Zuurstoftherapie thuis

KCE reports 156A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
2011

Het Federaal Kenniscentrum voor de Gezondheidszorg

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Zuurstoftherapie thuis

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Layout:	Ine Verhulst
Brussel, 7 juni 2011	
Studie nr 2009--14	

Domein: Health Technology Assessment (HTA)

MeSH: Oxygen inhalation therapy ; Heart Failure ; Palliative Care ; Meta-Analysis ; Costs and Cost Analysis ; Cost-Benefit Analysis ; Belgium ; Lung Diseases, Interstitial ; Pulmonary Disease, Chronic Obstructive ; Cystic Fibrosis ; Technology Assessment, Biomedical

NLM Classificatie: WF 145

Taal: Nederlands, Engels

Formaat: Adobe® PDF™ (A4)

Wettelijk depot: D/2011/10.273/23

Dit document is beschikbaar van op de website van het Federaal Kenniscentrum voor de gezondheidszorg.

Hoe refereren naar dit document?

Van Meerhaeghe A, Annemans L, Haentjens P, San Miguel L, Buysse B, Benoit K, Devriese S, Stroobandt S, Gailly J. Zuurstoftherapie thuis. Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE). 2011. Reports 156A. D/2011/10.273/23.

VOORWOORD

Lucht meer nog dan water is onontbeerlijk voor het leven en niemand haalt het in het hoofd om iemand de lucht te ontzeggen die hij nodig heeft. Toch is dit ergens de uitdaging waar deze studie voor stond: moet je zuurstof toedienen aan al wie te kampen heeft met ademhalingsmoeilijkheden? En verder, indien zuurstoftherapie effectief nodig is, stelt zich de vraag onder welke vorm, tegen welke prijs en binnen welk organisatiekader?

Deze vragen zijn niet zo triviaal als ze wel lijken. Vooreerst spreken we hier over zuurstof en niet over lucht. En deze zuurstof moet geproduceerd, opgeslagen, vervoerd en op de meest geschikte wijze ter beschikking worden gesteld. Vervolgens moet het toedienen van zuurstof aan de patiënt beantwoorden aan een reeks precieze antwoorden om echt doeltreffend te zijn. Tenslotte moeten ook de prijzen die door patiënt en maatschappij voor deze zuurstof worden betaald, redelijk blijven en zij hangen ongetwijfeld ook samen met de manier waarop de distributie wordt georganiseerd.

Deze veelheid aan kwesties heeft ook geleid tot een veelheid aan manieren waarop een antwoord werd geboden, en deze variatie zien we zowel in eigen land als tussen de landen onderling. Het was dus niet nutteloos om hierbij stil te staan en onze voorschrijfgewoonten, onze organisatiemodellen en onze financiering van nader te bekijken. In het licht van deze schijnbaar wat chaotische toestand was dit meer dan de moeite waard.

Het was niet onze ambitie om tot één enkele eenvoudige oplossing te komen; de problematiek blijft inderdaad nog steeds complex. Toch hopen we wat meer klaarheid te scheppen en zo het vinden van oplossingen voor een beter gebruik en een betere organisatie te vergemakkelijken. Als we hierin slagen zal het ondermeer dankzij de actieve medewerking van de Belgische Vereniging voor Pneumologie zijn, en dankzij de interuniversitaire samenwerking waarop we beroep konden doen in dit project. Daarom onze oprechte dank aan al wie zich met ons op deze uitdaging heeft geworpen.

Jean Pierre CLOSON
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Samenvatting

INLEIDING

Zuurstof wordt al jarenlang therapeutisch aangewend, voornamelijk bij patiënten die lijden aan chronisch obstructief longlijden (Chronic Obstructive Pulmonary Disease, COPD). Bij deze aandoening is de longfunctie dermate aangetast dat het bloed onvoldoende van zuurstof wordt voorzien. De mogelijk klinische indicaties voor een zuurstofbehandeling zijn met der tijd geëvolueerd. Dit verantwoordt een literatuuronderzoek waarbij wordt nagegaan bij welke patiënten het nuttig is om zuurstof voor te schrijven en onder welke vorm. Bovendien is de kost van een zuurstofbehandeling afhankelijk van de oorsprong van de gebruikte zuurstof.

De onderzoeksvragen die worden behandeld in dit rapport zijn:

1. Welke patiënten halen een klinisch voordeel uit een langdurige zuurstofbehandeling (Long-Term Oxygen Therapy, LTOT)? Zowel kortdurige behandelingen, behandelingen bij jonge kinderen, behandelingen naar aanleiding van clusterhoofdpijn als ziekenhuisbehandelingen worden buiten beschouwing gelaten.
2. Zijn de beschikbare toedieningsvormen voor langdurige zuurstoftherapie in de thuissituatie gelijkwaardig inzake klinische doeltreffendheid, veiligheid en gebruiksgemak?
3. Hoeveel bedragen de kosten in België volgens toedieningsvorm en patiëntengroep?
4. Hoe verhoudt zich het Belgische organisatiemodel tot andere organisatie-modellen uit Frankrijk, Nederland, het Verenigd Koninkrijk en Duitsland?

BESCHRIJVING VAN DE BELGISCHE SITUATIE

ZUURSTOFBRONNEN

Het individuele zuurstofverbruik hangt af van de dagelijkse toedieningsduur en het debiet dat de arteriële zuurstofniveaus voldoende laat toenemen, zonder dat daarbij een nefaste hypercapnie wordt uitgelokt.

Bij patiënten die thuis worden behandeld, kan zuurstof worden geleverd in drie toedieningsvormen: als gasvormige zuurstof, via een zuurstofconcentrator of als vloeibare zuurstof. Elke toedieningsvorm is verkrijgbaar in een vorm met grote afmetingen voor vast gebruik alsook in een gemakkelijk draagbare vorm met kleinere afmetingen. Men heeft dus:

- vaste zuurstofbronnen:
  - ofwel een grote fles (of cilinder) met gasvormige zuurstof onder een druk van 200bar. Deze heeft een opbrengst tot 4m3. Het opslaan van reserveflessen in de woning kan echter als erg hinderlijk worden ervaren. De voorraad moet regelmatig worden aangevuld door een gespecialiseerd bedrijf, naargelang het verbruik.
  - ofwel een zuurstofconcentrator (of zuurstofextractor). Dit toestel scheidt de zuurstof uit de omgevingslucht van de stikstof en levert geconcentreerde zuurstofrijke lucht (zuiverheid tussen 90 en 95%). De zuurstofvoorraad is onbegrensd, maar het toestel is vaak nogal lawaaierig. Het toestel vereist een aansluiting op het elektriciteitsnet alsook een regelmatige onderhoudsbeurt aan huis.
  - ofwel een tank met vloeibare zuurstof (40 liter) die de opslag van grote hoeveelheden zuurstof bij een zeer lage temperatuur (-185°) mogelijk maakt. Eén liter vloeibare zuurstof levert immers 850 liter gasvormige zuurstof bij een normale omgevingstemperatuur en -druk. Vloeibare zuurstof kan bovendien een groter debiet leveren dan andere zuurstofbronnen. Een gespecialiseerd bedrijf vult de tank regelmatig aan.

Hoe dikwijls dit dient te gebeuren, hangt af van het individuele verbruik van de patiënt (in de regel slechts één maal per week).

- Draagbare bronnen met kleinere afmetingen en lichter gewicht:
  - ofwel een kleine cilinder met gasvormige zuurstof (opbrengst: 0,4m^3)
  - ofwel een kleine fles (volume: 0,5 tot 1,2 l) met vloeibare zuurstof
  - ofwel een draagbare zuurstofconcentrator. Op dit ogenblik wordt dit toestel in België niet terugbetaald.

Figure 1: Zuurstofbronnen voor de thuisbehandeling

Bron: Hulpmiddelen Kompas 2004, Zuurstofapparatuur – ISBN 90-70918-38-2

Zuurstof geleverd door een vaste bron wordt aan de patiënt toegediend via een systeem van een ontspanner, slangen en canules. Hierbij blijft enige bewegingsvrijheid binnen de woning behouden. Bovendien is de behandeling hierdoor zowel overdag als 's nachts beschikbaar.

Draagbare systemen worden in samengang met vaste systemen gebruikt. Hierdoor behaalt de patiënt niet enkel een langere toedieningsduur, de lichamelijke inspanning bij het verlaten van de woning wordt mede ondersteund. De duur van de autonomie buitenshuis is echter beperkt en hangt af van het verbruikte debiet: van twee tot zes uur voor gasvormige zuurstof, langer als acht uur ononderbroken met vloeibare zuurstof . Een aantal draagbare zuurstofconcentratoren behalen een autonomie van méér dan acht uur.

De kleine cilinders met gasvormige zuurstof worden momenteel geleverd en gevuld door gespecialiseerde bedrijven. De draagbare flessen met vloeibare zuurstof kunnen door de patiënt zelf worden hervuld aan de vaste vloeibare zuurstoftank. De draagbare zuurstofconcentratoren dienen regelmatig te worden herladen aan het elektriciteitsnet. Het niet geringe gewicht van deze draagbare apparaten vereist het gebruik van een schoudertas of een wagentje bij verplaatsingen.

ORGANISATIE

Een thuisbehandeling met zuurstof vereist heel wat logistieke ondersteuning en tussenpersonen. Zo verloopt de levering van zuurstof via gespecialiseerd transport. Verder zijn er nog de levering van bijkomende uitrusting, de installatie en het onderhoud van de apparaten, de kwaliteitscontrole alsook de opleiding van de patiënt. Dit alles brengt aanzienlijke kosten met zich mee. Voor deze verschillende diensten en benodigdheden kunnen zowel de ziekenhuizen als private "home-care" zuurstofleveranciers instaan, al dan niet met tussenkomst van de apotheker. Deze firma's in onderaanneming verzorgen de technische opvolging en opleiding van de patiënt. Ze handelen echter buiten het reglementair kader van de ziektezorgverzekering.

Naargelang het geval, wordt de terugbetaling geregeld óf door een revalidatie-overeenkomst met de ziekenhuizen, óf door een overeenkomst met de apothekers (zie hierna). Een bijkomend gegeven is dat zuurstofconcentratoren medische apparaten zijn, terwijl vloeibare of gasvormige zuurstof wordt beschouwd als een geneesmiddel. Dit houdt in dat verschillende diensten van het RIZIV hierbij betrokken zijn. Naast de bevoegdhedenversnippering die dit veroorzaakt, bemoeilijkt deze bijkomende complexiteit het verkrijgen van een allesomvattend beeld over deze materie.

TERUGBETALING

Zuurstofbehandeling wordt terugbetaald door de ziekteverzekering:

- ofwel in het kader van revalidatieovereenkomsten tussen het Verzekeringscomité van het RIZIV en individuele ziekenhuizen met een longarts of een kinderarts met een bijzondere interesse voor pneumologie. Hierbij zijn eenduidige regels van kracht wat betreft de klinische kenmerken van de patiënt, de levering van zuurstof en de toepassingsvoorwaarden. Zowel vloeibare als gasvormige zuurstof, evenals zuurstofconcentratoren (onafhankelijk van het merk) worden onder deze overeenkomst terugbetaald. Indien van toepassing, ontvangt de patiënt financiële vergoeding voor de meerkost aan elektriciteit. Alle "home-care" firma's kunnen deelnemen.
- ofwel in het kader van de overeenkomst tussen de apothekers en de verzekeringsinstellingen. Om het even welke huisarts of specialist kan dit voorschrijven, zonder enige bijkomende klinische voorwaarden waaraan de patiënt dient te voldoen en bovendien onder veel flexibelere toepassingsvoorwaarden. Onder deze overeenkomst wordt enkel gasvormige zuurstof en één enkel merk zuurstofconcentrator terugbetaald, vloeibare zuurstof niet. Er is geen financiële vergoeding voor elektriciteitsverbruik en slechts enkele "home-care" firma's zijn toegelaten.

Zuurstoftherapie kan in België dus worden terugbetaald aan elke patiënt, op lange of korte termijn, zonder remgeld, voor eender welke klinische indicatie en voor eender welke voorschrijver.

TENDENSVERGELIJKING VAN DE OVEREENKOMSTEN

Onderstaande gegevens zijn afkomstig van Farmanet en uit data over RIZIV-overeenkomsten.

Uitgaven voor de ziekteverzekering stegen voor beide overeenkomsten tussen 2005 en 2009, weliswaar aan onderscheiden snelheden. Volgens de gegevens van Farmanet,

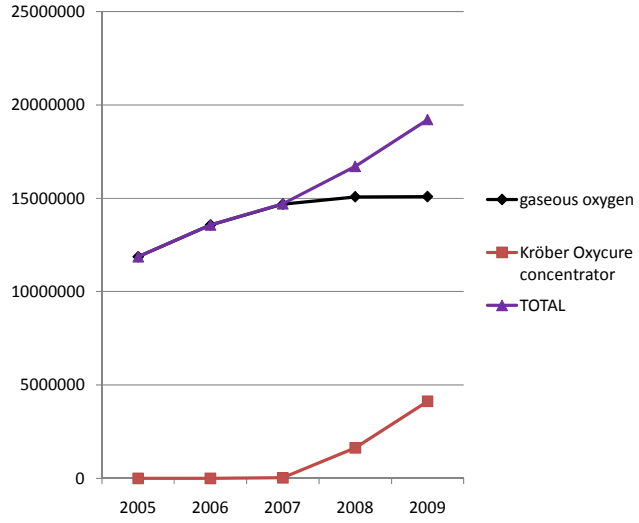
- stegen de uitgaven voor de revalidatieovereenkomsten met 16% (van 26.328.2004 tot 30.509.715 euro). Dit is een stijging van nauwelijks 3% per jaar.
- terwijl de uitgaven in het kader van de overeenkomst met de apothekers stegen met 62% (van 11.866.250 euro tot 19.215.330 euro). Dit is een stijging van meer dan 12% per jaar.

Overeenkomst met de apothekers

Onderstaande figuur toont voor de overeenkomst met de apothekers de globale uitgavenevolutie naar zuurstofbron tussen 2005 en 2009. Het aantal binnen deze overeenkomst behandelde patiënten kan hieruit niet worden afgeleid. De uitgaven werden aan de hand van nomenclatuurcodes geschat.

