respiratory condition other than ILD and pregnancy. Trials were completed over two days; mean participant age was 69.0 (6.0) years. *Note: Study was designed as a crossover RCT for two different POCs. Participants were randomized into groups of receiving Inogen One G2 POC or EverGo POC. We pooled the results obtained from the two POCs vs. RA, as the type of POC is not of interest to us.*
		[Trial 1] Mean difference in 6MWT distance, Inogen One G2 POC vs. RA (meters):	**MD: 38.47** (-61.41 to 89.41)	
		[Trial 1] Mean difference in post-6MWT Borg dyspnea, O2 vs. RA:	**MD: -0.25** (-2.38 to 1.88)	
		[Trial 1] Mean difference in post-6MWT Borg dyspnea, Inogen One G2 POC vs. RA (meters):	**MD: -0.40** (-2.63 to 1.83)	
		[Trial 1] Mean difference in post-6MWT Borg fatigue, O2 vs. RA:	**MD: -0.60** (-2.65 to 1.45)	
		[Trial 1] Mean difference in post-6MWT Borg fatigue, Inogen One G2 POC vs. RA (meters):	**MD: 0.65** (-2.78 to 1.78)	
		[Trial 2] Mean difference in 6MWT distance, O2 cylinder vs. RA (meters):	**MD: 41.00** (-118.04 to 200.04)	
		[Trial 2] Mean difference in 6MWT distance, EverGo POC vs. RA (meters):	**MD: 31.00** (-128.41 to 190.41)	
		[Trial 2] Mean difference in post-6MWT Borg dyspnea, O2 cylinder vs. RA (meters):	**MD: -0.10** (-1.93 to 1.73)	
		[Trial 2] Mean difference in post-6MWT Borg dyspnea, EverGo POC vs. RA (meters):	**MD: 0.10** (-1.65 to 1.85)	
		[Trial 2] Mean difference in post-6MWT Borg fatigue, O2 cylinder vs. RA (meters):	**MD: 0.65** (-0.83 to 2.13)	
		[Trial 2] Mean difference in post-6MWT Borg fatigue, EverGo POC vs. RA (meters):	**MD: 0.75** (-0.63 to 2.13)	

Abbreviations: 6MWD, six-minute walking distance; 6MWT, six-minute walking test; CA, compressed air; COPD, chronic obstructive pulmonary disease; l/min, liters per minute; LTOT, long-term oxygen therapy; OR, odds ratio; SF-36, 36-item short form health survey; $Sp\mathbf{O_2}$, peripheral capillary oxygen saturation

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Summary of Studies for PICO 6

Question: Should portable liquid oxygen be provided for adults with chronic lung disease who are prescribed continuous oxygen flow rates of more than 3 L/min during exertion?

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome		Study Design and Population Characteristics
Vergeret et al, 1989 (1) (RCT)	84 (76 male, 8 female)	Percent Difference, Number of Patients using O_2 > 18 hrs/day, LOX vs. GO:	**24%**	Study to determine whether the availability of ambulatory oxygen to LTOT patients (in addition to fixed O_2) improved physical activity. Patients included were aged 40-75 years (mean 63 (SD: 7.4) years for the fixed O_2 group, 61 (SD: 8.1) years for the portable O_2 group), with severe COPD, defined by the following criteria: forced expiratory volume in one second/forced vital capacity (FEV 1 /FVC < 60%, total lung capacity (TLC) > 80% of reference values, FEV1 < 1L, and with stable chronic respiratory insufficiency: arterial oxygen tension (PaO_2) < 8 kPa/60 mmHg and > 5.3 kPa/40 mmHg; arterial carbon dioxide tension ($PaCO_2$) < 8.2 kPa/62 mmHg. Patients already had LTOT by a fixed oxygen source. Only those able to walk more than 200 m with portable oxygen equipment during a 12 min walking test with gasometrical supervision were retained for the survey. Patients excluded already had portable oxygen, had been hospitalized more than three times in the previous year for respiratory failure, or had suffered left heart failure or an associated pathology influencing functional and/or vital prognosis. The study duration was 1 year, and the combined mean flow rate liquid and gaseous oxygen was 2.2 (SD: 0.7) L/min during exercise and 1.7 (SD: 0.6) L/min during rest.
		Percent Difference, Number of Patients using O_2 between 15 and 18 hrs/day, LOX vs. GO:	**5%**	
		Percent Difference, Number of Patients using O_2 < 15 hrs/day, LOX vs. GO:	**-29%**	
Lock et al, 1992 (2) (Crossover RCT)	15 (12 male, 3 female)	Median Difference, 6MWT Distance at Baseline, LOX vs, GO (meters):	**Median Difference: 2.5** (95% CI: -8.0 to 15.0)	15 patients with CLD, each of whom had previously undergone a standard POC assessment and improved their walking distance and/or visual analog score by at least 10%. Eleven of the patients were on LTOT and eight were using a POC prior to the study. The patients were randomly allocated to start either on liquid oxygen or gaseous oxygen cylinders (both at 2 L/min), after which they were switched to the other oxygen delivery system for a further 8 weeks. The mean age of the patients was 62 (7) years.
		Median Difference, Hours O_2 Used per Week, LOX vs. GO, hrs/wk:	**Median Difference: 10.0** (95% CI: 4.2 to 23.3)*	
		Median Difference, Hours Spent Outside, LOX vs. GO, hrs/wk:	**Median Difference: 4.0** (95% CI: 0.9 to 7.1)*	
		Median Difference, Hours Spent Using O_2 Concentrator, GO vs. LOX:	**Median Difference: 13.1** (95% CI: 1.57 to 27.92)*	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome		Study Design and Population Characteristics
		CRQ Results (no numbers reported in study):	The CRQ did not show any consistent change in any of its four domains (dyspnea, fatigue, mastery, and emotional function) during the study.	
Andersson et al, 1998 (3) (RCT)	51 (23 male, 28 female)	Mean Difference in SIP Physical Function – Mobility Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -4.57** p = 0.043*	Prospective, randomized multicenter trial comparing concentrator treatment using ambulatory oxygen cylinders to liquid oxygen treatment. Patients were randomized to C/C or L for a six-month period. Some patients in both groups also received occasional complementary treatment with compressed gas. The study was conducted as an ancillary study to the Swedish Oxygen Register, which covered 85% of all patients in Sweden receiving LTOT for chronic hypoxaemia. 51 patients from six departs of pulmonary medicine in Sweden were randomized to one of the two treatments. The inclusion criteria were chronic hypoxaemia caused by pulmonary disease (the cut-off point for hypoxemia was 7.0–7.5 kPa or, in the presence of signs of cor pulmonale or haematocrit above 50%, around 7.5 kPa), eligibility for treatment with liquid oxygen, the ability to use mobile equipment outside the home, and a need or desire to spend time outside the home on a weekly basis. Patients who already received oxygen treatment at home could also be included in the trial. Exclusion criteria were being unable to leave the home or being unable to use mobile oxygen equipment. The recommended oxygen flow rate was continuous oxygen flow for a minimum of 16 h, preferably 24 h, achieving an arterial oxygen tension (PaO2) when breathing oxygen of > 8 kPa/60 mmHg. The mean age of patients in the LOX group was 63 (9) years, and the mean age of patients in the oxygen cylinder group was 63 (8) years. LOX users had a mean flow of 1.7 (0.7) L/min, while O2 Cylinder users had a mean flow of 1.8 (1.1) L/min. *The SIP and the EuroQol instrument were correctly completed by 45 patients but had to be discarded for four patients due to inadequate answers.* *SD not reported for the change in O2 cylinder or LOX values, thus corresponding CI upper and lower bounds cannot be calculated.*
		Mean Difference in SIP Physical Function Total Score, ΔO2 Cylinder vs. ΔLOX:	**MD: -2.15** p = 0.308	
		Mean Difference in SIP Physical Function - Body Care Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -5.83** p = 0.011*	
		Mean Difference in SIP Physical Function – Ambulation Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -8.46** p = 0.017*	
		Mean Difference in SIP Psychosocial Function Total Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -2.08** p = 0.082	
		Mean Difference in SIP Psychosocial Function - Emotional Behavior Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -3.13** p = 0.135	
		Mean Difference in SIP Psychosocial Function - Social Interaction Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -5.27** p = 0.023*	
		Mean Difference in SIP Psychosocial Function – Alertness Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -3.47** p = 0.064	
		Mean Difference in SIP Psychosocial Function - Communication Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -0.43** p = 0.333	
		Mean Difference in SIP Independent Category - Work Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -1.27** p = 0.416	
		Mean Difference in SIP Independent Category - Sleep Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -4.18** p = 0.150	
		Mean Difference in SIP Independent Category - Eating Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -0.66** p = 0.276	
		Mean Difference in SIP Independent Category - Home Management Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: 3.97** p = 0.230	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome		Study Design and Population Characteristics
		Mean Difference in SIP Independent Category - Recreation Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -7.84** p = 0.065	
		Mean Difference in Total SIP Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -3.38** p = 0.018*	
		Mean Difference in EuroQol Mobility Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -0.04** p = 0.394	
		Mean Difference in EuroQol Self-Care Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: 0.00** p = 0.110	
		Mean Difference in EuroQol Usual Activity Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: 0.17** p = 0.298	
		Mean Difference in EuroQol Pain/Discomfort Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -0.21** p = 0.069	
		Mean Difference in EuroQol Anxiety/Depression Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -0.18** p = 0.061	
		Mean Difference in EuroQol Better/Worse Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: -0.12** p = 0.185	
		Mean Difference in EuroQol Scale Score, ΔO_2 Cylinder vs. ΔLOX:	**MD: 2.88** p = 0.217	
Nasilowski et al, 2008 (4) (Crossover RCT)	13 (7 male, 6 female)	Mean Difference in 6MWT Distance, LOX vs POC (meters):	**MD: 8.00** (95% CI: -60.99 to 76.99)	Fifteen patients with COPD and previously prescribed LTOT (based on ATS/ERS guidelines) were included in the study, though only 13 completed it. The study, completed in an outpatient clinic setting, compared three devices during a 6MWT: a liquid oxygen cylinder, a portable oxygen concentrator, and a compressed air cylinder. The flow rate for each was set to 3 L/min (or equivalent). The mean age of included patients was 66 (11) years.
		Mean Difference, End-6MWT Borg Dyspnea Score, LOX vs. POC:	**MD: -0.10** (95% CI: -1.23 to 1.03)	
		Mean Difference, During-6MWT SpO_2, LOX vs. POC:	**MD: -0.50%** (95% CI: -4.05% to 3.05%)	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome		Study Design and Population Characteristics
		Mean Difference, End-6MWT SpO_2, LOX vs. POC:	**MD: -0.60%** (95% CI: -6.41% to 5.21%)	
		Mean Difference, Percent of 6MWT Spent in Desaturation (SpO_2 < 88%), LOx vs. POC:	**MD: 12.00%** (95% CI: -11.83% to 35.83%)	
Strickland et al, 2009 (5) (Crossover RCT)	39 (37 male, 2 female)	Mean Difference, SpO_2 Value, Pre – Post-6MWT, LOX (Helios) vs POC (HomeFill) (%):	**MD: 1.00** (95% CI: -1.66 to 3.66)	39 subjects were recruited from the outpatient pulmonary clinic at the Harry S Truman Memorial Veterans' Hospital in Columbia, Missouri. All subjects had category IV COPD, as well as dyspnea and resting hypoxia (SpO2 < 90%). All the subjects had an LTOT prescription from their physician and had been issued the standard ambulatory oxygen system at the Veterans Affairs hospital, which includes a compressed oxygen cylinder, DODS system, cannula, and shoulder carrying bag. Per protocol, the subject uses a pulse-dose setting that is numerically equivalent to a continuous-flow oxygen prescription. The subjects were not tested on continuous-flow oxygen; only pulse-dose flow was used for the purposes of this study. The study examines the differences between 4 DODS. The mean age of the subjects was 68.1 (9.5) years. Prescribed home oxygen flow (n, %): 1 L/min: 4 (10) 2 L/min: 21 (54) 3 L/min: 14 (36)
		Mean Difference, SpO_2 Value, Pre – Post-6MWT, LOX (Helios) vs POC (FreeStyle) (%):	**MD: 1.00** (95% CI: -1.66 to 3.66)	
		Mean Difference, SpO_2 Value, Pre – Post-6MWT, LOX (Helios) vs O_2 Cylinder (%):	**MD: 0.00** (95% CI: -2.45 to 2.45)	
Su et al, 2012 (6) (Observational)	144 (78 male, 66 female)	Mean Difference, Oxygen Usage (hrs/day), LOX vs. POC:	**MD: 6.50** (95% CI: 4.43 to 8.57)*	This was a retrospective, cross-sectional observation study performed with data collected between July 2009 and April 2010. Patients using oxygen (either liquid or oxygen concentrator) at home were recruited through three major oxygen vendors in northern Taiwan. The inclusion criteria were: confirmed primary diagnosis of COPD from the hospital discharge data (or COPD diagnosis made by the patient's physician); stable clinical conditions without experiencing an acute exacerbation one month prior to measurement; and requirement for ambulatory oxygen at home. The mean age of liquid oxygen patients was 65.4 (14.9) years, and the mean age of oxygen concentrator patients was 60.2 (18.5) years. O2 flow rates during the 2MWT were 2.6 (1.7) l/min for the LOX group, and 3.0 (1.2) l/min for the oxygen concentrator group. Flow rates were not provided at other times. Note, only 19 LOX patients and 51 POC patients had data for 2MWT.
		Mean Difference, Percent of Group Spending No Time Outdoors, LOX vs. POC:	**MD: -1.4%**	
		Mean Difference, Percent of Group Spending < 4 hrs/day Outdoors, LOX vs. POC:	**MD: -17.1%**	
		Mean Difference, Percent of Group Spending 4 - 8 hrs/day Outdoors, LOX vs. POC:	**MD: 17.1%**	
		Mean Difference, Percent of Group Spending 8 - 12 hrs/day Outdoors, LOX vs. POC:	**MD: 1.4%**	
		Mean Difference in Outings Frequency (times/wk) 0-1, Percent of Group, LOX vs. POC:	**MD: -32.3%** p < 0.001*	
		Mean Difference in Outings Frequency (times/wk) 2-3, Percent of Group, LOX vs.POC:	**MD: -1.8%** p = 0.804	

Study (Type)	№ of Participants	Effect Estimate(s) by Outcome		Study Design and Population Characteristics
		Mean Difference in Outings Frequency (times/wk) 4-6, Percent of Group, LOX vs.POC:	**MD: 8.6%** p = 0.245	
		Mean Difference in Outings Frequency (times/wk) 7-9, Percent of Group, LOX vs.POC:	**MD: 7.4%** p = 0.158	
		Mean Difference in Outings Frequency (times/wk) 10+, Percent of Group, LOX vs.POC:	**MD: 14.5%** p = 0.012*	
		Mean Difference in 2MWT Exercise SpO_2, LOX vs.POC:	**MD: -0.40** (95% CI: -3.08 to 2.28)	
		Mean Difference in 2MWT Exercise Borg Score, LOX vs.POC:	**MD: -0.40** (95% CI: -1.36 to 0.56)	

Abbreviations**:** 2MWT, two-minute walking test; 6MWT, six-minute walking test; CI, confidence interval; D., difference; GO, gaseous oxygen; hrs, hours; hrs/day, hours per day; hrs/wk, hours per week; LOX, liquid oxygen; MD, mean difference; O_2, oxygen; POC, portable oxygen concentrator; RCT, randomized controlled trial; SIP, sickness impact profile; SpO_2, peripheral capillary oxygen saturation; wk, week

*Significant at $p < 0.05$

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EVIDENCE PROFILE TABLES

Table E2: Evidence Profile for PICO 1

Question: Should long-term oxygen be prescribed for adults with COPD who have severe chronic resting room air hypoxemia?