De stijging van de uitgaven is grotendeels te wijten aan de invoering in 2007 van de terugbetaling van één enkel merk van zuurstofconcentrator (Kröber), waarbij één enkele firma (Oxycure) het monopolie van alleenverdeler had. Sinds april 2011 mag ook een tweede firma (Linde) dit enig door de overeenkomst erkende merk verdelen.

Total costs / year (euro) of the RIZIV/INAMI pharmacist agreement including the oxygen drug



	2005	2006	2007	2008	2009
gaseous oxygen	11.866.250	13.571.189	14.679.673	15.074.365	15.083.242
Kröber Oxycure concentrator	0	0	24.298	1.636.576	4.132.088
TOTAL	11.866.250	13.571.189	14.703.971	16.710.941	19.215.330

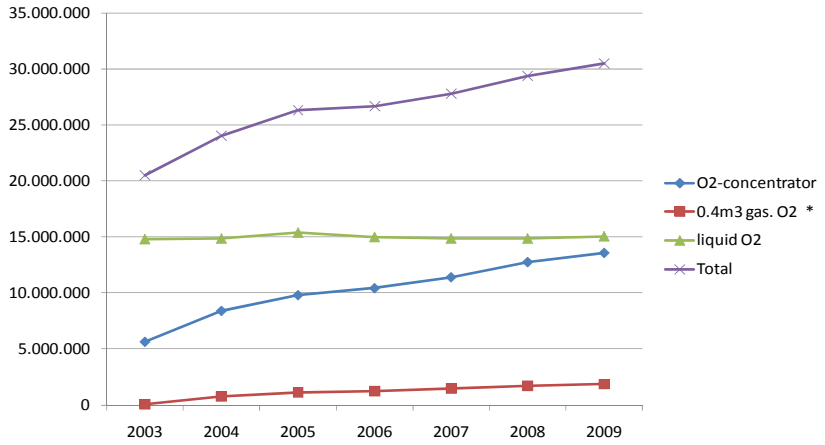
Functionele revalidatie-overeenkomsten

In 2009 werden in het kader van deze overeenkomsten 6 550 patiënten langdurig behandeld met zuurstof (doorgaans omwille van COPD). Hierbij bedroeg de gemiddelde leeftijd 71 jaar. Er werden slechts 56 mucovisidosepatiënten geteld, met een gemiddelde leeftijd van 42 jaar.

De invoering van de terugbetaling van zuurstofconcentratoren viel tot 2003 samen met een lichte daling in het gebruik van vloeibare zuurstof, daarna stabiliseerde het cijfer zich. In 2009 maakten de uitgaven voor vloeibare zuurstof nog steeds 50% uit van de uitgaven onder deze overeenkomsten.

Onderstaande figuur toont de evolutie tussen 2003 en 2009 van de globale uitgaven voor de revalidatie-overeenkomst naar zuurstofbron. De kleine flessen gasvormige zuurstof (0,4 m3) worden hierbij door dezelfde patiënten aangewend, als een aanvulling op de vaste zuurstofconcentraroren.

Total costs of functional rehabilitation and the oxygen drug / year (euro)



	2003	2004	2005	2006	2007	2008	2009
O2-concentrator	5.641.739	8.407.408	9.807.255	10.433.675	11.411.850	12.766.746	13.589.254
0.4m3 gas. O2 *	71.775	773.349	1.144.531	1.232.884	1.488.582	1.721.100	1.857.202
liquid O2	14.811.668	14.870.590	15.376.418	14.996.000	14.869.949	14.867.441	15.063.259
Total	20.525.182	24.051.347	26.328.204	26.662.559	27.770.381	29.355.287	30.509.715

* based on an estimation of the gaseous oxygen drug cost, cfr supra

MEDISCH LITERATUURONDERZOEK

VERGELIJKING VAN DE ZUURSTOFBRONNEN

Door het ontbreken aan vergelijkend onderzoek, bestaat er geen bewijs ter ondersteuning van het verkiezen van een zuurstofbron boven een ander. De onderzoeken bestudeerden de klinische werkzaamheid van een zuurstofbehandeling zonder daarbij een onderscheid te maken tussen vloeibare zuurstof, gasvormige zuurstof of zuurstof geleverd door een zuurstofconcentrator.

Het draagbaar gebruik van zuurstof werd weinig onderzocht en de beschikbare resultaten spreken elkaar tegen. Een onderzoek toonde weliswaar een langere dagelijkse behandelingsduur aan (17 uur +/-3,5 tegenover 14 uur +/-3), maar slechts 60% van de patiënten die erover beschikten, gebruikte ook daadwerkelijk hun draagbaar toestel. Een ander onderzoek toonde dan weer geen voordelen met betrekking tot levenskwaliteit, therapietrouw of inspanningstolerantie.

INVLOED OP DE GEZONDHEID VAN PATIËNTEN

Ons systematisch literatuuronderzoek selecteerde gerandomiseerde klinische studies (RCT) en meta-analyses (MA) van RCT's. Indien studies werden aangetroffen die gepubliceerd waren na datum van een bestaande meta-analyse, werden deze alsnog in een nieuwe eigen meta-analyse opgenomen.

Studies werden opgenomen indien ze handelen over ziektebeelden waarvoor een ononderbroken zuurstofbehandeling is aangewezen (COPD, palliatieve zorg, hartfalen, mucoviscidose en interstitiële longfibrose). Bovendien dienen deze studies zich ook uit te spreken over minstens één van de volgende beoordelingscriteria: mortaliteit of morbiditeit, levenskwaliteit aan de hand van gevalideerde schalen gemeten, lichaamsinspanningen, fysiologische parameters, patiëntvoorkeuren of productiviteits-verbetering.

COPD

COPD is de meest voorkomende indicatie voor een langdurige ononderbroken zuurstofbehandeling in de thuissituatie. COPD is immers een ziekte die geleidelijk degenereert in een steeds ernstig wordende ademnood met uiteindelijk de dood als gevolg.

Naar aanleiding van ons systematisch literatuuronderzoek, kan een meerwaarde worden bevestigd voor ononderbroken zuurstoftherapie bij COPD-patiënten met een ernstig zuurstoftekort (d.w.z. met een $PaO_2 \leq 55mmHg$; ofwel een $PaO_2 < 60mmHg$ met verstoring van de longhaemodynamica, rechterhartfalen of erytrocytose). Een levenslange, dagelijkse langdurige zuurstofbehandeling van meer dan vijftien uur per dag staat toe om de levensduur van deze patiëntengroep te verlengen. Deze patiënten vertonen bovendien een statistisch niet-significante verbetering van zowel de wandelafstand en de ademnood bij inspanning. Slechts een deel van de patiënten (10 tot 70% volgens de onderzoeken) behaalt de beoogde toedieningsduur van vijftien uur per dag.

Er werd geen bewijs gevonden voor een meerwaarde bij de behandeling van COPD-patiënten met een lichte tot matig zuurstoftekort of gewoonweg een nachtelijke desaturatie.

Patiënten met nood aan palliatieve zorgen

Terminale patiënten kunnen lijden onder ademnood en ademhalingsproblemen. Een zuurstofbehandeling is bij deze patiënten gericht op het verlichten van deze symptomen en het verbeteren van de levenskwaliteit. Ons systematisch literatuuronderzoek toont bij deze patiënten echter geen onderscheid tussen een zuurstofbehandeling en een beademing met omgevingslucht in een identieke toedieningsvorm. Deze vaststelling geldt zowel voor levenskwaliteit, vermoeidheid, ademnood, wandelafstand als het uitvoeren van dagelijkse handelingen. De studies met betrekking tot de patiëntenvoorkeur tonen tegenstrijdige resultaten

Hartfalen

Het gebruik van zuurstoftherapie bij hartfalenpatiënten met een Cheyne-Stokesademhaling is omstreden. Dit geldt ook voor hartfalenpatiënten in fysieke revalidatie. Ons systematisch literatuuronderzoek leverde geen eenduidige argumenten op. De ademnood aan het einde van een zesminuten-wandeltest neemt weliswaar gemiddeld genomen in geringe mate af, en een aantal fysiologische slaapparameters verbeteren. De klinische impact van deze verbeteringen op de gezondheidstoestand van de patiënt werd echter nooit objectief aangetoond. De controverse over het klinisch nut van een zuurstofbehandeling bij deze groep patiënten blijft dus bestaan.

Mucoviscidose

Mucoviscidose is een genetische ziekte waarbij de longfunctie geleidelijk aan verloren gaat. In een verder gevorderd stadium van de ziekte stelt zich de vraag of een behandeling met zuurstof ondersteuning bij activiteiten kan bieden. Uit ons systematisch literatuuronderzoek blijkt dat de maximale inspanningsduur wordt verlengd en dat ziekteverzuim op school of op het werk afneemt.

Interstitiële longaandoeningen

Interstitiële longaandoeningen zijn zeldzame en heterogene ziekten die kunnen leiden tot ernstige ademnood. Ons systematisch literatuuronderzoek toont een verbetering aan van een aantal fysiologische parameters. De klinische impact van deze verbeteringen op de gezondheidstoestand van de patiënt werd echter nooit objectief aangetoond. Ook voor deze groep patiënten blijft een controverse bestaan over het klinisch nut van een langdurige zuurstofbehandeling. Niettegenstaande zijn de selectiecriteria voor een behandeling wegens een chronisch zuurstoftekort gelijklopend met deze voor zuurstofbehandeling bij COPD.

ECONOMISCH LITERATUURONDERZOEK

Het systematisch onderzoek van de economische literatuur laat niet toe om eenduidige besluiten te trekken; Gebreken en beperkingen in de gepubliceerde studies en daaruit voortvloeiende onzekerheden verhinderen dit. Wel kan gemeld worden dat de kosteneffectiviteit van een zuurstofbehandeling in de thuissituatie vooral wordt beïnvloed door de incidentie van ziekenhuisopnames, de duur van deze ziekenverblijven en de prijzen. De onderzoeken vergelijken ofwel interventies, of procedures.

Samenvatting van de resultaten

zuurstof versus geen zuurstof	De incrementele kosteneffectiviteitsratio (ICER) wordt geschat op €18.000 per gewonnen levensjaar en €25.000 per QALY voor COPD-patiënten met een ernstige hypoxemie
gasvormige zuurstof versus zuurstofconcentratoren	Kostenanalyse duidt op een voorkeur voor zuurstof-concentratoren,… …dat vooral aanwezig is wanneer er een groot aantal cilinders wordt verbruikt.
vloeibare zuurstof versus gasvormige zuurstof	Er is geen conclusie mogelijk op basis van de beschikbare onderzoeken
herevaluatie van de patiëntengeschiktheid	Een herevaluatie van de patiëntengeschiktheid gedurende de behandeling leidt tot een kostenbesparing, zonder enige invloed op de klinische uitkomst. Een herevaluatie om de twee maanden in plaats van om de zes maanden lijdt niet tot een verdere kostenbesparing en komt zelfs duurder uit.
multidisciplinair team	Geen meerwaarde volgens één kosteneffectiviteitsstudie
thuis versus ziekenhuis	Programma's van thuiszorg: vermindering van de kosten dank zij een verminderd beroep op het ziekenhuis
verdeling	Voor de verdeling van zuurstof is er geen kostprijsverschil tussen de winstbeogende bedrijven en de niet-winstbeogende sector.

KOSTEN NAAR TOEDIENINGSVORM

De behandeling met vloeibare zuurstof kost naar schatting drie keer duurder dan de gemiddelde kost van een behandeling met één van de andere toedieningsvormen.

De kost van draagbare gasvormige zuurstof is momenteel afhankelijk van het gebruikte type zuurstoffles (met inwendige of uitwendige ontspanner) en het verbruikte aantal.

- Indien de patiënt maandelijks slechts twee cilinders verbruikt, is de lichtgewicht cilinder van 2,5kg met inwendige ontspanner goedkoper.
- Boven dit verbruik, is de zwaardere cilinder van 4 à 5kg met uitwendige ontspanner goedkoper. Voor een maandelijks verbruik van zeven cilinders, is de uitgave in dit geval twee maal kleiner.

KOSTENEFFECTIVITEITSSTUDIE

TOTALE MAANDELIJKSE KOSTEN VAN DE OVEREENKOMSTEN

Het monster aan patiënten van wie mag worden aangenomen dat zij in langdurige zuurstofbehandeling zijn, werd afgeleid uit de permanente steekproef (EPSR5). Hiertoe werden een aantal veronderstellingen gemaakt aangaande het zorgverbruik. Dit leidde onvermijdelijk tot de uitsluiting van een groot aantal betroffen patiënten en een mogelijke verminderde nauwkeurigheid van de behaalde resultaten. Van de patiënten in EPSR5 die voldeden aan de selectiecriteria, was 26% (n=509) aangewezen op een overeenkomst van het verzekeringscomité met een revalidatiecentrum en 74% (n=1447) op de overeenkomst tussen de apothekers en de verzekeringsinstellingen. De totale kost omvat de kosten van de zuurstof en de apparatuur, de kosten van de ambulante zorgverlening evenals de kosten van ziekenhuisopnames.

Onderstaande tabel toont geen grote verschillen tussen de twee soorten overeenkomsten voor wat betreft de totale kost per patiënt. De enige uitzondering hierop is de maandelijkse kost van de zuurstof zelf. Deze ligt hoger bij overeenkomsten van het verzekeringscomité met revalidatiecentra. Dit kan te wijten zijn aan het feit dat de patiënten in onze selectie, aangewezen op dit type overeenkomst, een hoger zuurstofverbruik vertonen. Een hoger zuurstofverbruik gaat namelijk samen met zowel de ernstgraad van het zuurstoftekort als de dagelijkse behandelingsduur.

Kosten van een zuurstofbehandeling volgens soort overeenkomst

	overeenkomsten van het verzekeringscomité met revalidatiecentra (n=509)	**de overeenkomst tussen de apothekers en de verzekeringsinstellingen (n=1447)**
totale maandelijkse kost per patiënt	**gemiddelde maandelijkse kost**	**gemiddelde maandelijkse kost**
totale kost van een LTOT-patiënt	€ 2.306	€ 2.242
totale kost zonder ziekenhuisopnames	€ 1.113	€ 1.316
kost van de zuurstof en de apparatuur	€ 350	€ 177
geschatte kost zonder zuurstof en zonder hospitalisatie (rij 2 min rij 3)	€ 764	€ 1.139
geschatte kost zonder zuurstof (rij 1 min rij 3)	€ 1.956	€ 2.066

INCREMENTELE KOSTENEFFECTIVITEITSRATIO (ICER) BIJ COPD

Het onderzoek naar de kosteneffectiviteit werd uitgevoerd aan de hand van een Markovmodel waarbij zuurstofbehandeling werd vergeleken met het ontbreken daaraan. De gegevens omtrent het sterftecijfer en de ziekenhuisopnames voor de vergelijkende arm werden afgeleid uit de permanente steekproef (EPSR5). In de interventie-arm worden deze waarden aangepast met relatieve risico's gehaald uit de literatuur over COPD-patiënten (met een ernstig zuurstoftekort of soms enkel nachtelijke desaturatie.)

Een zuurstofbehandeling levert in ons model een gezondheidswinst op van 0,626 QALY's per patiënt. De ICER over een horizon van vijf jaar wordt geraamd op 18.000 euro (CI 14.318-22.404) per gewonnen levensjaar en op 25.000 euro (CI 19.510-31.259) per gewonnen QALY.

Voor andere, niet met COPD-gerelateerde ziektebeelden werd de ICER van een zuurstofbehandeling niet berekend wegens een tekort aan evidentie over de effecten op het sterftecijfer en de levenskwaliteit.

INTERNATIONALE VERGELIJKING

Voorliggend rapport bestudeerde de toestand in Frankrijk, Duitsland en Groot-Brittannië en Nederland. Boven een bepaalde drempelwaarde van arteriële PaO2 wordt langdurige zuurstofbehandeling terugbetaald in alle landen. Dit stemt overeen met de terugbetalingsvoorwaarden voor de overeenkomsten van het verzekeringscomité met de revalidatiecentra. Er bestaan bijzondere voorwaarden voor het voorschrijven van een acute zuurstofbehandeling in het geval van clusterhoofdpijn, palliatieve zorgen of gedurende instabiele periodes bij hart- of longziekten.

Tussen de landen werden onderlinge verschillen opgemerkt voor wat betreft het opvolgen van de medische behandeling, de opleiding van de patiënten, de rookstop, de terugbetalingsmechanismen, de leveringskanalen, alsook het onderhoud en dringend herstel aan huis.

In Nederland zijn het de zorgverzekeringen die minimum behandelingsvoorwaarden opleggen om deze dan uit te besteden aan de goedkoopste leveranciers. Deze gang van zaken heeft over de laatste vijftien jaar geleid tot een aanzienlijke kostenbesparing bij langdurige zuurstofbehandeling. De kosten (inbegrepen de apparaten en toebehoren) waren 25.745.000 euro in 2009, voor 29.500 gebruikers, op een totale bevolking van 16.500.000 inwoners.

BESLUIT

Dit KCE-rapport geeft antwoorden op de volgende onderzoeksvragen:

1. Welke patiënten halen een klinisch voordeel uit een langdurige zuurstofbehandeling (Long-Term Oxygen Therapy, LTOT)?

COPD-patiënten met een ernstig zuurstofgebrek (d.w.z. met een $PaO_2 \leq 55$mmHg; ofwel een $PaO_2 < 60$mmHg met verstoring van de longhaemodynamica, rechterhartfalen of erytrocytose) halen uit zuurstoftherapie het voordeel van een verlaagde mortaliteit op voorwaarde dat de behandeling minstens vijftien uur per dag wordt aangehouden.

Mucoviscidosepatiënten, hartfalenpatiënten en patiënten die lijden aan een interstitiële longaandoening ondervinden weliswaar een symptoomverlichting van hun zuurstofgebrek, echter zonder enige invloed op hun mortaliteit.

Overzicht van de bevindingen inzake klinische werkzaamheid

Aangetoond klinisch voordeel voor	COPD-patiënten met ernstig zuurstofgebrek mucoviscidose met respiratoire insufficiëntie
Aangetoond ontbreken van enig klinisch voordeel voor	patiënten met nood aan palliatieve zorgen
Mogelijk, maar controversieel, klinisch voordeel voor	hartfalenpatiënten met Cheyne-Stokesademhaling hartfalenpatiënten tijdens fysieke revalidatie patiënten met interstitiële longfibrose
Momenteel geen aangetoond klinisch voordeel voor	COPD-patiënten met een licht tot matig zuurstofgebrek of met nachtelijke desaturatie:

De gemeten therapietrouw varieert aanzienlijk tussen studies (van 10 tot 70%). Een aantal patiënten vindt dat de voordelen van een zuurstofbehandeling niet opwegen tegen de beperkingen die dit met zich meebrengt. Zuurstofapparaten en -bronnen blijven in dat geval ongebruikt.

Een opleiding van de patiënten en hun naasten is noodzakelijk om een veilig en goed gebruik te waarborgen. Roken in de nabijheid van om het even welke zuurstofbron houdt een enorm risico in op ongevallen.

2. Vergelijking van de beschikbare toedieningsvormen voor langdurige zuurstofbehandeling

Zuurstof kan worden geleverd in drie toedieningsvormen: gasvormige zuurstof, zuurstofconcentrator of vloeibare zuurstof. Elke toedieningsvorm is verkrijgbaar in een vorm met grote afmetingen voor vast gebruik alsook in gemakkelijk draagbare vorm met kleinere afmetingen.

Vanuit het oogpunt van klinische werkzaamheid voor de patiënt, zijn de drie toedieningsvormen evenwaardig, ongeacht de bron vast of draagbaar is. De bronnen onderscheiden zich enkel in gebruiksgemak (lawaai, gebruik buitenshuis, beschikbaar volume, hervulbaarheid van draagbare bronnen door de patiënt,…) en kost voor de samenleving.

Het is noodzakelijk te beschikken over een draagbaar systeem:

- Bij COPD met een ernstig zuurstofgebrek wanneer de patiënt te dikwijls van huis is om een behandelingsduur van méér dan 15 uur te kunnen verzekeren, of
- Wanneer activiteiten buitenshuis steun hebben aan deze behandeling.

Het draagbare systeem met vloeibare zuurstof laat toe langer van huis te blijven (>8uur). Deze autonomie is ook haalbaar met draagbare zuurstofconcentratoren. Dit is echter niet mogelijk met draagbare flessen. Hierbij is de autonomie beperkt tot twee à zes uur, afhankelijk van het gevraagde debiet.

Recente technische ontwikkelingen zouden verdere kostenbesparingen mogelijk kunnen maken. Men denkt hierbij aan een verbruiksteller voor zuurstofconcentratoren of aan zuurstofconcentratoren die draagbare zuurstofflessen kunnen hervullen.

3. Hoeveel bedragen de kosten in België volgens toedieningsvorm en patiëntengroep?

De ziekteverzekeringsuitgaven stegen tussen 2005 en 2009 gemiddeld met 3% voor de overeenkomsten tussen het verzekeringscomité en de revalidatiecentra (30,5 miljoen euro in 2009). Voor de overeenkomst tussen de apothekers en de verzekeringsinstellingen bedroeg de stijging 12% (om te komen op 11,9 miljoen euro in 2009).

Vloeibare zuurstof is momenteel ongeveer drie maal duurder dan de andere toedieningsvormen (gasvormig of zuurstofconcentrator). De terugbetaling van vloeibare zuurstof is momenteel enkel voorzien binnen een overeenkomst tussen het verzekeringscomité en een revalidatieziekenhuis en bovendien slechts voor patiënten die zich dagelijks méér dan drie uur buitenshuis bevinden. Niettegenstaande deze beperkingen, zijn de uitgaven voor vloeibare zuurstof nog steeds goed voor 50% van de totale uitgaven onder dit type overeenkomsten.

Een zuurstofbehandeling bij ernstige COPD levert een gezondheidswinst op van 0,626 QALY's per patiënt. De ICER over een horizon van vijf jaar wordt geraamd op 18.000 euro (CI 14.318-22.404) per gewonnen levensjaar en op 25.000 euro (CI 19.510-31.259) per gewonnen QALY.

4. Hoe verhoudt zich het Belgische organisatiemodel tot andere organisatie-modellen uit Frankrijk, Nederland, het Verenigd Koninkrijk en Duitsland?

Momenteel is de thuisbehandeling met zuurstof in België uiterst ingewikkeld georganiseerd. Bovendien ontbreekt het aan onderling overleg bij de diverse betrokken partijen. De zogenaamde "home-care" toeleveringsbedrijven die de installatie aan huis verzorgen alsook de opleiding van de patiënt handelen ook nog eens buiten het regelgevend kader van de ziekteverzekering.

Twee soorten overeenkomsten bestaan naast elkaar en zijn op verschillende wijze gereglementeerd. De overeenkomsten van het verzekeringscomité met de revalidatieziekenhuizen kent strikte toekenningsvoorwaarden en handelt enkel over langdurige zuurstofbehandeling. De overeenkomst van de apothekers met de verzekeringsinstellingen maakt geen onderscheid tussen zuurstofbehandelingen van korte en lange duur. Bovendien kan iedere arts onder deze overeenkomst een voorschrift opstellen en worden er aan de patiënt geen toekenningsvoorwaarden gesteld. Onder geen van beide overeenkomsten betaalt de patiënt voor de zuurstof.

In de andere Europese landen waarnaar werd gekeken, hanteert men een drempelwaarde voor de partiële zuurstofdruk (PaO_2) in arterieel bloed als een dwingende voorwaarde tot de terugbetaling van langdurige zuurstoftherapie. Om de PAO_2 in arterieel bloed nauwkeurig te kunnen meten, dient het bloed na afname meteen in een laboratorium te worden geanalyseerd. De tussenkomst van een pneumoloog lijkt hierbij onontbeerlijk.

In Nederland werd een organisatiemodel ontwikkeld dat de uitgaven voor de thuisbehandeling met zuurstof aanzienlijk verlaagt. In dit organisatiemodel worden de verschillende deelverantwoordelijkheden duidelijk van mekaar gescheiden (zuurstofproductie, levering aan huis, aansluiten van de toestellen, patiëntenopleiding en -opvolging, de voorziening van draagbare zuurstofbronnen). Hierdoor werd een vrije markt geschapen waarbij leveranciers en zorgverleners openlijk met elkaar kunnen wedijveren.

AANBEVELINGEN[a]

- **Er zou een brede, allesomvattende visie moeten ontwikkeld worden, waarin de rol van alle betrokken actoren duidelijk gedefiniëerd en gecoördineerd wordt;**
- **De kortstondige zuurstofbehandeling voor acute en voorbijgaande indicaties zou voor elke voorschrijver toegankelijk moeten blijven, maar beperkt worden tot maximum 3 maanden**
- **De regelgeving voor LTOT zou moeten gelijk getrokken worden aan de hand van toekenningsvoorwaarden**
  - **op basis van klinische indicaties (COPD, mucoviscidose, hartfalen en interstitiële longfibrose), en gestaafd aan de hand van een PaO_2-meting van minder dan 55 of 60 mmHg (in functie van de comorbiditeit), overdag bepaald, onder maximale medicamenteuze behandeling en in een stabiele fase (2 maal te herhalen);**
  - **mits herevaluatie van de voorwaarden en van het daadwerkelijk gebruik van de zuurstoftherapie na drie maanden en vervolgens jaarlijks.**
- **LTOT zou best geïntegreerd worden in een zorgtraject met duidelijke afspraken tussen de longarts of kinderarts met een specialisatie in pneumologie en de huisarts, en met de nodige aandacht voor de opleiding van de patiënt, rookstopbegeleiding en compliantie;**
- **De uitgaven zouden kunnen verminderd worden:**
  - **door te kiezen voor de goedkoopste behandelingsopties, gezien de gelijkwaardige klinische doeltreffendheid;**
  - **door de vloeibare zuurstof voor te behouden voor patiënten met een langdurige dagactiviteit buitenshuis (school, werk…);**
  - **door het nauwgezet opvolgen van de kosten en de technologische ontwikkelingen;**
  - **door de prijszetting en toeleveringscircuits te herbekijken en de levering en dienstverlening te verbinden aan expliciete kwaliteitsvereisten.**
- **Men zal werk moeten maken van een actualisering van de richtlijnen (aan de hand van resultaten van gerandomiseerde onderzoeken die gaande zijn) voor COPD met minder ernstige vormen van hypoxemie.**

a Het KCE blijft als enige verantwoordelijk voor de aanbevelingen die aan de overheid worden geformuleerd.

Scientific summary

Table of contents

ABBREVIATIONS

AHI	Apnoea-hypopnoea index
CAI	Central apnoea index
CDSR	Cochrane database of systematic reviews
CF	Cystic fibrosis
CHF	Chronic heart failure
CI	Confidence interval
COLD	Chronic obstructive lung disease
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic respiratory questionnaire
CS	Cohort studies
CSB	Cheyne-Stokes breathing
CSR	Cheyne-Stokes respiration
CT90	Cumulative time spent below a saturation of 90%
DLco	Diffusing capacity
ESS	Epworth sleepiness scale
EuroQoL	European quality of life scale
FEV1	Forced expiratory volume in 1 second
FiO2	Fraction of inspired oxygne
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HCP	Home care program
HF	Heart failure
HOT	Home oxygen therapy
HR	Heart rate
HRQL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
L/min	Litres per minute
LTOT	Long term oxygen therapy
MA	Meta-analysis
MD	Mean difference
MQoLQ	McGill quality of life questionnaire
MRC	Medical research council
MV	Minute ventilation
ND	Nocturnal desaturation
NRS	Numerical rating scale
NYHA	New York Heart Association
O2	Oxygen therapy
OR	Odds ratio
OT	Oxygen therapy
PaCO2	Arterial carbon dioxide tension
PaO2	Partial pressure of oxygen in arterial blood
PC	Palliative care
QALY	Quality adjusted life years
QoL	Quality of life
RCT	Randomised clinical trial
REM	Rapid eye movement
SaO2	Arterial oxygen saturation
SAS	Specific activity scale
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF36	Short form Health Survey
SGRQ	Saint George respiratory questionnaire
SIP	Sickness impact profile
SMD	Standardized mean difference

SpO2	Pulse oxymetry oxygen saturation
SR	Systematic review
SRH	Severe resting hypoxaemia
TLC	Total lung capacity
UC	Usual care
VAS	Visual analog scale
VCO2	Carbon dioxide output
VO2	Oxygen uptake
VT	Tidal volume
WMD	Weighted mean difference
6MWT	Six minute walk test

INTRODUCTION

Adequate oxygen supply is necessary to meet metabolic demands of every cell in the organism. Hypoxemia induces several physiologic responses to maintain adequate oxygen delivery to the tissues. The vascular bed dilates, thereby inducing a compensatory tachycardia that increases cardiac output and improves oxygen delivery. The pulmonary vasculature constricts in response to alveolar hypoxia, thereby improving the matching between ventilation and perfusion in the affected lungs. Subsequently, the secretion of erythropoietin by the kidney causes erythrocytosis, thus increasing the oxygen-carrying capacity of the blood and oxygen delivery. These early benefits may have detrimental long-term effects, however, as prolonged vasoconstriction, erythrocytosis, and increased cardiac output cause pulmonary hypertension, right ventricular failure, peripheral edema, and often death[1].