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Direct Outcome Measures										
Mortality										
1-Year Mortality Risk (LTOT prescribed 24 hours/day vs. LTOT prescribed for nocturnal use)										
1 (1)	randomized trial	not serious	not serious	not serious	serious[a]	The control group in NOTT (1) received nocturnal oxygen therapy.	101	1-Year Mortality Risk (LTOT prescribed 24 hours/day vs. LTOT prescribed for nocturnal use) **RR: 0.53** (0.25 to 1.11)	⊕⊕⊕◯ MODERATE	CRITICAL
2-Year Mortality Risk (LTOT prescribed 24 hours/day vs. LTOT prescribed for nocturnal use)										
1 (1)	randomized trial	not serious	not serious	not serious	serious[a]	The control group in NOTT (1) received nocturnal oxygen therapy.	101	2-Year Mortality Risk (LTOT prescribed 24 hours/day vs. LTOT prescribed for nocturnal use) **RR: 0.45** (0.25 to 0.81)*	⊕⊕⊕◯ MODERATE	CRITICAL
5-Year Mortality Risk (LTOT prescribed for at least 15 hours/day vs. no LTOT)										
1 (2)	randomized trial	not serious	not serious	not serious	serious[a]	none	87	5-Year Mortality Risk (LTOT prescribed for at least 15 hours/day vs. no LTOT) **RR: 0.41** (0.17 to 0.98)*	⊕⊕⊕◯ MODERATE	CRITICAL
Exercise Capacity										
Treadmill Walk Test										
1 (3)	pre-post study	serious	not serious	serious[b]	serious[a]	none	3	**Treadmill walk[b]:** All participants experienced improvement in distance walked on treadmill at 0.75 mph at all grades. More significant increases were observed at milder grades (i.e., lower elevation)	⊕◯◯◯ VERY LOW	IMPORTANT
Indirect Outcome Measures										
Healthcare Resource Utilization										
Risk of Admission (LTOT vs. pre-LTOT)										
1 (4)	observational study	serious[c]	not serious	serious[d]	serious[a]	none	26	Hospital admissions (LTOT vs. pre-LTOT) **RR: 0.70** (CI: 0.15, 3.30)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Length of Stay										
2 (4, 5)	observational studies	serious[c] Error! Bookmark not defined.	serious[e]	not serious Error! Bookmark not defined.	serious	none	N bed days: 26 N for median hospital days: 421 Total N: 427	Bed days per patient-year of follow-up (LTOT vs. pre-LTOT) (4) **RR: 0.65** (0.40 to 1.05) Days in hospital (LTOT only) (5)[f] **Median: 18** (Range: 0 to 363)	⨁◯◯◯ VERY LOW	IMPORTANT
Number of Hospitalizations (LTOT vs. conventional therapy)										
1 (5)	observational	not serious	serious[g]	serious[h]	serious[a]	none	54	Hospitalizations (LTOT vs. conventional therapy) over 3 years **MD: -1.17** (95% CI: -1.73 to -0.59)*	⨁⨁◯◯ LOW	IMPORTANT

Abbreviations**:** 6MWT, 6-minute walk test; CI, Confidence interval; COPD, chronic obstructive pulmonary disease; LTOT, long-term oxygen therapy; m, meters; MD, mean difference; mos, months; MR, mortality rate; №, number; POMS, Profile of Mood States; RMR, relative mortality rate; s, seconds; SGRQ, St. George's Respiratory Questionnaire; SMD, standardized mean difference (aka, Cohen's *d*); SMR, standardized mortality rate; wks, weeks; yr, year.
*Indicates statistical significance at p<0.05

[a] The results of this outcome are based on the results of only one study.
[b] Levine et al, 1967 presented their results in figure-form, preventing quantitative effects from being estimable.
[c] High risk of bias, due to the limitations presented in observational studies.
[d] This outcome reports the mortality rate for patients receiving LTOT, with no comparison group. Consequently, this is downgraded for indirectness.
[e] Each of the included studies reported on length of stay using different measurements.
[f] Authors also found that 83% (SE=18.95%) of LTOT patients were admitted to the hospital, but authors did not compare against a control group
[g] Authors do not describe their method of randomization and concealment.
[h] Bao et al, 2017 found that length of stay was reduced by 35% per patient year of follow-up when patients began to receive LTOT vs. before LTOT.

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Table E3: Evidence Profile for PICO 2

Question: Should long-term oxygen be prescribed for adults with COPD who have moderate chronic resting room air hypoxemia?

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Mortality / Hospitalization										
Time to Death										
Participants with moderate resting hypoxemia (either moderate resting hypoxemia only or moderate resting hypoxemia and desaturation during 6MWT): **1** (1)	RCT	not serious	not serious	not serious	very serious[a]	none	590	Time to Death (LTOT vs No LTOT) **HR: 0.94** (0.59 to 1.50)	⨁⨁◯◯ LOW	CRITICAL
Quality of Life										
St. George's Respiratory Questionnaire (SGRQ)										
Participants with moderate resting hypoxemia only: **1** (1)	RCT	not serious	not serious	not serious	very serious[a]	none	4 Months: 378 12 Months: 358	SGRQ Total Score (LTOT vs No LTOT) **4 Months vs Baseline** **MD: -4.50** (-9.59 to 0.59) **12 Months vs Baseline** **MD: -2.90** (-8.58 to 2.78)	⨁⨁◯◯ LOW	IMPORTANT
Participants with moderate resting hypoxemia (either moderate resting only or moderate resting hypoxemia and desaturation during 6MWT): **1** (1)	RCT	not serious	not serious	not serious	very serious[a]	none	4 Months: 538 12 Months: 516	SGRQ Total Score (LTOT vs No LTOT) **4 Months vs Baseline** **MD: -3.30** (-6.50 to -0.10)* **12 Months vs Baseline** **MD: -1.00** (-4.23 to 2.23)	⨁⨁◯◯ LOW	IMPORTANT
Quality of Well-Being Scale (QWB)										
Participants with moderate resting hypoxemia only: **1** (1)	RCT	not serious	not serious	not serious	very serious[a]	none	4 Months: 380 12 Months: 371	QWB Total Score (LTOT vs No LTOT) **4 Months vs Baseline** **MD: 0.04** (0.00 to 0.08) **12 Months vs Baseline** **MD: 0.00** (-0.06 to 0.06)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Participants with moderate resting hypoxemia (either moderate resting only or moderate resting hypoxemia and desaturation during 6MWT): **1** (1)	RCT	not serious	not serious	not serious	very serious[a]	none	4 Months: 540 12 Months: 529	QWB Total Score (LTOT vs No LTOT) **4 Months vs Baseline** **MD: -0.01** (-0.04 to 0.02) **12 Months vs Baseline** **MD: 0.01** (-0.03 to 0.05)	⨁⨁◯◯ LOW	IMPORTANT

Abbreviations**:** CI, Confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LTOT, long-term oxygen therapy; MD, mean difference; №, number; QWB, Quality of Well-Being Scale.
*indicates statistical significance at p<0.05

[a] The results of this outcome are based on the results of only one study and have wide confidence intervals

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Table E4: Evidence Profile for PICO 3

Question: Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia ?

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Quality of Life										
Chronic Respiratory Disease Questionnaire (CRQ) Fatigue Score										
2 (1, 2) *All participants had isolated EIH*	Crossover RCTs	not serious	not serious	serious[a]	not serious	none	68	CRQ Fatigue Score, O_2 vs. CA) **SMD: 1.03** (-0.15 to 2.21) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
1 (3) *All participants had isolated EIH*	RCT	not serious	not serious	not serious	not serious	none	64	CRQ Fatigue Score, O_2 vs. CA) **SMD: -0.21** (-0.08 to 1.76) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
3 (1-3) *All participants had isolated EIH*	Crossover RCTs and RCT	not serious	serious[b]	serious[a]	not serious	none	132	CRQ Fatigue Score, O_2 vs. CA) **SMD: 0.84** (-0.15 to 2.21) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
Chronic Respiratory Disease Questionnaire (CRQ) Emotion Score										
2 (1, 2) *All participants had isolated EIH*	Crossover RCTs	not serious	serious[b]	serious[a]	not serious	none	68	CRQ Emotion Score, O_2 vs. CA) **SMD: 1.49** (-1.82 to 4.79) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
1 (3) *All participants had isolated EIH*	RCT	not serious	not serious	Not serious	not serious	none	64	CRQ Emotion Score, O_2 vs. CA) **SMD: 0.88** (-3.47 to 5.23) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
3 (1-3) *All participants had isolated EIH*	Crossover RCTs and RCT	not serious	serious[b]	serious[a]	not serious	none	132	CRQ Emotion Score, O_2 vs. CA) **SMD: 1.32** (-1.10 to 3.74) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Chronic Respiratory Disease Questionnaire (CRQ) Mastery Score										
2 (1, 2) *All participants had isolated EIH*	Crossover RCTs	not serious	serious[b]	serious[a]	not serious	not serious	68	CRQ Mastery Score, O_2 vs. CA) **SMD: 0.67** (-1.48 to 2.83) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
1 (3) *All participants had isolated EIH*	RCT	not serious	not serious	not serious	not serious	not serious	64	CRQ Mastery Score, O_2 vs. CA) **SMD: 0.26** (-2.56 to 3.08) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
3 (1-3) *All participants had isolated EIH*	Crossover RCTs and RCT	not serious	serious[b]	serious[a]	not serious	not serious	132	CRQ Mastery Score, O_2 vs. CA) **SMD: 0.58** (-1.02 to 2.17) *Meta-analysis depicted in Figure E1.*	⨁⨁◯◯ LOW	CRITICAL
Chronic Respiratory Questionnaire Dyspnea-Related Quality of Life Score (CRQ_D)										
2 (1, 2) *All participants had isolated EIH*	Crossover RCTs	not serious	not serious	not serious	not serious	none	68	CRQ Dyspnea Score (O_2 vs. CA) **SMD: 0.67** (0.18 to 1.16)* *Meta-analysis depicted in Figure E2.*	⨁⨁◯◯ LOW	CRITICAL
1 (3) *All participants had isolated EIH*	RCT	not serious	not serious	not serious[a]	not serious	none	64	CRQ Dyspnea Score (O_2 vs. CA) **SMD: 0.13** (-0.37 to 0.63) *Meta-analysis depicted in Figure E2.*	⨁⨁◯◯ LOW	CRITICAL
3 (1-3) *All participants had isolated EIH*	RCT and crossover RCTs	not serious	not serious	serious[a]	not serious	These are pooled results from one RCT (3) and two crossover RCTs (1, 2). Separate results by study design shown above.	132	CRQ Dyspnea Score (O_2 vs. CA) **SMD: 0.42** (0.04 to 0.79)* *Meta-analysis depicted in Figure E2.*	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
St. George's Respiratory Questionnaire (SGRQ)										
1 (1) *All participants had isolated EIH*	RCT	not serious	not serious	not serious	serious[c]	none	27	SGRQ Symptoms Score (O_2 vs. CA) **MD: -0.17** (-2.63 to 2.29) SGRQ Activity Score (O_2 vs. CA) **MD: 0.42** (-1.59 to 2.43) SGRQ Impacts Score (O_2 vs. CA) **MD: -0.79** (-2.75 to 1.17) SGRQ Total Score (O_2 vs. CA) **MD: -0.32** (-1.71 to 1.06)	⨁⨁⨁◯ MODERATE	CRITICAL
Short-Form Health Survey (SF-36)										
1 (2) *All participants had isolated EIH*	RCT	not serious	not serious	not serious	serious[c]	none	41	SF-36 physical functioning score (O_2 vs. CA) **MD: 1.6** (-5.26 to 8.46) SF-36 role physical score (O_2 vs. CA) **MD: 16.8** (6.02 to 27.58)* SF-36 bodily pain score (O_2 vs. CA) **MD: 5.3** (-4.50 to 15.10) SF-36 general health score (O_2 vs. CA) **MD: 6.1** (0.42 to 11.78)* SF-36 vitality score (O_2 vs. CA) **MD: 2.9** (-2.98 to 8.78) SF-36 social functioning score (O_2 vs. CA) **MD: 10.5** (0.31 to 20.69)* SF-36 role emotional score (O_2 vs. CA) **MD: 18.3** (3.21 to 33.39)* SF-36 mental health score (O_2 vs. CA) **MD: 4.0** (-1.29 to 9.29)	⨁⨁⨁◯ MODERATE	CRITICAL
Exercise Capacity										
5-Minute Walk Test										
1 (1) *All participants had isolated EIH*	RCT	not serious	not serious	not serious	serious[c]	none	27	Number of steps walked (O_2 vs. CA) **MD: 14.90** (0.85 to 28.94)* Endurance time, mins (O_2 vs. CA) **MD: 2.40** (0.58 to 4.22)*	⨁⨁⨁◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
6-Minute Walk Test										
Studies with isolated EIH: **2** (2, 4)	RCTs	not serious	not serious	not serious	not serious	none	84	Distance walked, m (O_2 vs. CA) in patients with isolated EIH **MD: 28.99** (16.06 to 41.92)*	⊕⊕⊕⊕ HIGH	IMPORTANT
Studies with LTOT: **1** (5)	RCT	not serious	not serious	not serious	serious[c]	none	13	Distance walked, m (O_2 vs. CA) in patients on or eligible for LTOT **MD: 25.00** (-44.34, 94.34)	⊕⊕⊕◯ MODERATE	IMPORTANT
All studies: **3** (2, 4, 5)	RCTs	not serious	not serious	not serious	not serious	none	97	Distance walked, m, (O_2 vs. CA) in all studies **MD: 28.85** (16.14 to 41.57)*	⊕⊕⊕⊕ HIGH	IMPORTANT
Incremental Shuttle Walk Test (ISWT)										
1 (6) *Participants were on or eligible for LTOT*	RCT	not serious	not serious	serious[d]	serious[c]	none	22	Distance walked, m (O_2 vs. RA) **MD:** 27.3 (14.7 to 39.8)* Endurance time, s (O_2 vs. RA) **MD:** -23.6 (-70.7 to 23.5)	⊕⊕◯◯ LOW	IMPORTANT
Maximum Distance Walked										
1 (7) *Participants were on or eligible for LTOT*	RCT	not serious	not serious	not serious	serious[c]	none	21	Maximum distance walked, m (O_2 vs. CA) **MD: 88.0** (-23.14 to 199.14)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
12-Minute Walk Test										
1 (8) *Participants were on or eligible for LTOT*	RCT	not serious	not serious	serious[d]	serious[c]	none	26	Distance Walked, m–Group 1, 2L O_2/min vs. RA **MD: 51.6** (25.92 to 77.28)* Distance Walked, m–Group 1, carrying 2L O_2/min v RA **MD: -73.6** (-99.28 to -47.92)* Distance Walked, m–Group 2, 4L O_2/min vs RA **MD: 53.0** (28.11 to 77.89)* Distance Walked, m–Group 2, 2L O_2/min walker v RA **MD: -25.0** (-49.89 to -0.11)* Distance Walked, m–Group 2, 4L O_2/min on walker v RA **MD: 13.0** (-11.89 to 37.89) Distance Walked, m–Group 3, 4L O_2/min vs RA **MD: 75** (35.21 to 114.79)* Distance Walked, m–Group 3, 2L O_2/min on trolley vs RA **MD: 34** (-5.79 to 73.79) Distance Walked, m–Group 3, 4L O_2/min on trolley vs RA **MD: 59** (19.21 to 98.79)*	⨁⨁⨁◯ MODERATE	IMPORTANT
Maximal Exercise										
1 (9) *All participants had isolated EIH*	RCT	unclear[e]	serious[f]	serious[g]	serious[c]	none	17	Work, watts, O_2 vs. RA **MD: 7.6** (-6.8 to 22.0)	⨁◯◯◯ VERY LOW	IMPORTANT
Exercise Tolerance										
1 (10) *All participants had isolated EIH*	Observational	serious[h]	serious[h]	serious[h]	serious[c]	none	15	Time to Exercise Tolerance, minutes, O_2 vs. RA **MD: 5.8** (2.23 to 9.37)*	⨁◯◯◯ VERY LOW	IMPORTANT
Symptom-Limited Low-Level Incremental Exercise										
1 (11) *All participants had isolated EIH*	RCT	not serious	not serious	not serious	serious[c]	none	14	Work, watts (O_2 vs. RA) **MD: 17.9** (8.10 to 27.70)*	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Symptom-Limited Peak Exercise										
1 (12) *Participants were on or eligible for LTOT*	RCT	unclear[e]	not serious	not serious	serious[c]	none	11	Endurance Time to Symptom-Limited Peak Exercise, minutes, O_2 vs. RA **MD: 4.70** (3.76 to 5.64)*	⊕⊕⊕◯ MODERATE	IMPORTANT
Dyspnea										
Borg Dyspnea Score										
Studies with isolated EIH: 2 (2, 4)	Crossover RCTs	not serious	not serious	serious[a]	not serious	none	84	Borg Dyspnea Score (O_2 vs. control) in participants with isolated EIH **MD: -0.95** (-1.39 to -0.52)* Note: The MCID in Borg Dyspnea Score is a change of 0.9 units (13), *Meta-analysis depicted in Figure E3.*	⊕⊕⊕◯ MODERATE	IMPORTANT
Studies with isolated EIH: 1 (10)	RCT	not serious	not serious	serious[a]	serious[c]	none	15	Borg Dyspnea Score (O_2 vs. control) in participants with isolated EIH **MD: -2.10** (-3.43 to -0.77)* Note: The MCID in Borg Dyspnea Score is a change of 0.9 units (13),	⊕⊕◯◯ LOW	IMPORTANT
Studies with isolated EIH: **3** (2, 4, 10)	RCT and Crossover RCTs	not serious	not serious	serious[a]	not serious	These are pooled results from one RCT (10) and two crossover RCTs (2, 4). Separate results by study design shown above.	99	Borg Dyspnea Score (O_2 vs. control) in participants with isolated EIH **MD: -1.11** (-1.69 to -0.59)* Note: The MCID in Borg Dyspnea Score is a change of 0.9 units (13), *Meta-analysis depicted in Figure E3.*	⊕⊕⊕◯ MODERATE	IMPORTANT
Studies with LTOT: **1** (12)	Crossover RCT	not serious	not serious	serious[a]	serious[c]	none	11	Borg Dyspnea Score (O_2 vs. control) in participants on or eligible for LTOT **MD: -0.20** (-0.83 to -0.43) Note: The MCID in Borg Dyspnea Score is a change of 0.9 units (13),	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Studies with LTOT: **2** (5, 6)	RCTs	not serious	not serious	not serious	not serious	none	35	Borg Dyspnea Score (O_2 vs. control) in participants on or eligible for LTOT **MD: -0.72** (-1.08 to -0.37)* Note: The MCID in Borg Dyspnea Score is a change of 0.9 units (13), *Meta-analysis depicted in Figure 3.*	⨁⨁⨁⨁ HIGH	IMPORTANT
Studies with LTOT: **3** (5, 6, 12)	RCTs and crossover RCTs	not serious	not serious	serious[a]	not serious	These are pooled results from one RCT (10) and two crossover RCTs (2, 4). Separate results by study design shown above.	46	Borg Dyspnea Score (O_2 vs. control) in participants on or eligible for LTOT **MD: -0.59** (-0.99 to -0.18)* Note: The MCID in Borg Dyspnea Score is a change of 0.9 units (13), *Meta-analysis depicted in Figure 3.*	⨁⨁⨁◯ MODERATE	IMPORTANT
All studies: **6** (2, 4-6, 10, 12)	RCTs and crossover RCTs	not serious	not serious	serious[a]	not serious	These are pooled results from RCTs and crossover RCTs for participants with isolated EIH and those with resting hypoxemia.	145	Borg Dyspnea Score (O_2 vs. control) for all studies **MD: -0.82** (-1.19 to -0.44)* Note: Borg Dyspnea Score MCID is 0.9 units (13), *Meta-analysis depicted in Figure 3.*	⨁⨁⨁◯ MODERATE	IMPORTANT