Long-term oxygen therapy (LTOT) is well established as the standard of care for patients suffering from chronic obstructive pulmonary disease (COPD) and severe chronic stable hypoxemia. The two key randomised controlled trials underpinning this evidence are 30 years old[2,3]. To date only two interventions – smoking cessation and LTOT (in patients with hypoxemia) have been found to alter the long-term course of COPD. Although, most studies have been performed in COPD, patients with other causes of chronic hypoxemia are also likely to benefit.

A large number of smoking baby boomers needing LTOT are just starting to receive prescriptions for domiciliary oxygen therapy. Hence, the incidence and prevalence for LTOT increase and this evolution is more striking among women than in men[4].

Currently, besides this increase in use, there is still a need for clear recommendations about specific groups of patients to be treated, and about the optimal treatment modalities. In establishing such recommendations evidence related to clinical, economic and organisational aspects as well as convenience of therapy must be taken into account.

Therefore the four main research questions related to this health technology assessment about LTOT were the following:

1. Which patients are most likely to benefit from home oxygen therapy?
2. How do the available products for home oxygen therapy compare with each other in terms of efficacy, safety, and convenience?
3. Cost comparison addressing the total cost in Belgium for home oxygen therapy between the different modalities and in different patient types.
4. Comparison of the Belgian model with models existing in France, the Netherlands, United Kingdom and Germany. The "a priori' idea was to capture any positive factors for improvement of LTOT in Belgium

The scientific approach and the information pertaining to these four main research questions are presented in five chapters:

Chapter1: Description of the Belgian context and data availability

Chapter 2: Systematic review of the clinical literature

Chapter 3: Systematic economic literature review

Chapter 4: Health economic evaluation in Belgium

Chapter 5: International comparison of the organisation of home oxygen therapy

A final chapter includes a summary of the main findings and limitations of this health technology assessment report and provides an answer to each of the four main research questions:

Chapter 6: Final Conclusions and Limitations of the Current HTA Report

Chapter 1
Description of the Belgian context

1 INTRODUCTION

In Belgium oxygen is registered as a drug according to the Royal Decree of the 3th July 1969 and the European Regulation 726/2004/EG of the European Parliament and Council of the 31st of March 2004. Oxygen was considered as a magistral preparation until 2001; hereafter it became a "speciality drug" and is encoded according to the ATC (= Anatomical, Therapeutic, Chemical) as V03AN01: liquid and gaseous medical oxygen.

Currently, there are over 5 million people in the world on long term oxygen at home.

Oxygen at home can only be delivered by specific equipments. Different equipments – cylinders, oxygen concentrators, liquid oxygen systems – can be used. Equipment supply is provided by hospitals or by health care companies, with or without the intervention of ambulatory pharmacies. Installation, education of the patients, home supervision of patients and surveillance of correct function of equipments are done by physicians or pharmacists with the help of nurses, physiotherapists, technicians from the hospital or from the health care companies (this task is in the majority of the cases delegated to health care companies). In Belgium the Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV) / Institut National d'Assurance Maladie Invalidité (INAMI) not only reimburses the drug but also the equipment, installation, education and supervision. There are two channels to get home oxygen installed and reimbursed:

- It can be prescribed within the functional rehabilitation convention between the RIZIV / INAMI and a hospital (in the further text the term " the RIZIV/INAMI - hospital convention" will be used).
- Prescription outside this context is also possible according to an agreement with reimbursement to the pharmacist (in the further text the term " RIZIV/INAMI agreement with the pharmacists" will be employed).

The present chapter discusses the use of and the expenditure for the provision of oxygen at home in Belgium. The chapter has two main paragraphs:

1. the content (including patient and physician characteristics, responsabilities of the prescriber, equipment used, ….) of and the differences between the two Belgian prescription and reimbursement channels. This paragraph will include a detailed overview of the costs of the therapy and evolution of costs over the last years in and out hospital convention. Costs will be separated in netto costs for the RIZIV / INAMI and costs for the patient.
2. an evaluation and comparison of the technical aspects of the different oxygen therapy equipments used in Belgium (in terms of efficacy, safety and convenience).

2 METHODOLOGY

2.1 BELGIAN PRESCRIPTION AND REIMBURSEMENT SYSTEMS

2.1.1 Study of the two Belgian prescription systems

Four legal texts from the RIZIV/INAMI were studied in detail.

1. The convention text of April 1, 2007(convention type 781) [a] : "Overeenkomst betreffende langdurige zuurstoftherapie thuis voor ernstige chronische ademhalingsinsufficiëntie afgesloten tussen het verzekeringscomité van de dienst voor geneeskundige verzorging van het rijksinstituut voor ziekte- en invaliditeitsverzekering en #benaming van de inrichtende macht# van #benaming van het ziekenhuis en eventueel de campus van een fusieziekenhuis# waarbinnen de bij deze overeenkomst bedoelde inrichting functioneert / Convention en matière d'oxygenothérapie de longue durée a domicile en cas d'insuffisance respiratoire chronique grave, conclue entre le comité de l'assurance du service des soins de santé de l'institut national d'assurance maladie-invalidité et #dénomination du pouvoir organisateur# de #dénomination de l'hopital et éventuellement, du site d'un hopital fusionné# dans le cadre duquel fonctionne l'etablissement vise par la présente convention".

2. The agreement with the pharmacists on the 1st of January1996 [b] : " Gecoördineerde tekst van de overeenkomst tussen apothekers en de verzekeringsinstellingen / Texte coordonné de la convention entre les pharmaciens et les organismes assureurs ".

3. The Royal Decree Published in July 13, 2007[c] .
   - Home oxygen therapy can be prescribed outside the convention channel by means of a concentrator: the Kröber[4] oxygen concentrator when distributed by Oxycure.

4. A Royal Decree issued on January 28/01/2011, also allows The Linde Company to prescribe the oxygen concentrator Kröber[d]

The working group's proposals (groepsgewijze herziening:zuurstof ; révision de groupe : oxygène) were not included in the text because this document is an internal document of the RIZIV/INAMI and has no legal status.

Data on the number of centres in convention was found on the website of the RIZIV/INAMI[e].

a http://www.riziv.fgov.be/care/nl/revalidatie/convention/respiratory-disease/pdf/agreementoxygen.pdf
b http://www.inami.fgov.be/drug/fr/pharmacists/agreements/pdf/agreement.pdf (2 last revised versions of June 5, 2009 and April 1, 2010)
c http://www.inami.fgov.be/drug/fr/other-pharmaceutical-supplies/medicaldevice/pdf/arkb200210241 (accessed in April 2010)
d http://www.ejustice.just.fgov.be/doc/rech_f.htm (Accessed in April 2011)
e http://www.inami.fgov.be/care/all/revalidatie/general-information/contacts/pdf/781.pdf (accessed in March 2010)

2.1.2 Number of reimbursements and costs

To estimate the costs for the drug "oxygen" the Pharmanet of the RIZIV/INAMI[f] was consulted. In addition Mr. A. De Swaef (president of the Pharmaceutical Policy Management Unit of the RIZIV/INAMI), Ms. D. Dethier (member of the Pharmaceutical Policy Management Unit of the RIZIV/INAMI), Mr. M. DeFalleur (Pharmanet – RIZIV/INAMI) and Mr. G. Verscuren (Advisor and coordinator of the Revalidation Unit of the RIZIV/INAMI) agreed to give us more information about the number of patients and differences in costs between the "hospital convention" and the pharmacist channel.

No national data were available to us on the number of patients undergoing chronic oxygen treatment as the RIZIV-INAMI data contained only the total number of reimbursements (and not the number of reimbursed patients except for the number of patients in the hospital convention) and no distinction can be made between chronic and acute oxygen use.

2.2 OXYGEN THERAPY EQUIPMENTS

In order to get a correct overview of the different equipments used in Belgium, information was asked:

1. to UNAMEC v.z.w./a.s.b.l – contact person Ms. A. Leys. UNAMEC is a professional society of commercial companies which produces, imports or distributes medical devices.
2. separately to, as far as we know, all different Belgian commercial companies dealing with oxygen therapy at home; mailing was done (March 2010) to the following companies:
   - companies member of UNAMEC
     - Airliquide/VitalAire (bruno.gaidoz@airliquide.com)
     - Air Products (vandrap@airproducts.com)
     - Linde Gas (guy.vanhulsel@linde.com)
     - Messer/Oxysphair (nik.decorte@oxysphair.be)
     - Vivisol (patrick.vanbever@vivisol.be)
   - others
     - Ijsfabriek Strombeek (harry.kuppers@ysfab.be)
     - Oxycure (oxycure@oxycure.be)

Prof. J-F. Muir and Mech. Eng. D. Forêt agreed to evaluate and compare the technical aspects of the different equipments. They are member (and Prof Muir the president) of ANTADIR which is a French non-for-profit organisation delivering 70% of all respiratory home therapy in France[g].

f http://www.riziv.fgov.be/drug/nl/statistics-scientific-information/index.htm#1 (accessed in March 2010)

g http://www.antadir.com (accessed in November 2009)

3 RESULTS

3.1 PRESCRIPTION AND REIMBURSEMENT SYSTEMS

3.1.1 The INAMI/RIZIV-hospital convention system

3.1.1.1 The content

Physicians allowed to prescribe

Reimbursement is only possible if the prescription is performed in a department of pulmonology of a hospital or a campus of a hospital admitted to the convention. This department should consist of at least 1 pulmonologist[h] (with a RIZIV/INAMI inscription number ending with 587, 620, 624, 631 or 638) and in case oxygen is prescribed to children at least 1 paediatrician with special interest in paediatric pulmonology.

The department should be able to perform spirometry, diffusion capacity, ventilatory mechanics, arterial blood gases and transcutaneous oxygen saturation. In addition the hospital or campus, should be able to measure pulmonary arterial pressure by catherisation and to start controlled or assisted continuous ventilation in case of an emergency[i].

Indications

Reimbursement is only possible for severe chronic hypoxemia. Chronic severe hypoxemia is defined as chronic daytime hypoxemia, but reimbursement for chronic nocturnal hypoxemia is possible too, and there is a separate regulation for patients who use home mechanical ventilation and need oxygen supplement.

A. Daytime chronic hypoxemia within convention is defined as two lowered PaO2-values measured at rest with a period in between of at least 3 months[j] taking into account that the measurements were performed in a period without acute exacerbation of the underlying pulmonary disease and in a patient following the appropriate medical and physical treatment including cessation of smoking.

Reimbursement is possible when the following lowered PaO2-values are reached:

1. the PaO2 is ≤ 55 mmHg, or
2. the PaO2 is > 55 and < 60 mmHg with co-morbidity:
   - hematocrit > 55% and/or
   - a clear picture of chronic cor pulmonale, or in case of doubt a mean
   - pulmonary arterial pressure (PAP) on catherisation > 20 mmHg or an
   - estimated systolic PAP > 40 mmHg on echocardiography;

In addition, a short oxygen trial with at least 1 l/min of oxygen supplement should demonstrate a significant amelioration of the oxygenation without worsening hypercapnia. Oxygen should be prescribed for at least 15 hours / 24 h.

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h The present existing convention dates from 2007. In case a hospital department already had an oxygen convention before, but signed by a specialist in internal medicine (with a RIZIV/INAMI inscription number ending with 580 or 584) or a paediatrician without the certification of specialisation in pulmonology (with a RIZIV/INAMI inscription number ending with 690 or 694), these physicians could still adhere to the convention (=a transitional measure).

i In case no catherisation or ventilation could be performed in the hospital or campus of the hospital, these "acta" could be delegated to another hospital or campus in the neighbourhood, but only with an explicit motivation and a contract between the hospitals or campi concerned

j In case daytime PaO2 is ≤ 55mmHg, a period of only 15 days in between is enough to ask reimbursement for a shorter period of 3 months, after which reimbursement can be asked, if applicable, for a whole year.

B. Reimbursement for chronic nocturnal hypoxemia is only possible if there is, in stable condition, over the night an oxygen desaturation < 90% during at least 2 hours on a continuous trancutaneous oxygen saturation measurement with

1. hematocrit > 55% and/or
2. a clear picture of chronic cor pulmonale, or in case of doubt a mean PAP on catherisation > 20 mmHg or on echocardiography an estimated systolic PAP > 40 mmHg and/or
3. neuropsychological dysfunction.

C. Patients on mechanical (continuous, discontinuous or nocturnal) home ventilation in whom the ventilatory modality is insufficient to maintain oxygen saturation > 90% during at least 2 hours, can get oxygen treatment reimbursed.

The reimbursement period is limited to maximal 1 year, but can be renewed. Renewal of reimbursement is possible after 1 year and further on every year in case the patients with daytime hypoxemia still demonstrate a lowered PaO2 within the ranges as indicated above and in case of oxygen treatment for patients with a baseline PaO2 ≤ 55 mmHg renewals of reimbursement are possible without a new arterial blood gas puncture but based on transcutaneous oxygen saturation ≤ 88% from the second renewal on. Renewal of reimbursement of oxygen is also possible for patients with nocturnal hypoxemia and patients on home ventilation, but the criteria needed are not mentioned in the convention text.

Equipment

Reimbursement is possible for the following equipments:

- oxygen concentrator
- oxygen concentrator plus 0,4 m3 compressed oxygen cylinder with saving valve (=portable cylinders)
- liquid oxygen.