Abbreviations**:** 6MWT, 6-minute walk test; CA, cylinder air; CI, Confidence interval; CRQ, Chronic Respiratory Disease Questionnaire; COPD, chronic obstructive pulmonary disease; hrs, hours; l, liter; LTOT, long-term oxygen therapy; m, meters; MD, mean difference; mm, millimeters; mos, months; №, number; POMS, Profile of Moods Disturbance; RA, room air; RMR, relative mortality rate; s, seconds; SGRQ, St. George's Respiratory Questionnaire; SF36, Short Form 36 (SF-36) Health Survey; SMD, standardized mean difference (aka, Cohen's *d*); SMR, standardized mortality rate; wks, weeks; yr, year.
*indicates statistical significance at p<0.05

[a] Due to the presence of crossover RCTs, we've downgraded for indirectness.
[b] I^2>50%, indicating significant heterogeneity
[c] The results of this outcome are based on the results of only one study.
[d] This was an observational study, lending itself to limitations in randomization and allocation concealment.
[e] Methods of randomization and concealment were not discussed.
[f] Wide confidence intervals
[g] Single-blinded study, where participants were blinded, but assessors were aware of treatment allocation.
[h] Evidence is considered indirect, as all participants from LOTT had *moderate* resting hypoxemia (SpO_2 89 to 93%) and *moderate* EIH (during 6MWT, SpO2>80% for >5 minutes and <90% for >10 seconds)

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PICO 3 Forest Plots

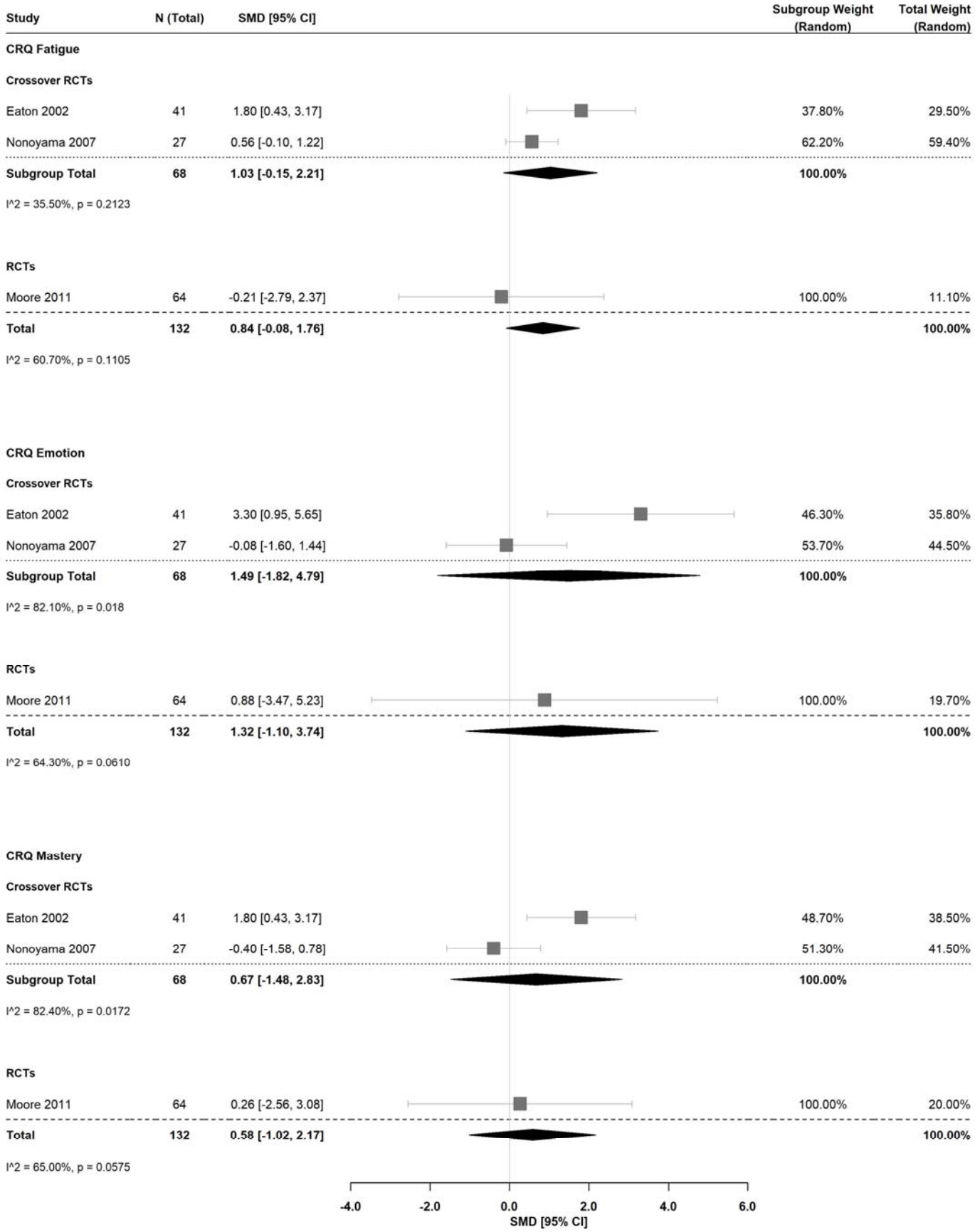

Figure E1: Standardized mean difference in CRQ scores in COPD patients with isolated exercise-induced hypoxemia (isolated EIH; not on or eligible for LTOT) receiving ambulatory oxygen vs. compressed air

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory [disease] questionnaire; EIH, exercise-induced hypoxemia; LTOT, long-term oxygen therapy; N, number; SMD, standardized mean difference

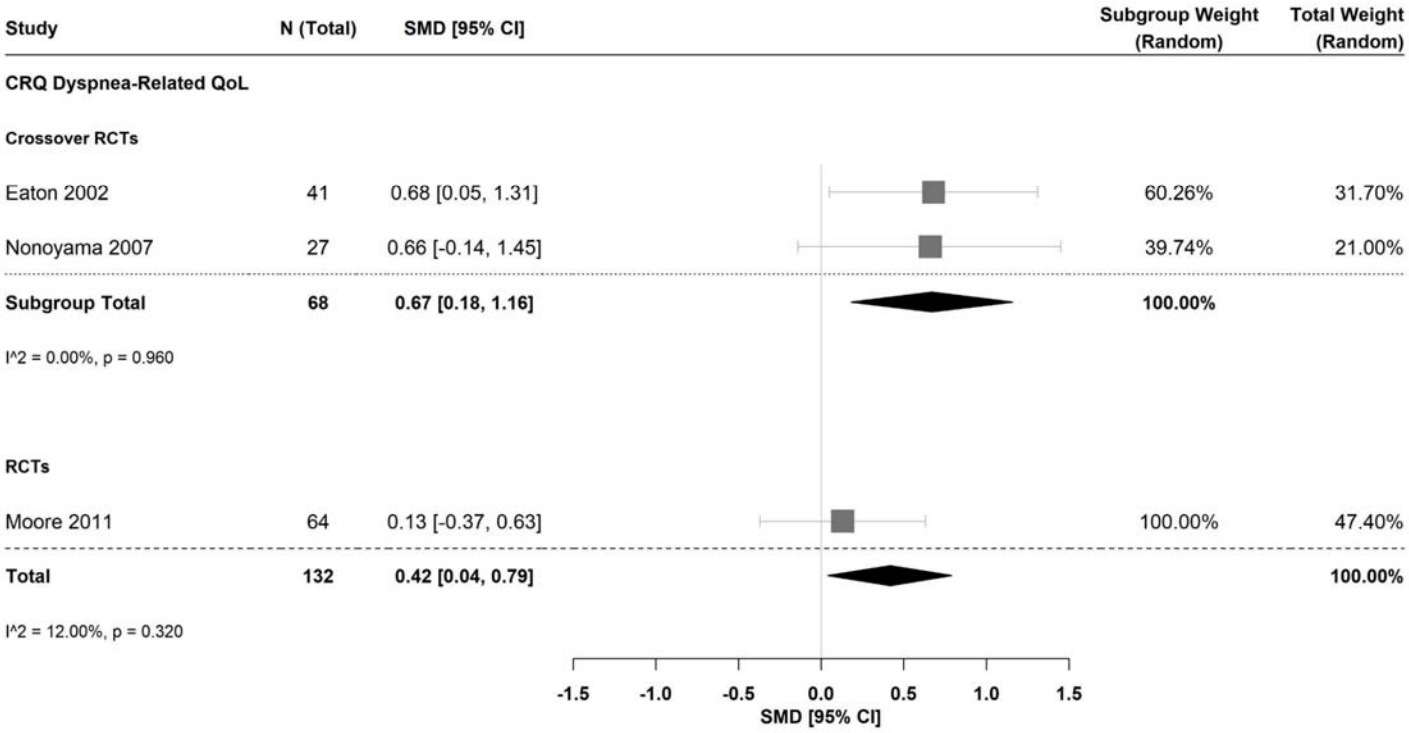

Figure E2: Standardized mean difference in CRQ dyspnea-related quality of life scores in COPD patients with isolated exercise-induced hypoxemia (not on or eligible for LTOT) receiving ambulatory oxygen vs. compressed air

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory [disease] questionnaire; EIH, exercise-induced hypoxemia; LTOT, long-term oxygen therapy; N, number; SMD, standardized mean difference

Note: The data from Moore 2011 and Eaton 2002 are on a 35-point scale and Nonoyama 2007 is on a 7-point scale. Therefore, standardized mean differences are depicted in this meta-analysis.