A. An oxygen concentrator is reimbursed to all patients fulfilling the indication criteria as mentioned above.

B. In order to be reimbursed for supplementary portable (0,4m3 compressed oxygen) cylinders with saving valves, the patient should prove ambulation:

- in case of daytime hypoxemia or mechanical home ventilation fulfill the criterion for oxygen supplement reimbursement described above and be ambulatory outside the home for at least a mean per day of 30 minutes averaged over 1 week or
- in case of nocturnal hypoxemia, demonstrate under stable condition, on two separate occasions with a minimal in between period of three months oxygen desaturation < 88% on a 6 minute walking test.

C. In order to get liquid oxygen reimbursed the patient should fulfil the criteria of daytime hypoxemia or the criterion of mechanical home ventilation needing oxygen supplement (criteria described above) and also prove ambulation, spending more time outside the home[k]: at least a mean per day (averaged over 1 week) of 3 consecutive hours, in the context of professional activities, school attendance, social and cultural activities.

A detailed flow chart of the decision tree:

see addendum 1.

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[k] There are two exceptions to this "3 consecutive hours rule outside the home":
1) in case of cystic fibrosis liquid oxygen is reimbursed if PaO2 > 55 (but < 65) mmHg and if on a 6 minute walking test oxygen saturation falls < 88%;
2) in case of proven daytime hypoxemia (cfr criteria described above) and restrictive pulmonary disease liquid oxygen is reimbursed if there is a need of > 3 l/min of oxygen supply.

Reimbursement conditions

The pulmonologist or paediatrician is responsible for:

1. prescription of the oxygen modality
2. prescription of the duration of hours oxygen use per day with surveillance of the therapeutical compliance
3. installation and surveillance of efficiency at home of
   - either an oxygen concentrator able to continously supply oxygen of a FiO2 ≥ 90% at a flow rate of 3 liter/min (the efficiency of the concentrator should be checked regularly). In case of agreement on adding compressed 0,4 m3 oxygen cylinders, the physician is also responsible to prescribe the amount of specific cylinders needed. These cylinders should be portable, delivered in a bag with a total weight in a 100% filled condition, including the flow control meter and saving valve, < 5 kg
   - or a liquid oxygen system consisting of a large static and small portable system.

In addition, the pulmonologist or paediatrician is responsible of delivery and renewal, when necessary, of all kind of filters needed, as well as nasal canulae or masks and connection tubes. The connection tubes should be adapted to the home of the patient enabling him or her to move in the house in a comfortable way.

4. education and motivation of the beneficial with oxygen therapy in general and especially in a safe and correct use of the specific device(s) with surveillance of the therapeutical compliance
5. help in case of an incident: 24 on 24 hours
6. retrievement of the equipment at the end of the therapy
7. contact with the general practitioner responsible for the patient, and in case of oxygen cylinders or liquid oxygen also the pharmacist of the patient
8. the administrative procedure to obtain (and if applicable renew) reimbursement of the therapy from the mutual health care fund (mutualiteit / mutualité) of the patient.

The general practitioner of the patient is involved in points 1,2 and 3: installation, information, motivation and adherence to the treatment. In case of oxygen cylinders or liquid oxygen the pharmacist is involved too. A lot of the above mentioned required conditions are often delegated to home health care companies (3,4,5).

The hospital or campus of the hospital is responsible for

1. a correct invoicing procedure (to start or renew the convention) to the mutual health care fund (mutualiteit / mutualité) of the patient with copy to the patient
2. a correct reimbursement of the patients' electricity costs in case an oxygen concentrator is used
3. a report mentioning the "production data" every 3 months
4. an accounting with income and expenses, to be send yearly to the RIZIV/INAMI
5. a year report about number of patients and the therapeutic modalities used, to be send yearly to the RIZIV/INAMI
6. a correct information and facturation procedure to the mutual health care fund (mutualiteit / mutualité) in case of hospitalisation of the patient the pseudocode(s) may not be reimbursed/facturated.

Number of hospital conventions

In total: 130

For comparison: according to the website of the Belgian government there are in Belgium 141 general hospitals or campi (113 acute ones, 20 specialised hospitals and 8 geriatric ones).

NUMBER PER PROVINCE:

Antwerpen: 19; Brabant Wallon: 4; Brussel Bruxelles: 15; Hainaut: 21; Liège: 13; Limburg: 7; Luxembourg: 3; Namur: 6; Oost-Vlaanderen: 18; Vlaams-Brabant: 5; West-Vlaanderen: 19

Overview of the pathway ~ distribution and reimbursement

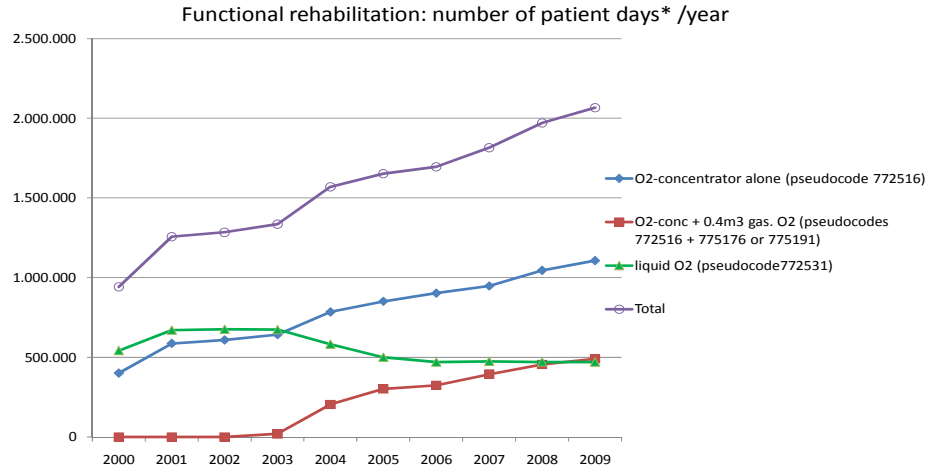
- for oxygen concentrator: see addendum 2
- for supplementary portable oxygen cylinders in addition to the oxygen concentrator: see addendum 3
- for liquid oxygen: see addendum 4

3.1.1.2 Number of reimbursements and costs

According to the RIZIV/INAMI data from 2009, 6.550 patients are reimbursed in the hospital convention mostly for COPD (but probably also for other diagnoses) with a median age of 71 year. There are 56 patients with cystic fibrosis with a median age of 42 year.

Evolution of number of convention pseudocodes per year

Pseudocodes are codes attributed to the rehabilitation intervention. Each 24 hour the patient is using an oxygen modality is 1 rehabilitation activity or pseudocode. The evolution of pseudocodes is represented in the first figure. In the second figure you can find the number of patient days on oxygen, taking into account that patients using portable oxygen cylinders also use an oxygen concentrator and consequently combine 2 pseudocodes.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
O_2-concentrator alone	400.237	586.831	608.154	642.016	783.927	850.629	901.982	946.993	1.045.237	1.106.216
O_2-conc + 0.4m³ gas. O_2	0	0	0	19.436	203.990	301.643	324.120	394.001	454.974	490.590
liquid O_2	541.799	670.716	676.169	673.631	582.257	500.078	469.658	474.424	470.375	469.754
Total	942.036	1.257.547	1.284.323	1.335.083	1.570.174	1.652.350	1.695.760	1.815.418	1.970.586	2.066.560

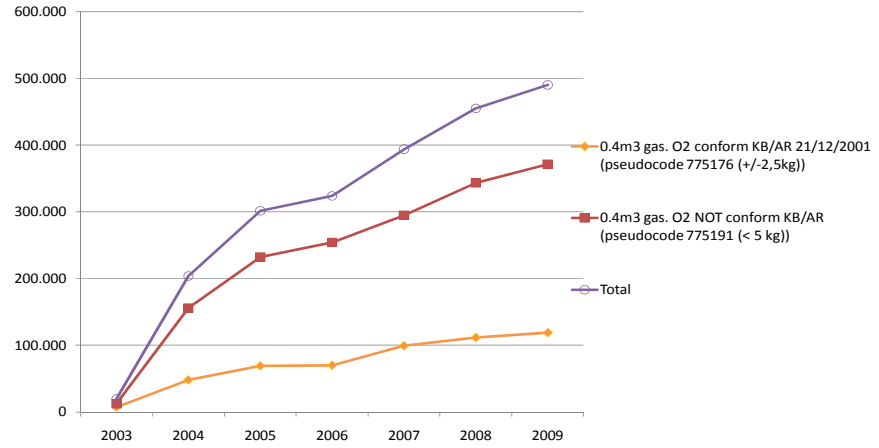
* Patients on 0.4 m³ cylinders all use an oxygen concentrator

As represented on the figures, there is from 2003 on, a clear reduction in prescription of liquid oxygen which might represent a substantial saving: the cost of the drug liquid oxygen is considerably higher than the cost of gaseous oxygen (cfr the topic "costs of the oxygen drug" on p. 17) and in case of the use of oxygen concentrators there are no costs for the drug at all.

Since 2003 implementation of portable gaseous oxygen cylinders of 0,4 m3 is possible in case of prescription of gaseous oxygen conform KB/AR 21th December 2001 §207: light weighted 0,4 m3 devices with integrated saving valve (=composite cylinders with aluminium liner fabricated by Luxfer, with VTE ventiltechnik and in Belgium only distributed by Oxysphair/Messer) (pseudocode 775176). Yet, based on the MB 10th January 2002 also other 0,4 m3 devices not conform to the KB/AR mentioned above, but delivered with an external saving valve and a total weight < 5 kg could be prescribed too (pseudocode 775191). These cylinders can be distributed in Belgium by different commercial companies. The light weighted devices with composite material and internal valve distributed by Oxysphair/Messer weights +/-2,5 kg, while the weight of the other cylinders is generally in between 4 to 5 kg.

As illustrated in the following figure the real light weighted cylinders of +/-2,5 kg with integrated saving valve are less frequently prescribed.

Number of pseudocodes or patient days on the different 0,4 m³ portable cylinders / year



	2003	2004	2005	2006	2007	2008	2009
0.4m³ gas. O_2 conform KB/AR 21/12/2001 (pseudocode 775176 (+/-2,5kg))	7.238	48.034	69.146	69.970	99.329	111.654	118.964
0.4m³ gas. O_2 NOT conform KB/AR (pseudocode 775191 (< 5 kg))	12.198	155.956	232.497	254.150	294.672	343.320	371.626
Total	19.436	203.990	301.643	324.120	394.001	454.974	490.590

Netto costs for the RIZIV/INAMI

A. FOR INSTALLATION, SURVEILLANCE, EDUCATION, ADMINISTRATION ETC…(= THE FUNCTIONAL REHABILITATION)

1. Fees, reimbursement to the medical department (pulmonology) / hospital:
   a. for an oxygen concentrator (pseudocode 772516):

      8,51 euro / 24 h, of which 0,92 euro / 24 h should be transferred to the patient for electricity costs

   b. for compressed 0,4 m3 oxygen cylinders there exist two different reimbursement regulations[1]:
      - either 1,3 euro / 24 h

        in case of prescription of gaseous oxygen conform KB/AR 21th December 2001 §207 and MB 10th January 2002: light weighted 0,4 m3 devices with integrated saving valve (pseudocode 775176)

[1] the discrepancy between the pseudocodes 775176 and 775191 is explained because the saving valve is in case of 775176 actually integrated in the price of the oxygen, see also on p.15

- or 3,81 euro / 24 h

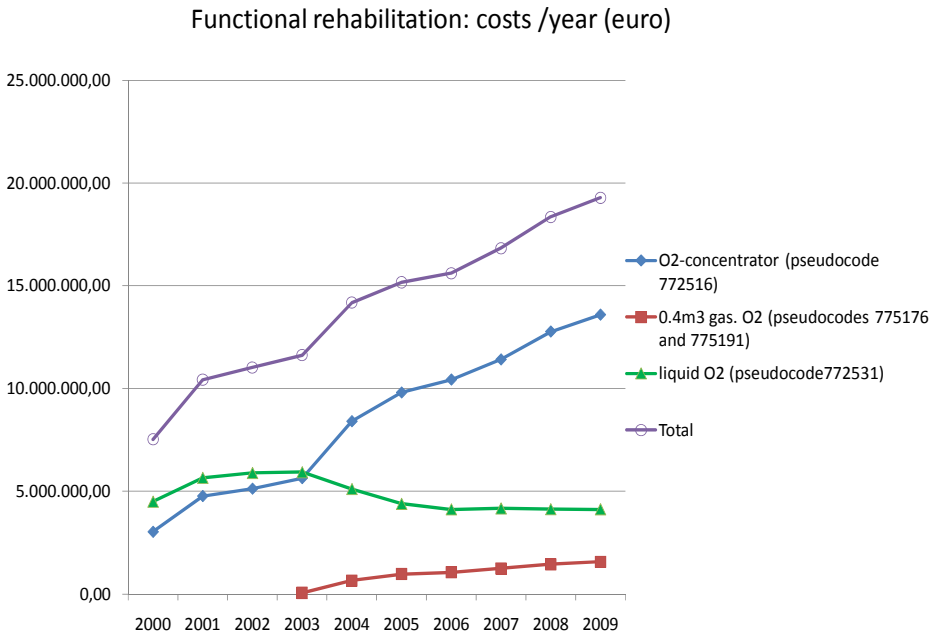
  in case of prescription of other 0.4 m3 devices not conform to the KB/AR mentioned above, but delivered with an external saving valve and a total weight < 5 kg (pseudocode 775191)

c. for liquid oxygen: 8,78 euro / 24 h (pseudocode 772531)

The prices mentioned are the flat amounts (forfaitaire bedragen / prix forfaitaires) of 2007 and VAT[m] included.