*The data depicted in the forest plot for Moore et al was sent to us by the authors directly

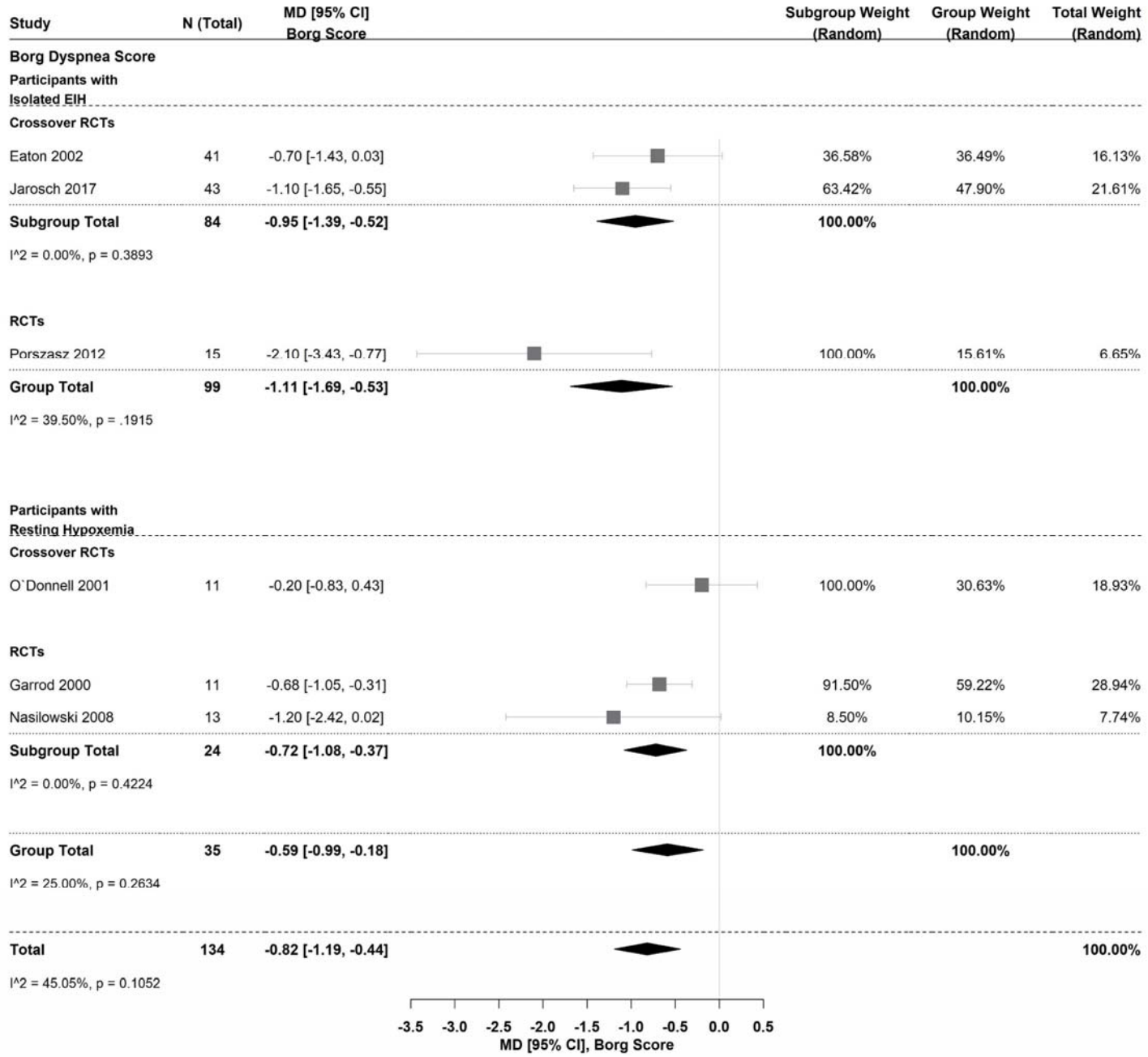

Figure E3: Mean difference for Borg dyspnea scores in COPD patients with severe exertional hypoxemia receiving ambulatory oxygen vs. control group

Note: Porszasz (34), Garrod (36), and O'Donnell et al (26) use room air as control group, while the other studies (25, 28, 29) use compressed air

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; LTOT, long-term oxygen therapy; MD, mean difference; N, number

Table E5: Evidence Profile for PICO 4

Question: Should long-term oxygen be prescribed for adults with ILD who have severe chronic resting room air hypoxemia?

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Mortality										
1 (1)[a]	Unpublished RCT	Serious[b]	Serious[c]	Not serious	Not serious	Serious[d]	37	Mortality at 12 months (LTOT vs. RA) **OR: 0.50** (0.15 to 1.61) Mortality at 24 months (LTOT vs. RA) **OR: 1.76** (0.64 to 4.86) Mortality at 36 months (LTOT vs. RA) **OR: 0.99** (0.16 to 6.26)	⨁◯◯◯ VERY LOW	CRITICAL

Abbreviations**:** LTOT, long-term oxygen therapy; OR, odds ratio; RA, room air; RCT, randomized controlled trial.

Note: Refer to PICO Question 1 for indirect evidence included from COPD literature: Should long-term oxygen be prescribed for adults with COPD who have severe chronic resting room air hypoxemia?

[a] This study does *not* meet our inclusion criteria, as it includes patients with a PaO_2 of 45-60 mmHg/6.0-8.0 kPa (our inclusion criteria is $PaO_2 \leq 55$ mmHg/7.3 kPa). However, as no other study was found on the effects of LTOT on patients with ILD and severe resting hypoxemia, we have reported the results of this study.

[b] Unclear allocation concealment.

[c] Results are based off one unpublished RCT.

[d] The results for this unpublished RCT were retrieved in the Crocket et al 2. Crockett AJ, Cranston JM, Antic N. Domiciliary oxygen for interstitial lung disease. *Cochrane Database Syst Rev* 2001: CD002883. systematic review.

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Table E6: Evidence profile for PICO 5

Question: Should ambulatory oxygen be prescribed for adults with ILD who have severe exertional room air hypoxemia?

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Quality of Life										
King's Brief Interstitial Lung Disease (K-BILD) Score										
1 (1) *All participants had isolated EIH*	RCT	Not serious	Not serious	Not serious	Serious[a]	None	76	K-BILD Total Score (O_2 vs. CA) **MD: 3.7** (1.8 to 5.6)* K-BILD Breathlessness/Activities Score (O_2 vs. CA) **MD: 8.6** (4.7 to 12.5)* K-BILD Chest Symptoms (O_2 vs. CA) **MD: 7.6** (1.9 to 13.2)* K-BILD Psychological Symptoms (O_2 vs. CA) **MD: 2.4** (–0.6 to 5.5) *Note: MCID for K-BILD Score is approximately 5 units (2).*	⨁⨁◯◯ LOW	CRITICAL
St. George's Respiratory Questionnaire (SGRQ) Score										
1 (1) *All participants had isolated EIH*	RCT	Not serious	Not serious	Not serious	Serious[a]	None	76	SGRQ Total (O_2 vs. CA) **MD: -3.6** (-6.7 to -0.6)* SGRQ Activity (O_2 vs. CA) **MD: -7.5** (-12.4 to -2.5)* SGRQ Symptoms (O_2 vs. CA) **MD: -1.7** (-6.6 to 3.3) SGRQ Impact (O_2 vs. CA) **MD: -2.1** (-5.6 to 1.3) *Note: MCID for SGRQ score is approximately 4 units (3).*	⨁⨁◯◯ LOW	CRITICAL
Dyspnea										
Borg Dyspnea Score										
Studies with isolated EIH: **3** (1, 4, 5)	RCTs	Serious[b]	Not serious	Not serious	Not serious	For control group, Khor (5) and Visca et al (1) use no intervention; Nishiyama et al (4) use CA.	136	Borg Dyspnea Score for participants with EIH (O_2 vs. control) **MD: -0.72** (-1.70 to 0.27) *Meta-analysis depicted in Figure E4.*	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Studies with resting hypoxemia: **1** (7)	RCT and Observational	Serious[bc]	Not serious	Not serious	Not serious	None	17	Borg Dyspnea Score for those with resting hypoxemia (O_2 vs. RA) **MD: -2.00** (-4.04 to 0.04)	⨁◯◯◯ VERY LOW	CRITICAL
All Studies: **4** (1, 4, 5, 7)	RCTs and Observational	Serious[bc]	Not serious	Not serious	Not serious	For control group, Khor et al (5), and Visca et al (1) use RA Nishiyama et al (4) use CA.	153	Borg Dyspnea Score for all studies (O_2 vs. control) **MD: -0.89** (-1.74 to -0.04)* *Meta-analysis depicted in Figure E4.*	⨁◯◯◯ VERY LOW	CRITICAL
The University of California, San Diego Shortness of Breath Questionnaire (UCSDSOBQ)										
1 (1) *All participants had isolated EIH*	RCT	Not serious	Not serious	Not serious	Serious[a]	None	76	UCSDSOBQ Score (O_2 vs. CA) **MD: -8.0** (-12.4 to -3.6)* *Note: MCID for the UCSDSOBQ is a change of 5 units.*	⨁⨁◯◯ LOW	CRITICAL
Exercise Capacity										
6-Minute Walk Test Distance										
Studies with isolated EIH: **3** (1, 4, 5)	RCTs	Serious[b]	Not serious	Not serious	Not serious	For control group, Khor et al (5) and Visca et al (1) use RA; Nishiyama et al (4) use CA	136	6MWT Distance, m, (O_2 vs. CA) for participants with EIH **MD: 18.57** (11.14 to 25.99)* *Meta-analysis depicted in Figure E5.*	⨁⨁⨁◯ MODERATE	IMPORTANT
Studies with LTOT: **1** (7)	RCT and Observational	Serious[bc]	Not serious	Not serious	Not serious	None	17	6MWT Distance, m, (O_2 vs. RA) for participants with resting hypoxemia **MD: 76.60 (**-26.01 to 179.21)	⨁⨁◯◯ LOW	IMPORTANT
All studies: **4** (1, 4, 5, 7)	RCT and Observational	Serious[bc]	Not serious	Not serious	Not serious	For control group, Khor et al (5), Vieira et al (7), and Visca et al (1) use RA; Nishiyama et al (4) use CA	153	6MWT Distance, m, (O_2 vs. control) for all studies **MD: 18.87** (11.46 to 26.28)*. *Meta-analysis depicted in Figure E5..*	⨁⨁◯◯ LOW	IMPORTANT
6-Minute Walk Test Endurance Time										
1 (8) *All participants had isolated EIH*	RCT	Serious[b]	Not serious	Not serious	Serious[a]	Data taken from abstract only	72	6MWT Endurance Time (s) (O_2 vs. RA) **MD: 118.70** (24.71 to 212.69)*	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Maximum Work Rate										
2 (6, 9) *All participants had isolated EIH*	RCTs	Serious[b]	Not serious	Not serious	Serious[a]	Data taken from Troy et al (9) taken from abstract only	13	Max Workload, watts (O_2 vs. RA) **MD: 10.34** (-3.59 to 24.25) *Meta-analysis depicted in Figure E6.*	⨁⨁◯◯ LOW	IMPORTANT
Exercise Duration										
2 (6, 9) *All participants had isolated EIH*	RCT	Serious[b]	Not serious	Not serious	Serious[a]	Data taken from Troy et al (9) taken from abstract only	13	Exercise Duration, s (O_2 vs. RA) **MD: 57.67** (0.22 to 115.12)* *Meta-analysis depicted in Figure E7.*	⨁⨁◯◯ LOW	IMPORTANT
Endurance Shuttle Walk Test Distance (ESWT)										
1 (9) *All participants had isolated EIH*	RCT	Serious[b]	Not serious	Not serious	Serious[a]	Data taken from abstract only	6	ESWT Distance, m (O_2 vs. RA) **MD: 265.00** (-297.88 to 827.88)	⨁⨁◯◯ LOW	IMPORTANT
Composite Index										
Borg Fatigue Score										
3 *(All participants had isolated EIH)* (1, 4, 5)	RCTs and Observational	Serious[bc]	Not serious	Not serious	Not serious	For control group, Khor et al (5) and Visca et al (1) use room air; Nishiyama et al (4) use CA.	136	Borg Fatigue Score for all studies (O_2 vs. control) **MD: -0.37** (-0.54 to -0.19)* *Meta-analysis depicted in Figure E8.* *Note: MCID for Borg Fatigue Score is approximately 1 unit (10).*	⨁◯◯◯ VERY LOW	IMPORTANT

Abbreviations**:** CA: compressed air; CI, Confidence interval; EIH, exercise induced hypoxemia; HADS, Hospital Anxiety and Depression Scale; K-BILD, King's Brief Interstitial Lung Disease; LTOT, long-term oxygen therapy; m, meters; MCID, minimal clinically important difference; MD, mean difference; №, number; s, seconds; RA, room air; SGRQ, St. George's Respiratory Questionnaire; UCSDSOBQ, The University of California, San Diego Shortness of Breath Questionnaire

* Significant at $p < 0.05$
[a] Results are based off only one study.
[b] Risk of bias present due to absence of allocation concealment.
[c] High risk of bias present in observational studies.

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PICO 5 Forest Plots

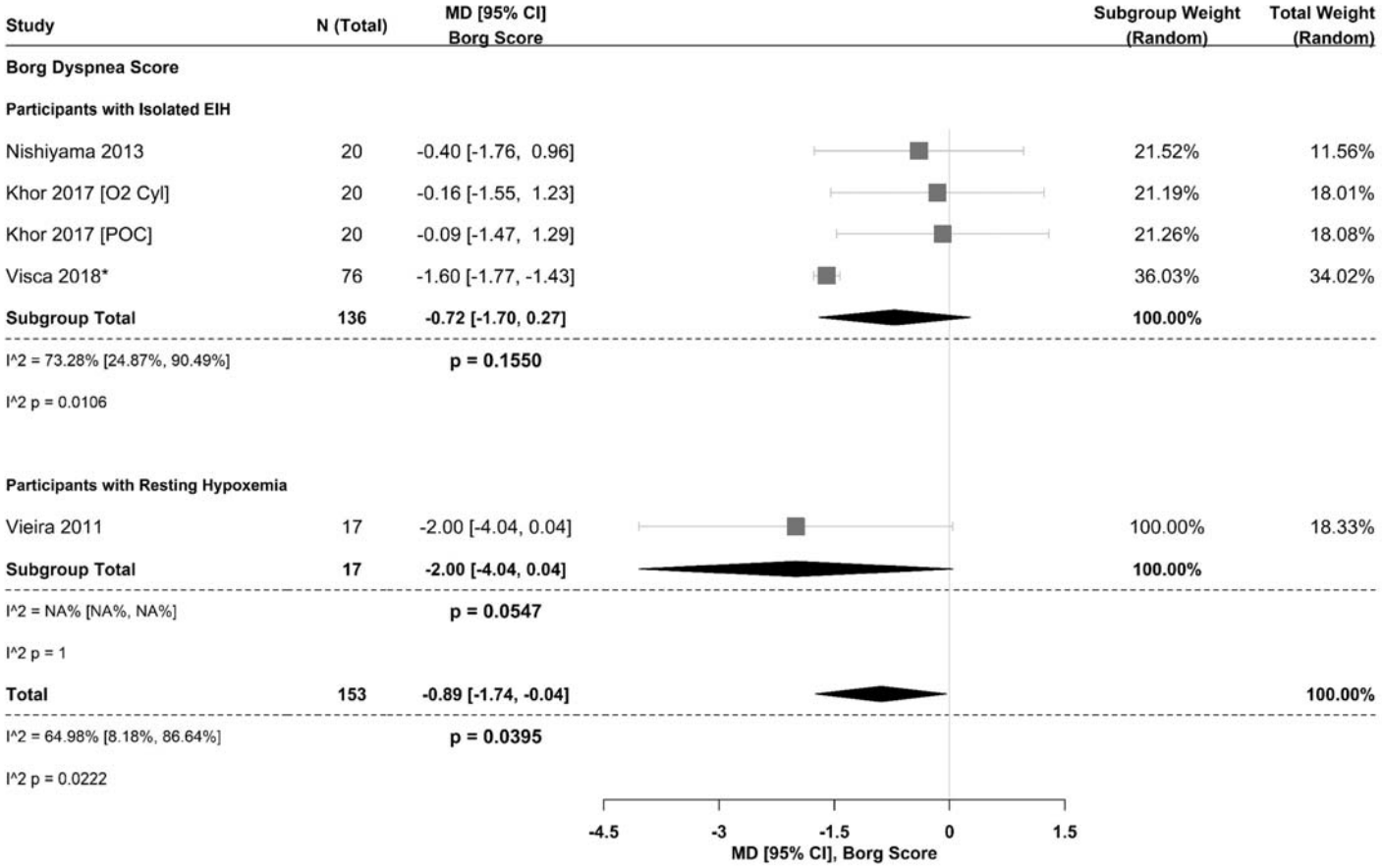

Figure E4: Mean difference in Borg dyspnea score in ILD patients with exertional desaturation receiving ambulatory oxygen vs. control

Note: For control groups, Khor et al Vieira et al, and Visca et al use room air, and Nishiyama et al use compressed air.

Abbreviations: CI, confidence interval; EIH, exercise induced hypoxemia; ILD, interstitial lung disease; LTOT, long-term oxygen therapy; MD, mean difference; N, number; O_2 cyl, oxygen cylinder; POC, portable oxygen cylinder.

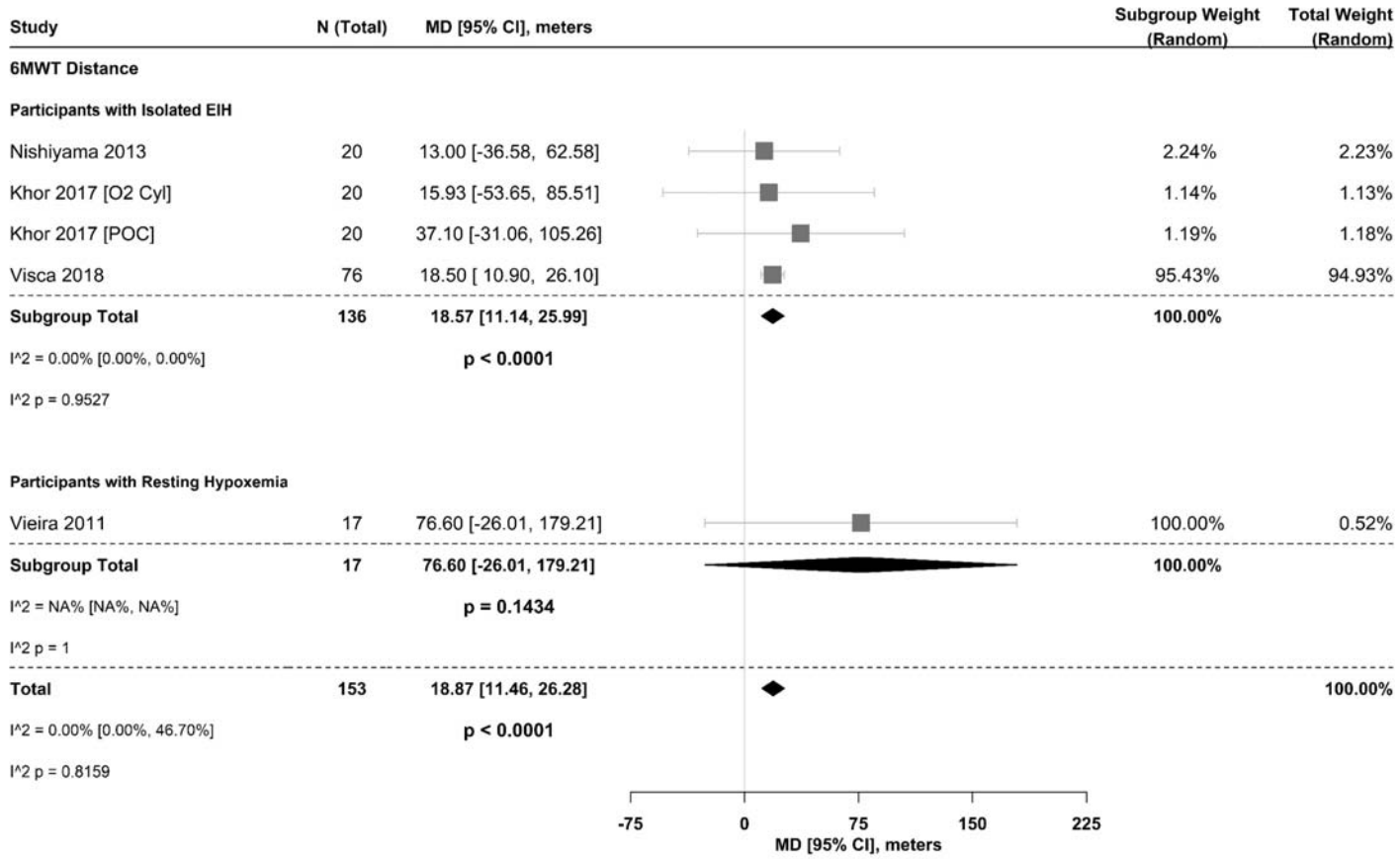

Figure E5: Mean difference in 6MWT distance (meters) in ILD patients with exertional desaturation receiving ambulatory oxygen vs. control

Note: For control groups, Khor et al, Vieira et and Visca et al use room air, whereas Nishiyama et al use compressed air.

Abbreviations: 6MWT, 6-Minute Walk Test; CI, confidence interval; EIH, exercise induced hypoxemia; ILD, interstitial lung disease; MD, mean difference; N, number; O_2 cyl, oxygen cylinder; POC, portable oxygen cylinder.

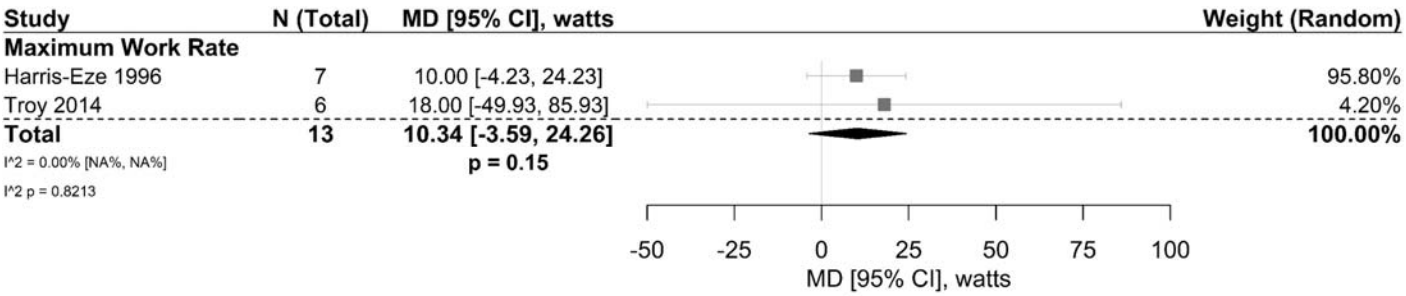

Figure E6: Mean difference in maximum work rate in ILD patients with exertional desaturation receiving ambulatory oxygen vs. control

Abbreviations: CI, confidence interval; ILD, interstitial lung disease; MD, mean difference; N, number.

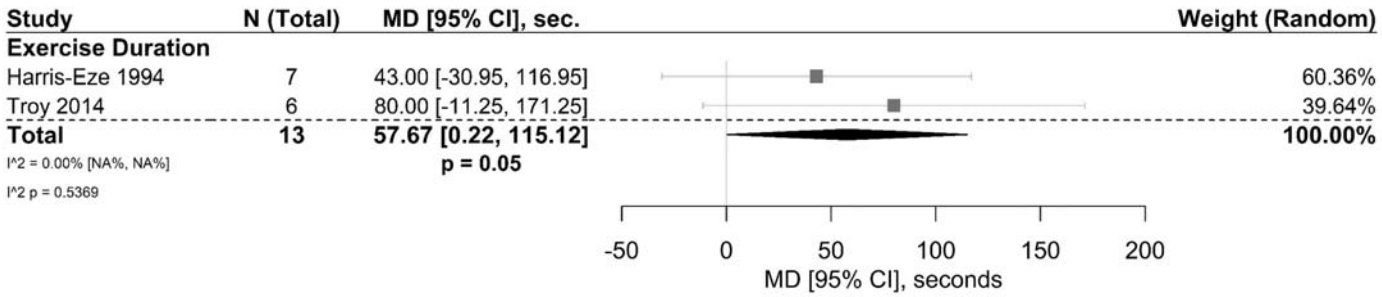

Figure E7: Mean difference in exercise duration in ILD patients with exertional desaturation receiving ambulatory oxygen vs. control

Abbreviations: CI, confidence interval; ILD, interstitial lung disease; MD, mean difference; N, number

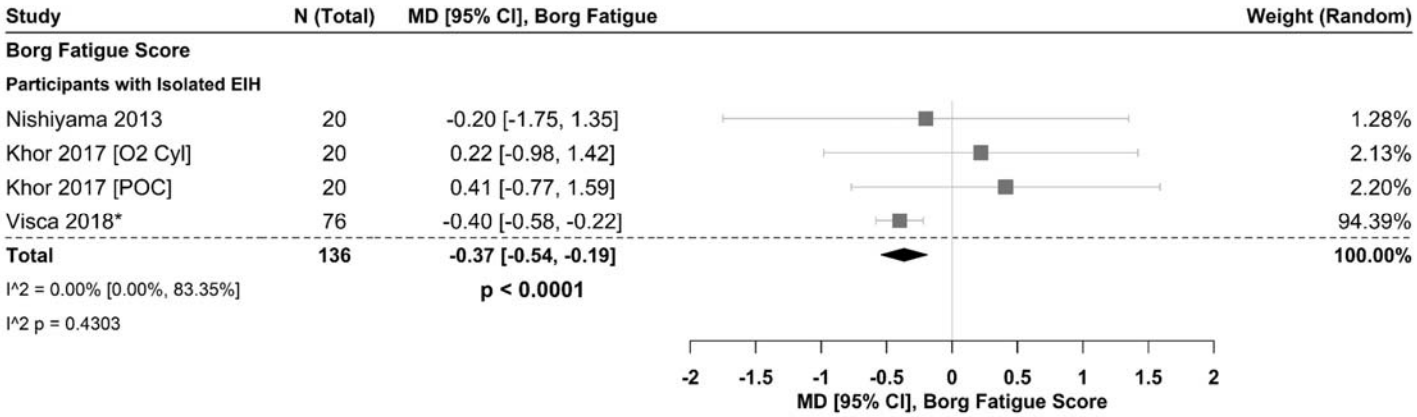

Figure E8: Mean difference in Borg fatigue score in ILD patients with exertional desaturation receiving ambulatory oxygen vs. control

Notes: For control groups, Khor et al and Visca et al use room air, and Nishiyama et al {Nishiyama, 2013 #62} use compressed air . All participants had isolated exertional desaturation.

MCID for Borg Fatigue Score is approximately 1 unit

Abbreviations: CI, confidence interval; EIH, exercise induced hypoxemia; ILD, interstitial lung disease; MCID, minimum clinically important difference; MD, mean difference; N, number; O_2 cyl, oxygen cylinder; POC, portable oxygen cylinder.

Table E7: Indirect[a] Evidence Profile for PICO 6

Question: Should portable liquid oxygen be provided for adults with chronic lung disease who are prescribed continuous oxygen flow rates of more than 3 L/min during exertion?