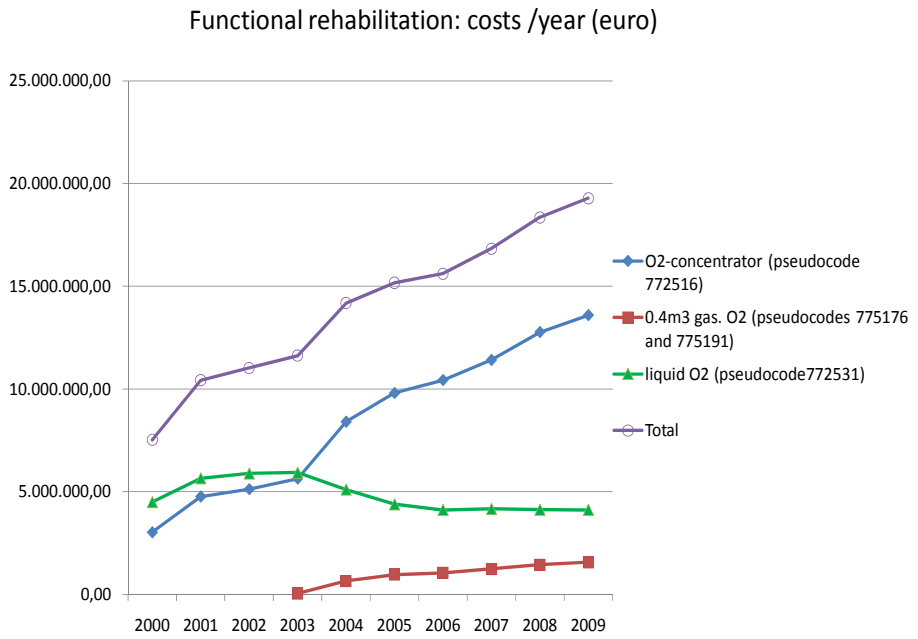
2. Evolution of the costs for the functional rehabilitation acta per year

a. Costs divided according to the different pseudocodes



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
O_2-concentrator	3.033.344	4.770.678	5.129.132	5.641.739	8.407.408	9.807.255	10.433.675	11.411.850	12.766.746	13.589.254
0.4m^3 gas. O_2				55.884	656.884	975.703	1.059.273	1.251.828	1.453.196	1.570.903
liquid O_2	4.497.989	5.660.598	5.893.983	5.932.979	5.115.547	4.390.468	4.123.430	4.165.454	4.129.893	4.124.440
Total	7.531.332	10.431.276	11.023.115	11.630601	14.179.839	15.173.426	15.616.378	16.829.132	18.349.834	19.284.597

[m] VAT is 21%, except for oxygen concentrators which can also deliver aerosol (VAT 6 %)



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
O_2-concentrator	3.033.344	4.770.678	5.129.132	5.641.739	8.407.408	9.807.255	10.433.675	11.411.850	12.766.746	13.589.254
0.4m^3 gas. O_2				55.884	656.884	975.703	1.059.273	1.251.828	1.453.196	1.570.903
liquid O_2	4.497.989	5.660.598	5.893.983	5.932.979	5.115.547	4.390.468	4.123.430	4.165.454	4.129.893	4.124.440
Total	7.531.332	10.431.276	11.023.115	11.630601	14.179.839	15.173.426	15.616.378	16.829.132	18.349.834	19.284.597

The rehabilitation costs of the 0,4 m3 cylinders with external valve (pseudocode 775191) is +/-10 times higher than the rehabilitation costs of the lighter weighted cylinders with internal valves, distributed by Oxysphair/Messer (pseudocode 775176). The explanation for this increased cost is double:

1. As illustrated in the figure on p. 13, significantly more patients are prescribed and using the cylinders with external valve (although heavier than the Oxysphair/Messer cylinders with composite material and internal valve!).
2. The rehabilitation fee for cylinders with external valves is higher. Yet, it is important to note that the higher reimbursement of the rehabilitation acta do not necessarily result in a higher total cost for the RIZIV/INAMI because the cost of the oxygen drug is lower: in case Oxysphair/Messer cylinders with internal valve are used the cost of the internal valve is integrated in a much higher reimbursement price for the oxygen drug, as will be illustrated in the figure in the text on p. 19. The total cost (functional rehabilitation and oxygen drug) for the RIZIV/INAMI can vary considerably depending on how many cylinders are used and this will be illustrated on p. 20.

    a. Data on total rehabilitation costs

In the figure on p. 14, there is an increase in costs. The figure below clearly illustrates that the further increase in costs since 2004 is mainly due to the increase in number of patients as the cost per patient / day was steadily increasing until 2004, but is from that year on +/- stable.

    b. Evolution of costs of the oxygen rehabilitation convention relative to the costs of the whole rehabilitation section of the RIZIV/INAMI

As represented below the % of costs of the oxygen convention within the whole functional rehabilitation is small and remains plus minus stable.

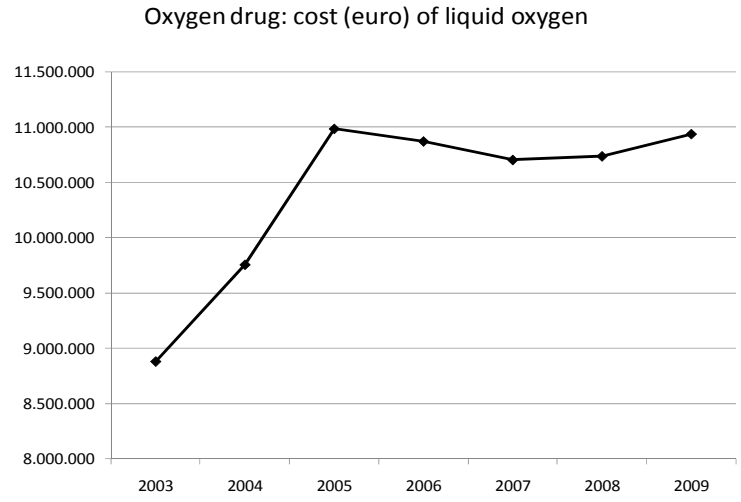
B. FOR THE OXYGEN DRUG

1. Amounts reimbursed to the pharmacists (the pharmacists reimburse the home care companies).

Total amount (VAT[n] included) reimbursed to the pharmacists is:

- for gaseous oxygen
  - in case of prescription of gaseous oxygen conform KB/AR 21th December 2001 §207 and MB 10th January 2002: light weighted 0,4 m3 devices with integrated saving valve 32,92 euro per cylinder
  - in case of prescription of other 0,4 m3 devices not conform to the KB/AR mentioned above, but delivered with an external saving valve and a total weight < 5 kg 2,48 euro per cylinder
- for liquid oxygen :
  - 6,57 euro /m3 before 1/4/2010, 6,03/ m3 since 1/4/2010.

2. Evolution of the costs for the drug oxygen per year
   a. for liquid oxygen



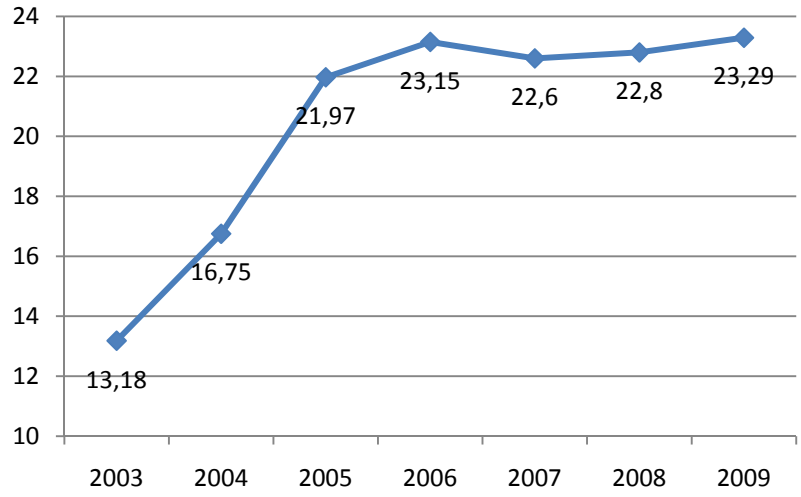
	2003	2004	2005	2006	2007	2008	2009
liquid oxygen	8.878.689	9.755.043	10.985.950	10.872.570	10.704.495	10.737.548	10.938.819

Data on evolution of the costs for liquid oxygen are available until 2009 and show a stabilisation since 2005. This stabilisation is due to proportional less patients on liquid oxygen, as illustrated on p. 12.

The following figure illustrates that the costs / patient for the liquid oxygen drug has increased since 2004, reflecting higher oxygen consumption (and probably using the liquid oxygen for more hours of ambulation, conform the requirement in the RIZIV/INAMI-hospital convention).

[n] the VAT on all oxygen drugs (liquid or gaseous) is 6%

Oxygen drug: cost (euro) of the liquid oxygen drug / patient / day



b. for portable compressed 0,4 m3 oxygen cylinders

The RIZIV/INAMI delivered data on the total costs of the gaseous oxygen drug: the sum of gaseous oxygen used by patients within the RIZIV-INAMI hospital convention and the RIZIV-INAMI agreement with the pharmacists. It is quite more complex to obtain correct separate data from considering the evolution of the costs for the gaseous oxygen drug used in the portable light weight cylinders within the RIZIV/INAMI-hospital convention.

Yet, an estimation can be performed and data are represented in the figure below, based on

1) the number of rehabilitation pseudocodes on the different 0,4 m3 portable cylinders / year (cfr figure p. 13)

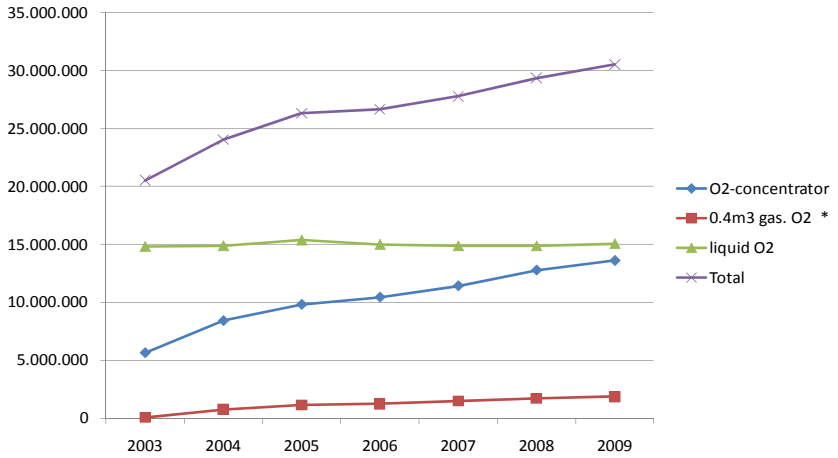
2) the calculation of a home care company distributing 0,4 m3 oxygen cylinders with external valve (AirLiquide/VitalAire) that the mean consumption of portable cylinders / patient / month is 1,8.

As mentioned previously, on p. 15, the significantly higher cost of the oxygen drug when using the very light weighted cylinders with internal valves, is explained by the fact that the internal valve cost is integrated in the cost of the oxygen drug.

C. FOR THE SUM OF FUNCTIONAL REHABILITATION AND OXYGEN DRUG

As represented in the following figure, the total cost for the functional rehabilitation fee plus the oxygen drug cost is increasing from year to year. Yet, the slope of increase in costs is lowered from 2004 on, which is due to a proportional clear increase in prescription of portable gaseous oxygen in addition to an oxygen concentrator instead of liquid oxygen. The costs of the rehabilitation fee for a concentrator is only little lower than the fee for liquid oxygen, yet in case of use of an oxygen concentrator with portable cylinders gaseous oxygen is added which is considerably cheaper than liquid oxygen.

Total costs of functional rehabilitation and the oxygen drug / year (euro)



	2003	2004	2005	2006	2007	2008	2009
O2-concentrator	5.641.739	8.407.408	9.807.255	10.433.675	11.411.850	12.766.746	13.589.254
0.4m3 gas. O2 *	71.775	773.349	1.144.531	1.232.884	1.488.582	1.721.100	1.857.202
liquid O2	14.811.668	14.870.590	15.376.418	14.996.000	14.869.949	14.867.441	15.063.259
Total	20.525.182	24.051.347	26.328.204	26.662.559	27.770.381	29.355.287	30.509.715

* based on an estimation of the gaseous oxygen drug cost, cfr supra

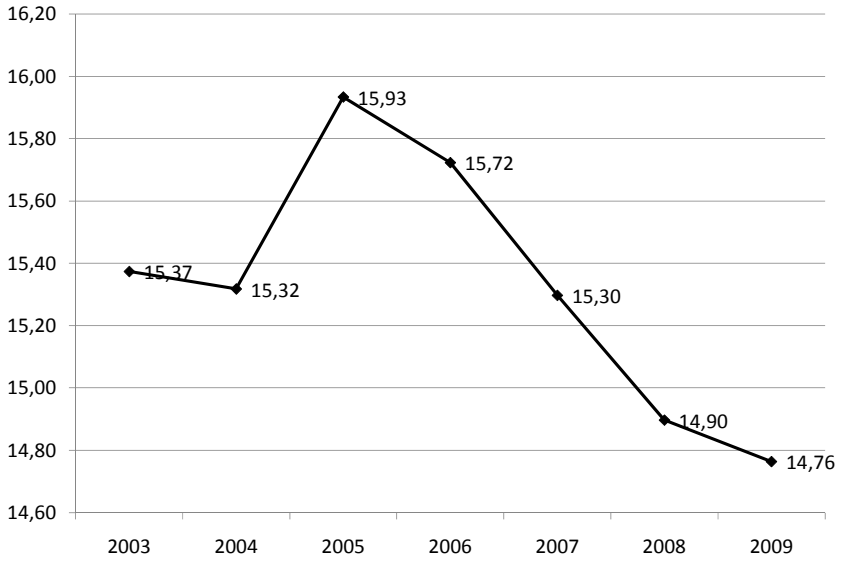
Note: The total cost (functional rehabilitation and oxygen drug) of gaseous portable oxygen cylinders is different between the 2 modalities. In case the patient is using only 1-2 cylinders per month, the total cost of the modality with internal valve and lighter weight is cheaper than in case the somewhat heavier cylinders with external valve are prescribed; yet, once the patient is using more than 2 cylinders the modality with internal valve becomes more and more expensive which is illustrated below.

Total costs (rehabilitation and oxygen drug) / month (euro) for 1 patient depending on the different portable O2-cylinder modalities and the amount of cylinder used

	1 cylinder / month	2 cylinders / month	3 cylinders / month	4 cylinders / month	5 cylinders / month	6 cylinders / month	7 cylinders / month
0.4m3 gas. O2 conform KB/AR 21/12/2001 (with internal valve - total weight +/-2,5 kg)							
rehabilitation	39,65	39,65	39,65	39,65	39,65	39,65	39,65
oxygen drug	32,92	65,84	98,76	131,68	164,6	197,52	230,44
TOTAL	72,57	105,49	138,41	171,33	204,25	237,17	270,09
0.4m3 gas. O2 NOT conform KB (with external valve, total weight 4-5 kg)							
rehabilitation	116,21	116,21	116,21	116,21	116,21	116,21	116,21
oxygen drug	2,48	4,96	7,44	9,92	12,40	14,88	17,36
TOTAL	118,69	121,17	123,65	126,13	128,61	131,09	133,57

The increase in total costs (functional rehabilitation and oxygen drug) from year to year is explained by an increasing number of patients, as already shown on p. 11 and 12. The following figure clearly illustrates the cost saving per patient over the last years.

Evolution of the total cost (rehabilitation and drug cost) per patient / day in the RIZIV-INAMI hospital convention



Note: for the gaseous oxygen drug cost, the same estimation was performed as mentioned supra

D. ADDENDUM

Since 1/4/2010 a supplementary cost must be taken into account. The RIZIV-INAMI has decided to reimburse the pharmacists for their coordination, support and tarification acta of the oxygen drug (gaseous as well as liquid) with P 13,41 (VATincluded) euro / patient / month.

Costs for the patients

There is no patient contribution ("REM geld / ticket modérateur").

In case a concentrator is installed, a fixed amount (0,92 euro / 24 h) for electricity costs is reimbursed. This amount is a part of the functional rehabilitation fee paid to the medical department (pulmonology) / hospital.

3.1.2 Study of the RIZIV/INAMI agreement with the pharmacists

3.1.2.1 The content

Physicians allowed to prescribe

All physicians, both general practitioners and specialists of any speciality can prescribe oxygen.

Indications

In the agreement text there is no need to fulfil any indication or criterium. Prescription is based on the estimation of medical need. No smoking cessation is demanded.

Equipment

Reimbursement is possible for the following equipments:

1. oxygen gas cylinders
2. one single type of oxygen concentrator "Kröber", distributed by one single home care company "Oxycure"

Reimbursement conditions

In this agreement patients are not asked to use the oxygen for a minimum duration / 24 hours and the prescription can be renewed, without any check up of the clinic of the patient and/or the therapeutical compliance, for an unlimited duration.

The reimbursement conditions within the agreement between the community pharmacists and the health insurance companies (mutualiteiten/mutualités) for the home oxygen provision outside the hospital convention are found in article 6 Bis/

A. PROVISION OF OXYGEN GAS CYLINDERS

During the duration of the period of oxygen provision, the health insurance companies commit to refund the pharmacists for providing home oxygen and all the required equipment, including stocking of the oxygen cylinders and manometers, to meet the needs of the patients.

For this type of home oxygen prescription, a physician has to order gaseous oxygen. The prescription has to mention the following items:

- Quantity of oxygen to be delivered (liters)
- Period of the prescription (DD/MM/YYYY to DD/MM/YYYY)
- The flow rate (L/min)
- Disposable humidifier if required

The pharmacist in agreement with the patient or the prescribing physician can choose to deliver the gaseous oxygen with provision of all the equipment or to ask a commercial home care company to supply, install and maintain the equipment. The terms "all required equipments" encompass:

- Nasal canula or mask
- Oxygen supply tubing
- Disposable humidifier
- Oxygen cylinders with or without an integrated manometer

Home oxygen provision by the pharmacist

In case the pharmacist decides to deliver and install the gaseous oxygen and all the required equipment, he will be responsible for:

1. The control of the installation
2. Informing the patient with inclusion of a written text about the correct utilization of the accessories and the flow rate(s) of oxygen to be used
3. Not to account to the patient higher prices than P 21,10 included VAT for installation. The letter P is a coefficient with a monetary value that regularly changes for example the P value was 1,702250 in 2010. The installation costs can be requested only once during the duration of the treatment. A therapy is considered new if the previous one has expired at least six months before. In this case the pharmacist can bill new installation costs.

Moreover, the pharmacist must attend to:

1. Supply the patient with oxygen cylinders (Max: 3) and ensure a proper stock rotation of the cylinders
2. Rent a manometer integrated or not at the cylinders
3. Provide a guarantee for the supply of masks or nasal canulae and tubing for the correct delivery of oxygen
4. Supply monthly the patient with a disposable humidifier
5. Stick to the official prices listed beneath.

Once monthly, the pharmacist provides a certificate to the mutual healthcare funds consistent with the official model (listed in appendix 1 of the agreement), which includes:

- The CNK codes (Code national (e) Kode = the unique identification number for each conditioning of a drug or a device in Belgium) and description of the accessories used during the period under consideration.
- For the accessories listed at points 1 and 2 of the preceding paragraph:
  - The renting price per unit per day or per month in accordance with the prices sent to insurers for the involved months.
  - The number of rental units
  - The number of days during which these accessories were really rented. In case of a monthly rental basis, the pharmacist mentions in the form "1 month"
- For the accessories listed at points 3 and 4 of the preceding paragraph, the price per unit in accordance with the prices sent to the insurance companies for the involved months.

If the forms are correctly completed, the health insurers agree to give a refund in accordance with the amount mentioned by the pharmacist with a maximum per calendar month of:

- € 27,72 VAT included for the renting of cylinders and pressure regulator
- € 3,18 VAT included for the masks and/or nasal cannulae
- € 2,12 VAT included for the oxygen supply tubing
- € 5,51 VAT included for the disposable humidifiers

Per calendar month, only one mask or one nasal cannula, one oxygen supply tubing and one disposable humidifier are refundable.

A charter defining the general principles to follow in this convention has been established between the RIZIV/INAMI and professional associations of pharmacists.

Home oxygen provision by a home care company

The pharmacist can ask a home care company to deliver oxygen at home of the patient. The commercial supplier may charge the pharmacist for the installation costs.

The health insurance companies agree to refund the pharmacist with a maximum of P 21,10 VAT included. As previously noted a new therapy can only be considered if the previous one expired at least six months before.

For every submitted prescription correctly fulfilled, the health insurance companies agree to refund the pharmacist with a maximum per calendar month of:

- € 27.72 VAT included for the renting of cylinders and manometer
- € 3.18 VAT included for the masks and/or nasal cannulae
- € 2.12 VAT included for the oxygen supply tubing

- € 5.51 VAT included for the disposable humidifiers

Per calendar month, only one mask or one nasal cannula, one oxygen supply tubing and one disposable humidifier are refundable.

Until very recently (01/04/2010), the refund was increased by an amount of P 2,65 (VAT included) for the coordination of the pricing by the pharmacist. This specific remuneration was due per patient and per month. Since April 2010, this fee has been replaced by 22,83 euros (VAT included) irrespective of the quantity of oxygen delivered to the patient.

In case the amount billed by the home care companies is higher than the official remuneration of the RIZIV/INAMI, the pharmacist may request the difference to the patients. The pharmacist has to communicate this amount to the mutual health care company of the patient.

The items and services that may be delivered by the commercial oxygen suppliers in connection with the provision of gaseous oxygen at home are listed by the Belgian pharmaceutical association and the cooperative association of pharmacists in Belgium, based on the prices provided by the suppliers. An updated version of this list is sent monthly to the RIZIV/INAMI, to the insurance companies and to the pricing offices. The parties involved who signed the agreement; require from the oxygen suppliers a full list of delivered materials even if these are not reimbursable.

A charter signed between the non-hospital pharmacies and the home care companies ensures compliance with all procedures involved in the "short-term" oxygen therapy convention.

B. Provision of the Kröber oxygen concentrator by Oxycure and Linde

This is the second modality for domiciliary oxygen therapy outside the RIZIV-INAMI hospital convention channel.

Since the publication of the Royal Decrees in the Belgian Monitor (13/07/2007 and 28/01/2011), the hiring of the Kröber concentrator (which was only until recently distributed by the home care company Oxycure and now also by Linde) is entirely refunded following a prescription of any physician. The patient has to give this prescription to his pharmacist. The pharmacist orders one of the two companies to deliver a Kröber oxygen concentrator to the patient's home.

Refunding by the health insurance companies covers the hiring, the installation, the maintenance costs, the accessories necessary to the application of the therapy and the education of the patient.

The prescription must mention the following indications: name of the oxygen concentrator (Kröber Oxycure or Kröber Linde), flow rate and number of hours daily, humidifier. One prescription must be written per calendar month.

Costs of the provision of oxygen by the Kröber oxygen concentrator:

- Installation and patient's education: 31,80 Euros. The installation and patient's education costs can be requested only once during the duration of the treatment. A new therapy can only be considered if the previous one expired at least six months before.
- Renting price for the oxyconcentrator and maintenance: 90,10 Euros/ month
- Humidifier: 5,51 Euros/ month
- Coordination of the therapy by the pharmacist: 4,15 Euros/month.

It should be reminded that electricity is not reimbursed in this type of prescription.

Within this agreement hospital pharmacists can prescribe gaseous oxygen or the Kröber concentrator to patients hospitalized in nursing homes.

In this prescription channel, patients have - by definition - less severe hypoxemia than patients included in the hospital convention. This could induce a weak compliance with therapy. In this case, the delivery of an oxygen concentrator with unrestricted use may lead to a waste of money.

Overview of the pathway ~ distribution and reimbursement

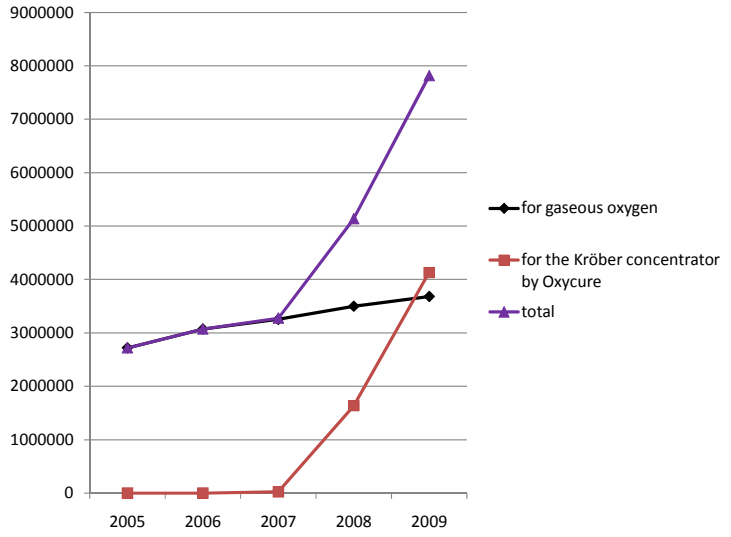
See Addendum: 5-6

3.1.2.2 Costs

Netto costs for the RIZIV/INAMI

For installation, administration, accessories,... conform the agreement with the pharmacists

Costs / year (euro) of the RIZIV/INAMI pharmacist agreement



	2005	2006	2007	2008	2009
for gaseous oxygen (pseudocode 755370)	2.720.145	3.071.655	3.253.578	3.499.117	3.682.431
for the Kröber concentrator by Oxycure (pseudocode 754132)	0	0	24.298	1.636.576	4.132.088
total	2.720.145	3.071.655	3.277.876	5.135.693	7.814.519

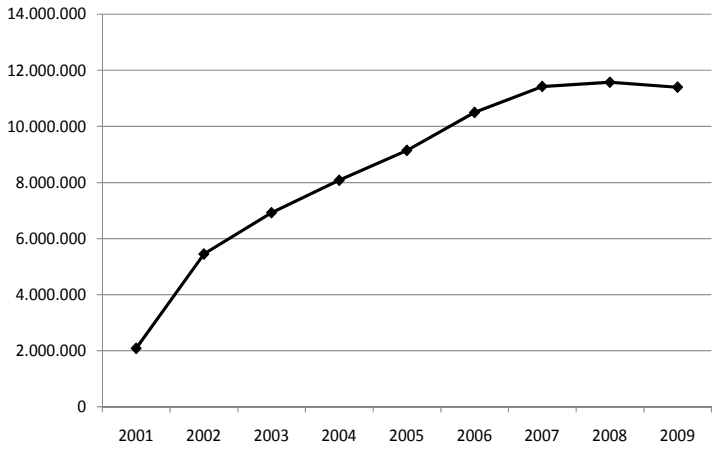
The figure above clearly illustrates an increase in costs over the years with a steep increase since 2007 due to the start of reimbursement of the Kröber Oxycure concentrator.

It is important to note that from april 2010 on there will be a supplemental cost in case of gaseous oxygen prescription. A fee of 22,83 euros (VAT included) per month per patient will be paid to the pharmacists for their coordination and tarification acta of the oxygen drug. The refund was previously only P 2,65 (VAT included, P value for 2010 was 1,702250).

B. For the gaseous oxygen drug within the RIZIV/INAMI agreement with the pharmacists*

* As already mentioned, there are only data on the total costs of gaseous oxygen drug, the sum of gaseous oxygen used by patients within the RIZIV-INAMI hospital convention and the RIZIV-INAMI agreement with the pharmacists. Yet, by substracting the estimated costs of gaseous oxygen within the RIZIV/INAMI-hospital convention, the data represented in the figure below could be obtained. The figure illustrates a stabilisation, even a small decline in the amount of gaseous oxygen prescription outside the RIZIV/INAMI-hospital convention since 2007, the year of the reimbursement of the Kröber Oxycure concentrator.