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Quality of Life										
Sickness Impact Profile (SIP) — Total Score										
1 (1)	RCT	Serious[bc]	Not serious	Serious[ad]	Not serious	None	51	Total SIP Score, ΔOC vs. ΔLOX **MD: -3.38** p = 0.018* *Note: It has been suggested that a change of 5 points on the SIP is considered to be the MCID (2).*	⊕⊕◯◯ LOW	CRITICAL
Sickness Impact Profile (SIP) — Physical Function										
1 (1)	RCT	Serious[bc]	Not serious	Serious[a]	Not serious	None	51	SIP Physical Function Total Score, ΔOC vs. ΔLOX **MD: -2.15,** p = 0.308 SIP Physical Function – Mobility Score, ΔOC vs. ΔLOX **MD: -4.57,** p = 0.043* SIP Physical Function - Body Care Score, ΔOC vs. ΔLOX **MD: -5.83,** p = 0.011* SIP Physical Function – Ambulation Score, ΔOC vs. ΔLOX **MD: -8.46,** p = 0.017* *Note: It has been suggested that a change of 5 points on the SIP is considered to be the MCID (2).*	⊕⊕◯◯ LOW	CRITICAL
Sickness Impact Profile (SIP) — Psychosocial Function										
1 (1)	RCT	Serious[bc]	Not serious	Serious[a]	Not serious	None	51	SIP Psychosocial Function Total Score, ΔOC vs. ΔLOX **MD: -2.08,** p = 0.082 SIP Psychosocial Function - Emotional Behavior Score, ΔOC vs. ΔLOX **MD: -3.13,** p = 0.135 SIP Psychosocial Function - Social Interaction Score, ΔOC vs. ΔLOX **MD: -5.27,** p = 0.023* SIP Psychosocial Function – Alertness Score, ΔOC vs. ΔLOX **MD: -3.47,** p = 0.064 SIP Psychosocial Function - Communication Score, ΔOC vs. ΔLOX **MD: -0.43,** p = 0.333	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Sickness Impact Profile (SIP) — Independent Category										
1 (1)	RCT	Serious[bc]	Not serious	Serious[a]	Not serious	None	51	SIP Independent Category - Work Score, ΔOC vs. ΔLOX **MD: -1.27,** p = 0.416 SIP Independent Category - Sleep Score, ΔOC vs. ΔLOX **MD: -4.18,** p = 0.150 SIP Independent Category - Eating Score, ΔOC vs. ΔLOX **MD: -0.66,** p = 0.276 SIP Independent Category - Home Management Score ΔOC vs. ΔLOX **MD: -3.97,** p = 0.230 SIP Independent Category - Recreation Score, ΔOC vs. ΔLOX **MD: -7.84,** p = 0.065	⨁⨁◯◯ LOW	CRITICAL
EuroQol										
1 (1)	RCT	Serious[bc]	Not serious	Serious[a]	Not serious	None	51	EuroQol Mobility Score, ΔOC vs. ΔLOX **MD: -0.04,** p = 0.394 EuroQol Self-Care Score, ΔOC vs. ΔLOX **MD: 0.00,** p = 0.110 EuroQol Usual Activity Score, ΔOC vs. ΔLOX **MD: 0.17,** p = 0.298 EuroQol Pain/Discomfort Score, ΔOC vs. ΔLOX **MD: -0.21,** p = 0.069 EuroQol Anxiety/Depression Score, ΔOC vs. ΔLOX **MD: -0.18,** p = 0.061 EuroQol Better/Worse Score, ΔOC vs. ΔLOX **MD: -0.12,** p = 0.185 EuroQol Scale Score, ΔOC vs. ΔLOX **MD: 2.88,** p = 0.217	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Exercise Capacity										
Oxygen Saturation During 6 Minute Walk Test (6MWT)										
2 (3, 4)	RCT	Serious[b]	Serious[e]	Serious[af]	Not serious	Strickland (3) compared LOX vs. 2 POCs and O_2 cylinder, Nasilowski (4) compared LOX vs. POC	52	SpO_2, Pre – Post-6MWT, LOX vs Other Oxygen Devices (%) **MD: 0.55** (-0.89 to 2.00)	⨁◯◯◯ VERY LOW	IMPORTANT
Percent of Time Spent in Desaturation (SpO_2 < 88%) During 6MWT										
1 (4)	RCT	Serious[b]	Serious[e]	Serious[a]	Not serious	None	13	Percent of 6MWT Time Spent in Desaturation (SpO_2 < 88%), LOX vs, POC (%) **MD: 12.00** (-11.83 to 35.83)	⨁◯◯◯ VERY LOW	IMPORTANT
Oxygen Saturation During 2 Minute Walk Test (2MWT)										
1 (5)	Observational	Serious[g]	Serious[e]	Serious[a]	Not serious	Serious[hi]	70	2MWT Exercise SpO_2, LOX vs POC **MD: -0.40** (-3.08 to 2.28)	⨁◯◯◯ VERY LOW	IMPORTANT
Borg Score										
Borg Exercise Score from 2 Minute Walk Test (2MWT)										
1 (5)	Observational	Serious[g]	Serious[e]	Serious[a]	Not serious	Serious[hi]	70	2MWT Exercise Borg Score, LOX vs. POC **MD: -0.40** (-1.36 to 0.56)	⨁◯◯◯ VERY LOW	IMPORTANT
Dyspnea										
Borg Dyspnea Score from 6MWT										
1 (4)	RCT	Serious[b]	Serious[e]	Serious[a]	Not serious	None	13	End-6MWT Borg Dyspnea Score, LOX – POC **MD: -0.10** (-1.23 to 1.03)	⨁◯◯◯ VERY LOW	IMPORTANT
Adherence										
Hours O_2 Used per Week										
1 (6)	RCT	Not serious	Serious[e]	Serious[a]	Not serious	None	15	Hours O_2 Used per Week, LOX vs. GO (hrs/wk) **MD: 10.0** (4.2 to 23.3)*	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Hours O_2 Used per Day										
1 (7)	RCT	Unclear[b]	Serious[e]	Serious[a]	Not serious	None	84	Duration of LOX vs. GO (hrs/day) **MD: 0.6**, p>0.05	⨁◯◯◯ VERY LOW	IMPORTANT
1 (5)	Observational	Serious[g]	Serious[e]	Serious[a]	Not serious	Serious[h]	144	Oxygen Usage (hrs/day), LOX vs. POC **MD: 6.50** (4.43 to 8.57)*	⨁◯◯◯ VERY LOW	IMPORTANT
Hours per Week Spent Using O_2 Concentrator										
1 (6)	RCT	Not serious	Serious[e]	Serious[a]	Not serious	None	15	Hours Per Week Spent Using O_2 Concentrator, GO vs. LO **Median Difference: 13.1** (1.57 to 27.92)*	⨁⨁◯◯ LOW	IMPORTANT
Physical Activity										
Hours Spent Outside										
1 (6)	RCT	Not serious	Serious[e]	Serious[a]	Not serious	None	15	Median Difference in Hours Spent Outside, LOX vs. GO (hrs/wk) **Median Difference: 4.0** (0.9 to 7.1)*	⨁⨁◯◯ LOW	IMPORTANT
1 (5)	Observational	Serious[g]	Serious[e]	Serious[a]	Not serious	Serious[h]	144	Percent of Group Spending No Time Outdoors, LOX vs. POC **MD: -1.4%** Percent of Group Spending < 4 hrs/day Outdoors, LOX vs. POC **MD: -17.1%** Percent of Group Spending 4 - 8 hrs/day Outdoors, LOX vs. POC **MD: 17.1%** Percent of Group Spending 8 - 12 hrs/day Outdoors, LOX vs. POC **MD: 1.4%**	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients	Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Outings per Week										
1 (5)	Observational	Serious[g]	Serious[e]	Serious[a]	Not serious	Serious[h]	144	Outings Frequency (times/wk) 0-1, Percent of Group, LOX vs. POC **MD: -32.3%** p < 0.001* Outings Frequency (times/wk) 2-3, Percent of Group, LOX vs. POC **MD: -1.8%,** p = 0.804 Outings Frequency (times/wk) 4-6, Percent of Group, LOX vs. POC **MD: 8.6%,** p = 0.245 Outings Frequency (times/wk) 7-9, Percent of Group, LOX vs. POC **MD: 7.4%,** p = 0.158 Outings Frequency (times/wk) 10+, Percent of Group, LOX vs. POC **MD: 14.5%,** p = 0.012*	⨁◯◯◯ VERY LOW	IMPORTANT

Abbreviations**:** 2MWT, two-minute walk test; 6MWT, six-minute walk test; CI, confidence interval; D., difference; GO, gaseous oxygen; hrs, hours; hrs/wk, hours per week; LOX, liquid oxygen; MD, mean difference; O_2, oxygen; OC, oxygen concentrator; POC, portable oxygen concentrator; RCT, randomized controlled trial; SIP, sickness impact profile; SpO_2, peripheral capillary oxygen saturation; wk, week

*Significant at $p < 0.05$

[a] Studies included in this section do not meet the 3 L/min prescription requirement but meet all other PICO requirements.
[b] Randomization method not discussed.
[c] Intervention and control were not concealed.
[d] This study compares LOx users to those using a stationary OC plus portable cylinders, where 92% use a fixed OC and only 8% used theportable cylinders. Due to the nature of this control group, there is a potential for confounding in the results, but this is also a form of indirect evidence for our research question.
[e] Results based off of only one study.
[f] The subjects in Strickland et al were not tested on continuous-flow oxygen; only pulse-dose flow was used for the purposes of this study.
[g] Observational study, no randomization or blinding performed.
[h] Study did not have access to data on the patients' initial arterial blood gas analysis; presumed that all our participants met the criteria for long-term oxygen therapy.
[i] 2MWT does not test the real-life tolerability of oxygen devices for portability and ambulatory design.

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EVIDENCE-TO-DECISION FRAMEWORKS

Table E8: Evidence-to-Decision (EtD) framework for PICOs 1 to 3

Problem **Is the problem a priority?**		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Hypoxemia in patients has a variety of negative health effects on patients, including pulmonary hypertension, systemic inflammation, skeletal muscle dysfunction, and neurocognitive dysfunction, and right ventricular failure, among others (1). Hypoxemia risk increases as severity of COPD increases. The WHO estimates that, globally, 65 million people have moderate to severe COPD, and COPD accounted for 5% of all deaths globally in 2005 (2). In the US alone, there are approximately 16 million people diagnosed with COPD (3), and the trend of deaths from COPD rose from 119,524 in 1999 to 133,965 in 2009. The COPD-related age-adjusted death rate per 100,000 people in 2009 was 41.2 (and was noticeably higher in males at 48.6 vs. females at 36.6) (4).	The impact of other lung diseases along with COPD, such as ILD, must also be considered.
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Hypoxemia risk increases as COPD severity increases. Most clinical guidelines make recommendations for patients with severe resting or exertional hypoxemia, but moderate hypoxemia is rarely mentioned, unless patient has cor pulmonale.	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Although COPD patients with severe exertional room air hypoxemia do not suffer the health effects of hypoxemia at all times, they do have reduced activity and increased overall disability due to their severe exertional desaturations with ambulation.	
Desirable Effects		

How substantial are the desirable anticipated effects?		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	LTOT was associated with decreased 2-year (LTOT prescribed 24 hours/day vs. nocturnal only) and 5-year mortality (LTOT prescribed at least 15 hours/day vs. no LTOT) (critical outcome). Dyspnea was found to decrease with LTOT when compared to controls. Health care utilization (including number of hospitalizations, risk of admission, and length of stay) trended towards a decrease with LTOT, although no statistically significant results were found. Analysis of exercise capacity, measured via the 6MWT, showed improvement in distance walked and a decrease in length of time stopped. Results from the BODE Index, a composite scale that measures but does delineate factors such as quality of life and exercise capacity, found an improvement in scores when patients began receiving LTOT vs. before they began receiving LTOT.	It is worth noting that the quality of life questionnaires may not appropriately capture the patient experience. It may be too generic or unclear for patients how they should answer. For example, should the answers encompass the last 48 hours, last several days, on oxygen, or off oxygen? Additionally, treatment modalities and the demographics of the disease have changed over the last 35 years so size of desirable effects may be at different time points.
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Currently, there is only one study, known as the Long-Term Oxygen Treatment Trial (LOTT) (5) that assesses LTOT in COPD patients with moderate resting room air hypoxemia (SpO_2 89 to 93%). The study also assesses patients with moderate exertional hypoxemia only and patients with both moderate resting and exertional hypoxemia. Only the outcome of time to first all-cause death or hospitalizations reported separately for participants with resting room air hypoxemia. The authors found no significant difference between those receiving LTOT and those on room air in participants with moderate resting hypoxemia (HR: 0.96, 95% CI: 0.63, 1.47), moderate resting and exertional hypoxemia (HR: 0.95, 95% CI: 0.72, 1.27), and the combined population of those with moderate resting or moderate resting plus exertional hypoxemia (HR: 0.95, 95% CI: 0.75, 1.21). We reached out to the authors of LOTT (5) to obtain additional data pertaining to mortality and quality of life. No difference was found in time to death for those with only moderate resting hypoxemia or with both moderate resting and exertional hypoxemia. Quality of life, measured through the St. George's Respiratory Questionnaire (SGRQ) favored the use of LTOT at four-month follow-up versus baseline in those with both moderate resting and exertional desaturation (MD: -3.30, 95% CI: -6.50, -0.10). A follow-up study to LOTT was recently published, and they found that readiness, confidence, and importance to use LTOT at initiation significantly improved adherence (6).	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*For patients on or eligible for LTOT:* Ambulatory oxygen in patients who are already on or eligible for LTOT significantly reduced the Visual Analog Score during an exercise test (control group used compressed air), increased the distance walked in the increment shuttle walk test (control group were on room air), increased the distance walked over 12 minutes when not carrying a walker (control group used room air), and improved endurance time to symptom-limited peak exercise (control group used room air). Mortality risks of ambulatory oxygen versus controls were not reported in the literature. Physical activity in daily life was not reported.	As mentioned before, the quality of life questionnaires may not appropriately capture the patient experience. Additionally, treatment modalities and the demographics of the disease have changed over the last 35 years so size of desirable effects may be more or less at different time points. It is also important to consider that the effect size for dyspnea may be underestimated, since the majority of these studies do not measure dyspnea at peak exertion (isotime).
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*For patients with isolated exercise-induced hypoxemia (EIH):* For COPD patients with isolated EIH, ambulatory oxygen did not result in a significant change in HRQL measured by the CRQ, SGRQ, or the SF-36 (all moderate GRADE). Exercise capacity was improved in the 5MWT (number of steps and endurance time) and 6MWT (distance walked). Time to exercise intolerance was also improved, along with work (watts) and endurance time measured through CPET. No significant change was found in the Borg Dyspnea score during an exercise test. Readiness, confidence, and self-reported importance to use oxygen at initiation improved adherence to oxygen therapy.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

QUESTIONS 1 & 2 LTOT FOR COPD PATIENTS WITH SEVERE & MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is a substantial body of evidence showing that patients report inconvenience of using LTOT: reduced ability to travel outside of the home if not eligible for AO, fear of cylinders running out, equipment noise that may affect sleep, and accessing information about appropriate use of oxygen equipment (7, 8). There are also reported cases of fires, burns from smoking around oxygen equipment, nosebleeds, and tripping over the equipment (5).	

QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is a substantial body of evidence showing that patients report inconvenience of using AO: weight of equipment, being embarrassed using it outside the home, fear of cylinders running out, reduced ability to travel outside the home, equipment noise that may affect sleep, difficulty obtaining portable oxygen concentrators, and accessing information about appropriate use of oxygen equipment (7, 8). There are also reported cases of fires, burns from smoking around oxygen equipment, nosebleeds, and tripping over the equipment,	

	though the latter concerns are primarily applicable to LTOT users and not necessarily ambulatory oxygen users (5).	

Certainty of Evidence What is the overall certainty of the evidence of effects?		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The studies are quite heterogenous in their methods, as some prescribed LTOT 24 hours/day or at least 15 hours/day, and controls included nocturnal LTOT, room air, or cylinder air as a control group. Several outcomes of interest are not reported on, and most studies had very small sample sizes. However, for the critical outcome of mortality, we have moderate certainty about the evidence supporting benefits of LTOT. Additionally, most studies are unblinded due to the nature of oxygen use via tanks. The NOTT (9) and MRC (10) included smokers, there is no evidence that LTOT is not effective in smokers, but does increase risk of AE's.	
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	There is only one RCT that reports on the effects of LTOT in patients with moderate resting desaturation, defined as PaO_2 of 56 to 60 mmHg/7.5-8.0 kPa or SpO_2 of 89 to 93%. We only have data available for time to mortality or first hospitalization from the study, but we reached out to the authors and were able to obtain data on time to death and quality of life. While each outcome is from this one study, the sample size is sufficient.	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The studies are quite heterogeneous in their methods, as some use room air as their control group, while others use cylinder air as a placebo. Several outcomes of interest are not reported on, and most studies had very small sample sizes. Most studies report the acute effects of oxygen during exercise tests, rather than its effects during use in daily life. However, for our critical outcome of quality-of-life, we had moderate GRADE quality of evidence for both subgroups of patients on/eligible for LTOT and those with isolated exertional desaturation.	The majority of evidence is based off of lab tests and not indicative of activities of daily living, resulting in the evidence on physical activity being downgraded for indirectness.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The critical outcome for this question is mortality for which there is some variability, depending on the patient's severity of illness. Some patients may not experience any value added on additional life years if they are very ill.	
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The critical outcome for this question is mortality for which there is some variability, depending on the patient's severity of illness. Some patients may not experience any value added on additional life years if they are very ill. However, this is less likely in patients with moderate hypoxemia, as they tend to have less severe COPD than those with severe resting hypoxemia.	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The critical outcome for this question is quality of life, for which there is little variability on values.	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Most of the evidence favors the use of supplemental oxygen in adults with COPD who have severe resting room air hypoxemia, though the undesirable effects may be particularly bothersome for some patients, particularly for ambulatory oxygen.	
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is currently no evidence to support the use of LTOT in COPD patients with moderate resting hypoxemia, and there are potential undesirable effects of therapy.	The panel felt it worth noting that areas needing further evaluation include reevaluation and reassessment of oxygen needs of patients over time, incorporating shared decision making with patients regarding changes to therapy, and considering stoppage of therapy if no longer needed
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The weak evidence for the use of ambulatory oxygen in COPD patients with isolated severe exertional hypoxemia is complicated by the potential undesirable effects of the therapy.	

Resources required How large are the resource requirements (costs)?		
QUESTIONS 1 & 2 LTOT FOR COPD PATIENTS WITH SEVERE & MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	According to a 2012 study published by Health Quality Ontario (HQO), the average cost per patient to the Ministry of Health in Canada for supplying LTOT (in 2007, the last reported year) was approximately $2,261 CAD; this is nearly a 19% (or ~2.1% per year) decrease from the first reported year (1997), where the cost was $2,780 CAD (11). There appears to be a significant downward trend in the cost of providing oxygen therapy as technology and delivery methods advance. The total cost per patient of LTOT in the US in 1993 was approximately $2,273 (~$1.4 billion across 616,000 patients), though some estimates projected as high as $4,870 ($3 billion across 616,000 patients) (12). Assuming a similar cost reduction rate per year as observed by HQO, the US cost per patient in 2007 would have been between $1,691 and $3,624. While LTOT is generally covered by Medicare, coverage does not include support service costs (which can vary depending on patient needs) or patient out of pocket costs, such as electricity of portable concentrators, building of ramps, or inhalers and nebulizers.	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	New ambulatory oxygen devices are quite expensive, resulting in higher out of pocket costs for patients, particularly if devices such as concentrators are not covered. In recent years, Medicare has reduced these costs to patients, but the ambulatory oxygen devices available may not be appropriate for patient needs, particularly in ILD patients, who may require higher flow rates than COPD patients. Additionally, coverage does not include support service costs (which can vary depending on patient needs) or patient out of pocket costs, such as electricity of portable concentrators, building of ramps, or inhalers and nebulizers.	The panel noted that it is prudent to ensure that the appropriate ambulatory oxygen devices are prescribed to patients based on their needs.
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
QUESTIONS 1 & 2 LTOT FOR COPD PATIENTS WITH SEVERE & MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate	Given the variability in reimbursement rates for medical expenses in the US, it is difficult to project the true cost per person for LTOT. In the US, Medicare typically covers 80% of the Medicare-approved amount (the amount changed by the doctor or supplier assigned) (13). However, costs may vary depending on patient insurance.	

○ High ○ No included studies		
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Given the variability in reimbursement rates for medical expenses in the US, it is difficult to project the true cost per person for AO. In the US, Medicare typically covers 80% of the Medicare-approved amount (the amount changed by the doctor or supplier assigned) (13). However, coverage for ambulatory oxygen may not be applicable to appropriate devices for patients' needs. There is uncertainty in the evidence regarding the resources to provide the best treatment in ILD patients, as they tend to require higher flow rates than COPD patients.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The incremental cost-effectiveness ratio for LTOT is $16,124 per quality-adjusted life-year (QALY) in the United States, and this is within bounds considered to be cost-effective (14). Note that cost variables were based on the Medicare reimbursement rate for the 2009 published study and on appropriate sources (14).	
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There is no evidence regarding cost effectiveness for oxygen for moderate hypoxemia, but the effectiveness outcomes do not favor the intervention.	

QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There is no evidence regarding cost effectiveness for ambulatory oxygen, and the costs vary significantly among types of portable systems,	
Equity **What would be the impact on health equity?**		
QUESTIONS 1 & 2 LTOT FOR COPD PATIENTS WITH SEVERE & MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Oxygen therapy in the past was often cost-prohibitive (and in some cases, continues to be today) and thus not available to all patients who could benefit from it. Programs that reduce the cost of oxygen therapy to the patient could increase availability to patients of lower socioeconomic status and thus increase their quality of life (15), and many such programs require or at least consider the recommendations and guidelines of various organizations to obtain or increase funding.	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Due to the high cost and lack of availability of ambulatory oxygen (particularly in some parts of the world), patients often do not have access to this equipment, which prevents them from leaving the home and even working. In addition, because of variable funding criteria across health regions as well as frequent discrepancies among guideline recommendations (particularly with that constitutes “severe” exertional hypoxemia) (16, 17), there is confusion among patients and healthcare providers, which indicates that updated guidelines from major organizations would increase health equity by providing clear and consistent recommendations (18).	

Acceptability **Is the intervention acceptable to key stakeholders?**		
QUESTION 1: LTOT FOR COPD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	LTOT is generally recognized as an approved and recommended therapy for patients with COPD exhibiting hypoxemia, particularly if it is severe at rest. This recommendation is included in guidelines from major organizations, including the BTS (19) and combined statement from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and the European Respiratory Society (20), and GOLD (21). However, studies have shown that patient-level adherence to LTOT is often incomplete.	
QUESTION 2: LTOT FOR COPD PATIENTS WITH MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Only one guideline was found that makes recommendations on regarding the use of LTOT in patients with moderate resting desaturation. The 2019 GOLD guidelines state, "In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. However, individual patient factors must be considered when evaluating the patient's need for supplemental oxygen" (21). The LOTT trial found that readiness, confidence, and importance to use LTOT at initiation are significantly associated with long-term oxygen adherence (5).	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	A 2015 guideline by the British Thoracic Society (BTS) on home oxygen use states that ambulatory oxygen should *not* be routinely offered to patients without chronic hypoxemia at rest or not eligible for LTOT. Further, they state that ambulatory oxygen *not* be routinely offered to patients who are already on LTOT (19). This is because despite the evidence on the benefits of ambulatory oxygen in patients who desaturate during exercise, regardless of their hypoxemia status at rest, the panel argues that there is limited data on whether these benefits outweigh the practical difficulties associated with ambulatory oxygen on a daily basis. Regional criteria for funding supplemental oxygen are heterogeneous, with many areas not funding those with exertional desaturation at all. Studies have found that some patients (even those with an acute response who saw benefits) specifically did not want to be considered for the clinical provision of ambulatory oxygen, citing poor acceptability or tolerability (22-24).	

Feasibility Is the intervention feasible to implement?		
QUESTIONS 1 & 2 LTOT FOR COPD PATIENTS WITH SEVERE & MODERATE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**JUDGEMENT**	**JUDGEMENT**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	While oxygen is generally available, the main barrier that remains is the cost of oxygen therapy. Additionally, depending on the region, reimbursement costs can vary, particularly due to the requirements that must be met for funding (16, 17).	
QUESTION 3: AMBULATORY OXYGEN FOR COPD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Funding for ambulatory oxygen is either not available in cases of isolated exertional hypoxemia, or patients may have considerable out-of-pocket costs before any insurance coverage might apply (8). Additionally, depending on the region, reimbursement costs can vary, particularly due to the requirements that must be met for funding (16, 17). In the US, oxygen is reimbursed on a prospective payment basis by The Center for Medicare and Medicaid Services (CMS), with no requirement concerning the type of equipment being provided (oxygen and oxygen delivery equipment are considered “durable medical equipment” and are reimbursed as medical equipment at 80% of the allowable charge once the applicable forms have been filled out by the clinician, with the remaining 20% being covered by supplemental insurance or the patient). CMS considers all oxygen delivery systems to be equal and modality-neutral for the purpose of reimbursement. For patients requiring ambulatory oxygen, a small additional reimbursement for a portable add-on device is available, if ordered by the clinician (25). It is important to note that within these guidelines, it is the clinician's responsibility to be involved in selection of appropriate equipment and provision of an individualized prescription.	

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Table E9: Evidence-to-Decision (EtD) framework for PICOs 4 and 5

Problem **Is the problem a priority?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Hypoxemia in patients have a variety of negative health effects on patients, including dyspnea (both at rest and exertional), pulmonary hypertension, systemic inflammation, skeletal muscle dysfunction, and neurocognitive dysfunction, and right ventricular failure, among others (1). Hypoxemia risk increase as severity of ILD increases.	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Although ILD patients with severe exertional room air hypoxemia do not suffer the health effects of hypoxemia at all times, they do have reduced activity and increased overall disability due to their severe exertional desaturations with ambulation.	

Desirable Effects **How substantial are the desirable anticipated effects?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Only one unpublished RCT was found on ILD, and no statistically significant difference was observed between the LTOT and RA groups. Consequently, we referred to the evidence from COPD (PICO 1). In PICO 1, for COPD patients with severe resting room air hypoxemia, we found 14 studies reporting on several different outcomes: Mortality: A significant decrease in mortality was observed at 2 years and 5 years, with LTOT prescribed at least 15 hours per day. There was no significant difference in mortality between women and men at 1 and 5 years. Mortality was reduced with LTOT in those with high levels of mood disturbance, as measured by POMS, but no significant association was observed between mortality risk and SGRQ. Dyspnea: While no evidence was found on whether LTOT impacted dyspnea severity, dyspnea (measured using BDI) was found to be a predictor of mortality in LTOT patients. Composite Index: A significant decrease in the BODE Index was observed with LTOT. And finally, health care utilization (including number of hospitalizations, risk of admission, and length of stay) trended towards a decrease with LTOT, although no statistically significant results were found. It is important to note that the variability in control groups across studies, with some of them using compressed air as a sham device, which may affect the observed difference in outcomes across studies.	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
For participants with isolated exertional desaturation: ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*For participants with isolated exertional desaturation:* Quality of life: AO was found to improve our critical outcome of HRQOL, measured through the K-BILD and SGRQ, and the majority of participants were found to want to continue using AO after the study. Dyspnea: No significant difference was observed in dyspnea, measured with the Borg Dyspnea Score or UCSDSOBQ, although a significant improvement in the Borg fatigue score was seen Exercise capacity: AO improved the distance walked in the 6MWT, but no significant change in the distance walked with the ESWT. Significant improvements in maximal work rate and exercise duration were observed with the incremental bicycle ergometer exercise test, but no difference was found in endurance time measured through CPET. It is important to note that the evidence available on exercise capacity are lab tests and not indicative of activities of daily living.	The panel discussed that while no significant differences were observed in the outcome of dyspnea, an RCT by Schaffer et al found that while dyspnea did not differ during exertion did between groups, there was a significant drop at isotime (2). The panel cited Ekstrom et al, recommending that standardization of level of exertion is necessary to assess effects of oxygen on dyspnea,

For participants with resting hypoxemia: ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*For participants with resting hypoxemia:* While no direct evidence is available for our critical outcome of interest of quality of life for participants who have resting hypoxemia, we can make inferences from the evidence available on patients with isolated EIH. Dyspnea: No significant change in the Borg dyspnea score between AO and room air Exercise Capacity: No significant difference in 6MWT distance compared to room air	particularly when evaluating patients for AO eligibility (3).

Undesirable Effects
How substantial are the undesirable anticipated effects?

QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is a substantial body of evidence showing that patients report inconvenience of using LTOT: reduced ability to travel outside of the home if not eligible for AO, fear of cylinders running out, equipment noise that may affect sleep, and accessing information about appropriate use of oxygen equipment (4-7). There are also reported cases of fires, burns from smoking around oxygen equipment, nosebleeds, and tripping over the equipment (8).	

QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is a substantial body of evidence showing that patients report inconvenience of using AO: weight of equipment, being embarrassed using it outside the home, fear of cylinders running out, reduced ability to travel outside the home, equipment noise that may affect sleep, difficulty obtaining portable oxygen concentrators, and accessing information about appropriate use of oxygen equipment (4-7). There are also reported cases of fires, burns from smoking around oxygen equipment, nosebleeds, and tripping over the equipment, though the latter concerns are primarily applicable to LTOT users and not necessarily AO users (8).	

Certainty of Evidence What is the overall certainty of the evidence of effects?		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Only one unpublished RCT was found regarding the use of AO in ILD patients with severe resting room air hypoxemia. Consequently, the panel chose to include all of the studies on COPD patients with severe resting room air hypoxemia, and our outcomes were downgraded for indirectness.	There is a lack of direct evidence for ILD patients, but the panel noted that due to the distinct nature of ILD patients with COPD patients, there may never be an RCT appropriate for this cohort.
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Many outcomes of interest are not reported on, and several studies very small sample sizes and did not adjust for potential confounders (2). The results for most outcomes that were reported on are based only from one study, but in a few cases, we were able to pool results. Particularly with regards to exertional hypoxemia in ILD, prospective RCTs are needed to assess clinically meaningful outcomes for the prescription of ambulatory oxygen (9).	
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The critical outcome for this question is mortality for which there is some variability, depending on the patient's severity of illness. Some patients may not experience any value added on additional life years if they are very ill.	

QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The critical outcome for this question is quality of life, for which there is little variability on values.	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Due to the paucity of evidence on LTOT in patients with ILD, our results are based entirely off of indirect evidence. We included one unpublished RCT on ILD patients, as well as all of the evidence from PICO 1 pertaining to patients with COPD and severe resting room air hypoxemia. Most of the evidence from this analysis favors the use of supplemental oxygen in adults with COPD who have severe resting room air hypoxemia, including the critical outcome of interest of mortality. However, the undesirable effects may be bothersome for some patients, particularly for ambulatory oxygen.	The panel noted that the majority of evidence is based off of lab tests and not indicative of activities of daily living.
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
For participants with isolated exertional desaturation: ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	*For participants with isolated exertional desaturation:* Significant improvements were observed for our critical outcome of interest of quality of life, measured through the K-BILD and SGRQ, and the majority of participants were found to want to continue using AO after the study. However, the undesirable effects may be bothersome for some patients.	The panel noted that the majority of evidence is based off of lab tests and not indicative of activities of daily living. They also noted that standardization of level of exertion is necessary to assess effects of oxygen on dyspnea, particularly when evaluating patients for AO eligibility (3).

For participants on/eligible for LTOT: ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	*For participants on or eligible for LTOT:* For patients who are on or eligible for LTOT and exhibit exertional desaturation, AO showed no significant change in the Borg dyspnea score, Borg fatigue score, or 6MWT distance compared to room air, although limited evidence is available.	

Resources required
How large are the resource requirements (costs)?

QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	According to a 2012 study published by Health Quality Ontario (HQO), the average cost per patient to the Ministry of Health in Canada for supplying LTOT (in 2007, the last reported year) was approximately $2,261 CAD; this is nearly a 19% (or ~2.1% per year) decrease from the first reported year (1997), where the cost was $2,780 CAD (10). There appears to be a significant downward trend in the cost of providing oxygen therapy as technology and delivery methods advance. The total cost per patient of LTOT in the US in 1993 was approximately $2,273 (~$1.4 billion across 616,000 patients), though some estimates projected as high as $4,870 ($3 billion across 616,000 patients) (11). Assuming a similar cost reduction rate per year as observed by HQO, the US cost per patient in 2007 would have been between $1,691 and $3,624. While LTOT is generally covered by Medicare, coverage does not include support service costs (which can vary depending on patient needs) or patient out of pocket costs, such as electricity of portable concentrators, building of ramps, or inhalers and nebulizers.	

QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	New ambulatory oxygen devices are quite expensive, resulting in higher out of pocket costs for patients, particularly if devices such as concentrators are not covered. In recent years, Medicare has reduced these costs to patients, but the ambulatory oxygen devices available may not be appropriate for patient needs, particularly in ILD patients, who may require higher flow rates than COPD patients. Additionally, coverage does not include support service costs (which can vary depending on patient needs) or patient out of pocket costs, such as electricity of portable concentrators, building of ramps, or inhalers and nebulizers.	The panel noted that the need for high flow ambulatory devices is much higher in ILD patients than COPD patients. It is prudent to ensure that the appropriate AO devices are prescribed to patients based on their needs.

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Given the variability in reimbursement rates for medical expenses in the US, it is difficult to project the true cost per person for LTOT. In the US, Medicare typically covers 80% of the Medicare-approved amount (the amount changed by the doctor or supplier assigned) (12). However, costs may vary depending on patient insurance.	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Given the variability in reimbursement rates for medical expenses in the US, it is difficult to project the true cost per person for AO. In the US, Medicare typically covers 80% of the Medicare-approved amount (the amount changed by the doctor or supplier assigned) (12). However, coverage for AO may not be applicable to appropriate devices for patients' needs. There is uncertainty in the evidence regarding the resources to provide the best treatment in ILD patients, as they tend to require higher flow rates than COPD patients.	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	The incremental cost-effectiveness ratio for LTOT is $16,124 per quality-adjusted life-year [QALY] in the United States, and this is within bounds considered to be cost-effective (13). Note that cost variables were based on the Medicare reimbursement rate for the 2009 published study and on appropriate sources (13).	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There were no results from the searches assessing cost incremental ratios or cost effectiveness for ambulatory oxygen in addition to usual care.	
Equity **What would be the impact on health equity?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Oxygen therapy in the past was often cost-prohibitive (and in some cases, continues to be today) and thus not available to all patients who could benefit from it. Programs that reduce the cost of oxygen therapy to the patient could increase availability to patients of lower socioeconomic status and thus increase their quality of life (14), and many such programs require or at least consider the recommendations and guidelines of various organizations to obtain or increase funding.	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Due to the high cost and lack of availability of AO (particularly in some parts of the world), patients often do not have access to this equipment, which prevents them from leaving the home and even working. In addition, because of variable funding criteria across health regions as well as frequent discrepancies among guideline recommendations (particularly with that constitutes “severe” exertional hypoxemia) (15, 16), there is confusion among patients and healthcare providers, which indicates that updated guidelines from major organizations would increase health equity by providing clear and consistent recommendations (9). The ultimate goal is to raise the standard of care for ILD globally.	
Acceptability		

Is the intervention acceptable to key stakeholders?		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	LTOT is generally recognized as an approved and recommended therapy for patients with ILD exhibiting hypoxemia. This recommendation is included in statements from major organizations (17), including a joint statement from the American Thoracic Society (ATS), The European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) (18).	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A multisociety guideline provided a positive recommendation for supplemental oxygen in IPF patients who were breathless, mobile, and desaturate upon exercise (SpO2 < 90%), provided there is an improvement in exercise capacity and/or breathlessness with supplemental oxygen (17). However, the majority of international guidelines do not provide specific criteria for AO in patients with isolated exertional hypoxemia. Other studies have shown that some patients (even those with an acute response who saw benefits) specifically did not want to be considered for the clinical provision of AO, citing poor acceptability or tolerability and embarrassment from using the equipment (4-7, 19).	
Feasibility **Is the intervention feasible to implement?**		
QUESTION 4: LTOT FOR ILD PATIENTS WITH SEVERE CHRONIC RESTING ROOM AIR HYPOXEMIA		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	While oxygen is generally available, the main barrier that remains is the cost of oxygen therapy. Additionally, depending on the region, reimbursement costs can vary, particularly due to the requirements that must be met for funding (15, 16).	
QUESTION 5: AMBULATORY OXYGEN FOR ILD PATIENTS WITH SEVERE EXERTIONAL ROOM AIR HYPOXEMIA		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Funding for AO is either not available in cases of isolated exertional hypoxemia, or patients may have considerable out-of-pocket costs before any insurance coverage might apply (7). Additionally, depending on the region, reimbursement costs can vary, particularly due to the requirements that must be met for funding (15, 16). In the US, oxygen is reimbursed on a prospective payment basis by The Center for Medicare and Medicaid Services (CMS), with no requirement concerning the type of equipment being provided (oxygen and oxygen delivery equipment are considered "durable medical equipment" and are reimbursed as medical equipment at 80% of the allowable charge once the applicable forms have been filled out by the clinician, with the remaining 20% being covered by supplemental insurance or the patient). CMS considers all oxygen delivery systems to be equal and modality-neutral for the purpose of reimbursement. For patients requiring AO, a small additional reimbursement for a portable add-on device is available, if ordered by the clinician (20). It is important to note that within these guidelines, it is the clinician's responsibility to be involved in selection of appropriate equipment and provision of an individualized prescription.	

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Table E10: Evidence-to-Decision (EtD) framework for PICO 6

Problem **Is the problem a priority?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with chronic lung disease may be able to spend more time outside of the home, thereby improving quality of life and enhancing rehabilitation, if they had a longer duration of oxygen supply. Liquid oxygen (LOX) takes up less space and is much lighter than a standard oxygen cylinder. Therefore, portable LOX may benefit patients who are mobile and require more than 3 L/min of continuous flow.	Some patients requiring higher flow rates may be unable to leave the house because either they need multiple, heavy compressed gas cylinders, or they are unable to physically manage them.
Desirable Effects **How substantial are the desirable anticipated effects?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The literature search did not yield any studies that met our inclusion criteria, where patients are prescribed continuous oxygen flow rates of more than 3 L/min during exertion. Most studies do not report the prescribed flow rates; rather, they report the average flow rate of their cohort. Due to the absence of any other form of evidence, we synthesized the literature for these studies, downgrading for indirectness. In this synthesis, six studies (1-6) were included as forms of indirect evidence for our research question. Five of those studies tested subjects on continuous-flow liquid oxygen (LOX) (1-5), while one study by Strickland et al (6) used pulse-flow oxygen. Strickland et al measured patient preferences for portable oxygen devices, and found that very few preferred aluminum oxygen cylinders, and most of their patients preferred liquid oxygen (6). For the outcome of Health-Related Quality of Life (HRQoL), there were significant improvements in the body care, ambulation, and social interaction domains of the SIP score. A general trend of improvement in HRQoL was shown in the LOX group versus oxygen cylinder group (1).	
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	In regard to safety, the following were reported for adverse events related to supplemental oxygen use (all in 100 person-years): 0.08 fires, 0.12 burns from smoking around oxygen equipment, 0.04 burns from using oxygen around open flame, 0.16 burns from liquid oxygen frost, 0.35 nosebleeds, and 0.90 falls from tripping over oxygen equipment. In total, 8.6% of supplemental oxygen users reported at least 1 adverse event (7). However, this is a summary for all types of oxygen devices, and not specific to LOX with the exception of burns.	Use of LOX requires manual ability to fill portable tanks from a large reservoir, which is not required compared to other portable oxygen devices.

Certainty of Evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Several outcomes of interest are not reported on, and many studies had very small sample sizes or substantial confounding. In terms of our critical outcome of interest, HRQoL, the evidence was quite variable, with only some domains of SIP favoring the use of liquid oxygen versus oxygen cylinders, but no domain of EuroQol showed a difference. Most importantly, as the literature search did not yield any studies that met our inclusion criteria, we downgraded the certainty of our evidence due to indirectness. Additionally, there is the potential of confounding, as the disease severity of the control group in one of the studies reporting on the frequency of participation in activities outside of the home is not comparable to the LOX group.	
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The critical outcome of interest is Health-Related Quality of Life; there is little uncertainty and/or variability that people want increased quality of life if it is available.	
Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	In terms of our critical outcome of health-related quality of life, the evidence shows significant improvements in the body care, ambulation, and social interaction domains of the SIP score, but no changes in the EuroQol scores. No difference in oxygen saturation in the 6MWT and 2MWT was observed, along with the distance walked in the 6MWT. No significant difference was observed in the Borg dyspnea score as well. However, LOX showed better adherence when compared to both GO and POC, and LOX users may spend more time outside and go on more outings per week. Users also preferred LOX versus other portable oxygen devices when asked on a questionnaire, but their flow rates ranged from 1 to 3 L/min.	It is important to consider individual characteristics of the patient and his/her lifestyle. LOX would benefit patients who require or need oxygen for a longer duration outside of the home, and at higher flow rates, compared to those who spend less time out of the home.

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	According to a 2012 study published by Health Quality Ontario (HQO), the average cost per patient to the Ministry of Health in Canada for supplying LTOT (in 2007, the last reported year) was approximately $2,261 CAD; this is nearly a 19% (or ~2.1% per year) decrease from the first reported year (1997), where the cost was $2,780 CAD (8). There appears to be a significant downward trend in the cost of providing oxygen therapy as technology and delivery methods advance, but this may be attributed due to the overall decrease in use of LOX. In the US, the 10-fold reduction in the number of Medicare recipients receiving portable LOX has been largely attributed to the competitive bidding program, which was intended to reduce the cost of home medical equipment and services, but it has also caused providers to phase out LOX because they cannot pass the high cost of LOX to Medicare or the consumers (9). The total cost per patient of LTOT in the US in 1993 was approximately $2,273 (~$1.4 billion across 616,000 patients), though some estimates projected as high as $4,870 ($3 billion across 616,000 patients) (10). Assuming a similar cost reduction rate per year as observed by HQO, the US cost per patient in 2007 would have been between $1,691 and $3,624. As of now, portable gaseous oxygen and LOX are combined into one payment class by CMS. While CMS is in the midst of splitting it and adding a class for LOX, this change will be 'budget-neutral' for CMS to ensure the payments in other oxygen classes are reduced to accommodate the increase in reimbursement for LOX (11).	DME suppliers may state that providing LOX would cause them to close due to the high costs associated with weekly deliveries, the purchase of special delivery truck and equipment, etc)
Certainty of evidence of required resources **What is the certainty of the evidence of resource requirements (costs)?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Given the variability in reimbursement rates for medical expenses in the US, and the unknown number of patients utilizing LOX, it is difficult to project the true cost per person for portable liquid oxygen. In the US, Medicare typically covers 80% of the Medicare-approved amount (the amount changed by the doctor or supplier assigned) (12). However, costs may vary depending on patient insurance. Andersson et al conducted a multicenter prospective randomized trial, and they noted that the average cost per patient for the oxygen cylinder group for their six-month follow-up period was US$1,310 and for the LOX group was US$4,950 (1).	
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are currently no studies on the cost effectiveness of portable liquid oxygen.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	LOX is the most expensive oxygen delivery system. As a result, suppliers have decreased its availability because they cannot charge enough cover their expenses or to make a profit. This has made LOX less available, although still expensive, and therefore not as accessible to everyone. On the other hand, high-flow patients are selectively placed at a disadvantage, so access to LOX may increase equity by allowing high flow oxygen patients to leave the home, go to medical appointments, work, and exercise or attend pulmonary rehabilitation programs.	LOX is not offered in all countries, and even in the regions where it is offered, it is not always accessible.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	In the past, Medicare has set up a bidding process for its suppliers, offering exclusive contracts to its lowest bidders. The companies that received these contracts were locked into contracts with Medicare and were unable to increase their prices to turn a profit, resulting in a slow phase-out of LOX due to its high cost. This is why in many parts of the USA, LOX is not offered as an option. LOX is also uncommon in areas with universal healthcare due to the cost (11). However, as of January 2019, Medicare put competitive bidding for durable medical equipment on a two year hold while it considers possible changes to its payment system (13).	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	In the US, oxygen is reimbursed on a prospective payment basis by The Center for Medicare and Medicaid Services (CMS). They have a competitive bidding policy, which has resulted in many suppliers phasing out LOX due to its high cost. However, as of 2019, Medicare put competitive bidding for durable medical equipment on hold in 2019 while it considers possible changes to its payment system (13). While this is being done, there is a current lack of availability of LOX and tighter limits on number of gas cylinders and delivery schedules (14). As of now, portable gaseous oxygen and LOX are combined into one payment class by CMS. While CMS is in the midst of splitting it and adding a class for LOX, it is required that CMS ensure the payments in other oxygen classes are reduced to accommodate the mark-up to LOX to maintain budget neutrality (11). We must also consider the feasibility of using liquid oxygen by the patient. Certain oxygen devices limit how long a patient can be outside the home without needing to carry multiple devices with them.	

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Table E11: Approximate duration of supply for selected portable oxygen devices*†

	Setting	POC single battery (2.8-5 lbs)	M 6 Tank§ (4.5 lbs)	E tank with stroller§ (20 lbs single tank)	Liquid Oxygen Medium – Lg. Canister (5.6- 8 lbs)
Continuous flow	2 L/min	2.5 hrs	1.4 hrs	5.7 hrs	6.1 hrs
	4 L/min	N/A	<1 hr	2.8 hrs	4 hrs
	6 L/min	N/A	0.4 hrs	1.9 hrs	3.0 hrs
	8L/min	N/A	N/A	<1 hr	2.3 hrs
	"2"	3.5 hrs	4.3 hrs	17 hrs	22 hrs
Pulse-dose‡	"4"	2.5 hrs	3 hrs	8.6 hrs	11 hrs
	"6"	Rarely available	N/A	N/A	N/A

N/A = not available
*Duration of device does not confirm device's ability to adequately meet oxygen needs of patient
†Device nomenclature and model availability vary internationally
‡Pulse-dose oxygen delivery mechanism and volume varies across devices
§This estimated duration is for tanks pressurized to 2000 pounds per square inch (p.s.i.)

References for estimated duration of devices:
Liquid Oxygen:
http://files.chartindustries.com/LOX-Time_use-ML LOX0007%20B_%20LOX%20time%20use%20chart.pdf

E Cylinders:
https://www.phc-online.com/O2-tank-duration_a/151.htm

Homefill M6 Tanks
http://www.jonesmed.com/jonesmed/Oxygen_files/Cylinder%20Run%20Times%20.pdf

E, D, M6 tanks
https://upstatehomecare.com/assets/approximate-oxygen-tank-duration-times.pdf