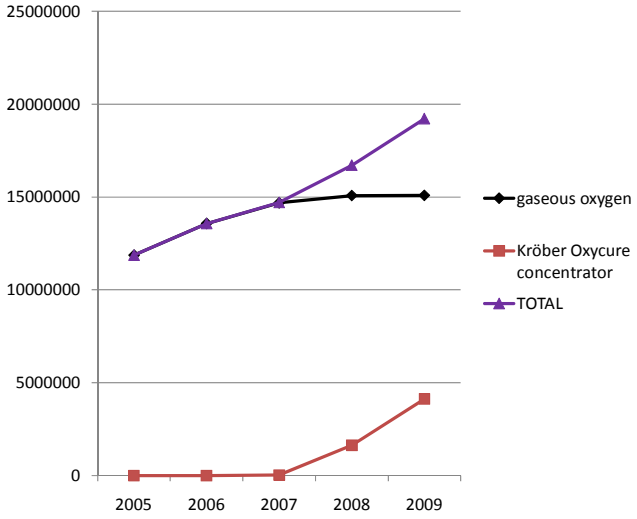
Costs / year (euro) of gaseous oxygen used outside the RIZIV/INAMI-hospital convention



	2001	2002	2003	2004	2005	2006	2007	2008	2009
costs of gaseous oxygen within the RIZIV/INAMI-pharmacist agreement	2.086.229	5.448.624	6.924.123	8.079.841	9.146.105	10.499.534	11.426.095	11.575.248	11.400.811

C. for the costs of both the pharmacist agreement and the drug oxygen

Total costs / year (euro) of the RIZIV/INAMI pharmacist agreement including the oxygen drug



	2005	2006	2007	2008	2009
gaseous oxygen	11.866.250	13.571.189	14.679.673	15.074.365	15.083.242
Kröber Oxycure concentrator	0	0	24.298	1.636.576	4.132.088
TOTAL	11.866.250	13.571.189	14.703.971	16.710.941	19.215.330

The figure above clearly illustrates an increase in total costs over the years with a change in the slope since 2007 (= the year of the start of reimbursement of the Kröber Oxycure concentrator). Although the use of an oxygen concentrator implies no costs for the oxygen drug, we observe a steeper increase in total costs since the Kröber Oxycure concentrator is reimbursed.

This finding suggests that an increasing number of patients is started and/or is using oxygen for a long time outside the RIZIV/INAMI-hospital convention and are placed on the Kröber Oxycure concentrator without any further control.

COSTS FOR THE PATIENTS

In case an oxygen concentrator is used, there is no reimbursement to the patient of the costs of electricity. This is in contrast with oxygen concentrator use within the RIZIV/INAMI-hospital convention: the patient gets a reimbursement of 0,92 euro / 24 hour.

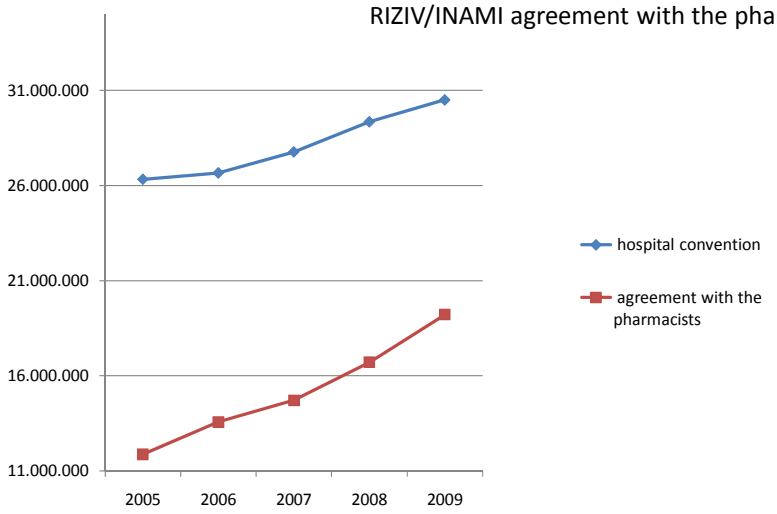
3.1.3 Study of the main differences between both prescription channels

3.1.3.1 The content

RIZIV/INAMI-hospital convention	RIZIV/INAMI agreement with the pharmacists
Physicians allowed to prescribe The physicians allowed to prescribe are pulmonologists or paediatricians with special competence in pulmonology.	All physicians both general practitioners and specialists of any discipline can prescribe oxygen.
Indications A correct diagnosis of severe chronic hypoxemia is mandatory. The severity is well described and arterial blood gases and/or oxygen saturation measurements are mandatory, as is a proof of amelioration of oxygen level when using oxygen. Although "chronic" is not specified in detail in the text, there should be in case of daytime hypoxemia proof of a severe hypoxemia problem present for at least 3 months before the oxygen therapy can be prescribed for 1 year.	There is no need for fulfilling a certain level of oxygen desaturation, there is even no arterial blood gas or transcutaneous oxygen saturation mandatory.
A proof of amelioration of oxygen level is obligatory and the amount of oxygen needed should be clear.	There is no need to check the level of oxygen needed to increase oxygen level.
A blood gas control is obligatory in order to be sure that the oxygen delivery does not result in increasing hypercapnia.	This safety measurement is not mandatory.
A regular check of blood gases in order to follow whether oxygen is still needed is obligatory.	Treatment can be continued without any check of gas exchange, even for years.
The patient should stop smoking. Stop smoking is not only a medical proven beneficial measure for the patient, it is also a safety measure to inhibit burns and risk on explosion.	This smoking cessation stipulation is absent.
Equipment Oxygen concentrators, liquid oxygen and light weight oxygen cylinders with saving valve can be prescribed. These devices are provided by different home care companies.	Oxygen cylinders and oxygen concentrators can be prescribed. Different oxygen gas producing companies can provide the pharmacists. In case of oxygen concentrators only 1 type of oxygen concentrator delivered by 1 home care company can be reimbursed.
Reimbursement conditions The criteria considering installation and surveillance are far more stringent. In case of daytime hypoxemia, it is mandatory that oxygen is prescribed for at least 15 hours / 24 h and the therapeutical compliance of the patient should be checked.	This criterion is absent.
In addition there should be 24 / 24 h help in case of an incident. Besides, when prescribing a concentrator, it is stipulated that the efficiency of the concentrator should be checked regularly.	There is no legal obligation but this is provided in the charters of good practice between the RIZIV/INAMI and the pharmacists and between pharmacists and home care companies.
Costs for the patient None. In case an oxygen concentrator is used, electricity costs are reimbursed.	No reimbursement of electricity costs.

3.1.3.2 The costs

Evolution of total costs (rehabilitation and drug costs) according to the 2 different prescription channels: the RIZIV/INAMI-hospital convention and the RIZIV/INAMI agreement with the pharmacists



	2005	2006	2007	2008	2009
hospital convention	26.328.204	26.662.559	27.770.381	29.355.287	30.509.715
agreement with the pharmacists	11.866.250	13.571.189	14.703.971	16.710.941	19.215.330

There is a significantly higher total cost for the RIZIV/INAMI-hospital convention. Yet, the evolution of the costs is also different between the two prescription channels. Although costs are increasing in both prescription channels, the increase is more pronounced in the RIZIV/INAMI agreement with the pharmacists. In the RIZIV/INAMI agreement with the pharmacists there is in 2009 an increase of 7.349.080 euro compared with 2005 (an increase of 62%), while in the RIZIV/INAMI-hospital convention the increase in costs is 4.181.511 euro (16%).

3.2 OXYGEN THERAPY EQUIPMENTS

3.2.1 Devices used in Belgium

3.2.1.1 In the RIZIV/INAMI-hospital convention

Oxygen concentrators°*
Air Sep VisionAire
Air Sep Quiet Life
Air Sep New Life Elite
Devilbiss Compact 5
Devilbiss Compact 515
Devilbiss Compact 525
Invacare Perfect O2
Krober O2
Nidek Nuvo Q
Nidek Lite
Respironics EverFlo
Mediline Precise 6000

Liquid oxygen systems
Cryopal Freelox + portable system
Caire - Chart Liberator 30, 37, 45, 20 + stroller or Spirit 300 and 600
Covidien standard ambulox 31 l or 41 l + ambulox portable
Covidien sHelios 46 l + Marathon portable

Saving valves used on light weighted 0.4 m3 cylinders
Ceodeux M706 and other Ceodeux saving valves
Weinman Oxytron 3
Kröber Aeroplus SE
GCE mediline Ecolite 4000 and 3000
GCE mediline Combi
Medicap Precise 3000
Devilbiss PD 1000

° the following portable concentrators are (rarely) used, but currently are too expensive to be reimbursed, within the RIZIV/INAMI-hospital convention:
Respironics EverGo,
Inogen One and OneG2
Airsep LifeStyle
Airsep FreeStyle
Devilbiss iGo

3.2.1.2 In the RIZIV/INAMI convention with the pharmacists

Cylinders

- with different content (B2, B5, B10, B20); a B2 = water content of 2 liter, a B5 5 liter etc…,
- can be filled under a pression of 150 or 200 bar,
- can be
  - compact cylinders (with an integrated pressure regulator system)
  - traditional cylinders (with an external pressure regulator system to be installed),
- can have a traditional connection modality or a DIN modality (to be attached to a ventilator)
- material of the cylinders could be steel, aluminium, hoop wrap (aluminium inner wall with Kevlar at the outside) or carbon (note: the aluminium cylinders are the most often used)

Oxygen concentrators

The home care distributor Oxycure can deliver the Kröber oxygen concentrator. This type of oxygen concentrator is the only one allowed to be prescribed outside the hospital convention. Since april 2011, the Krôber concentrator may also be delivered by the home care distributor Linde.

3.2.2 Quality control

Independently discovered by Carl Wilhelm Scheele, in 1773, and Joseph Priestley in 1774, oxygen had its first medical use in 1798 at the Pneumatic Institution for inhalation gas therapy founded by Thomas Beddoes (1760-1808). Later, Haldane used oxygen for gas poisoned soldiers during the First World War and the use of oxygen in hospitals spread widely during the following decades [5].

Cotes and al. described the use of portable oxygen to improve exercise ability in chronic respiratory insufficiency in 1956 [6]. Petty's group began to use domiciliary oxygen in Denver for chronic obstructive pulmonary disease (COPD) patients in the 1960s [7]. In the late 60s, Bishop's group studied the effects of continuous, long-term oxygen therapy on pulmonary circulation in six COPD patients and demonstrated an effect on pulmonary hypertension [8]. These studies became the basis for two controlled studies of long term oxygen therapy (LTOT), the Nocturnal Oxygen Therapy Trial [3] and the medical Research Council Working Party Trial (MRC) [2]. Both studies demonstrated in the early 80s improvement of severe COPD with hypoxic cor pulmonale when oxygen was used at least 12 hours per day. These two landmark studies formed the basis of subsequent development of LTOT technology.

The British Thoracic Society describes three types of home oxygen therapy:

- LTOT for "continuous use at home for patients with chronic hypoxemia (PaO2 at or below 7.3 kPa, (55mmHg). Once started, this therapy is likely to be for life. LTOT is usually given for at least 15 hours daily, including night time.
- Ambulatory oxygen (AO) refers to "the provision of oxygen during exercise and activities of daily living". The oxygen is delivered by a portable system. Most patients on ambulatory oxygen therapy will be also using LTOT.
- Short burst oxygen (SBOT) for "intermittent use of supplemental oxygen at home usually for periods of about 10 to 20 minutes to relieve dyspnoea".

The following paragraphs related to the use of different oxygen sources and the methods of oxygen delivery are based on narrative reviews. We used the titles and abstracts of the formal systematic search of chapter 2 to check the availability of additional clinical studies comparing different oxygen supply systems. New relevant findings, such HTA reports, were added in this chapter. There was no critical appraisal of the relevant studies.

3.2.2.1 Oxygen Sources

Oxygen is produced industrially by fractional distillation of liquefied air, use of zeolite to remove carbon dioxide and nitrogen from air, or by electrolysis of water.

The administration of hyper oxygenated gas mixtures compared to atmospheric air can be provided from diverse gas sources provided from oxygen storing systems, be they gaseous, liquid or oxygen concentrators. These sources require different materials and are based on different physical principles, and thus have different administrative status. Each method has its advantages and disadvantages, but all are capable of providing super concentrated oxygen as required by patients. Thus the choice of materiel is not only based on medical criteria nor flow rate or duration of oxygen therapy required since the sources are very similar in these regards. The criteria of choice are more based on facility of use, security issues, cost and possibilities for transportation and deambulation, as the majority of LTOT users require oxygen during ambulation [9].

Addendum 7 shows the characteristics versus the advantages/disadvantages of the different sources currently used for long-term oxygen therapy.

Gazeous oxygen

Compressed oxygen at 200 bars (200 times atmospheric pressure) allows storage of a large volume of gaseous oxygen in a small container. The oxygen provided is pure and dry, and in conformity with European requirements. It can be categorized as an 'industrial medicine". The bottles are in steel, aluminum or composite materials. Gaseous oxygen was first used at home by the 60s.

A pressure regulator attached to the gas bottle allows decompression of the oxygen to 3.5 bars for delivery to the patient. The pressure regulator may be soldered or screwed on. The bottles are of varying volumes from four cubic meters used as large fixed reservoirs to 400 liters (weighing about 3.5 kg) for the smaller ones used for mobility. The pressure regulator allows control of the flow rate and the pressure of the gas coming out from the cylinder. Unfortunately the manipulation of the flow control knob may be difficult for some patients. The possibilities for storage are limited and thus the patient is dependent on regular delivery of oxygen. Systems with economizing valves are available, but their possibilities need to be verified for each individual. Cost of gaseous oxygen can be high at large flow rates.

Liquid oxygen

Oxygen can be stored at low pressure in a reduced volume if liquefied at very low temperature (-173°C at 1.4bar) in double wall isolation vacuum containers. There is a permanent small evaporation of gaseous oxygen (0.1 to 0.3 L/min) and this produces the coldness required to maintain low temperature. Thus a large amount of gaseous oxygen can be stored in a low volume. One liter of liquefied oxygen releases 850 liters of gaseous oxygen at ambient temperature and pressure. The oxygen is 99.9% pure and complies with pharmacy requirements. The delivered gas is very dry. The system consists of a bulk storage reservoir unit that remains in a permanent place in the home and a portable, refillable lightweight carrying container. Liquid oxygen is the most expensive source to be used at home. The fixed reservoir weighs 35 to 70kg, and may contain 20 to 44 liters of liquid oxygen. This permits the vaporization of 16 to 32 cubic meters of gaseous oxygen. There is no need for electric supply. Portable reservoirs can contain 0.5 to 1.0 liters of liquid oxygen and thus patient autonomy may extend to 12 hours at a flow rate of 1.5L/min. Flow rate can be high (limited to 6 liter/min however on most models). The autonomy depends on the volume of the reservoir and the flow rate required. The liquid oxygen source is silent.

There is no gas under pressure and no danger of explosion. However the patient must master manipulation of equipment and be able to fill the portable reservoir from the storage unit. This can be a delicate operation for some and the patient needs a certain minimum strength. The patient needs to know how to react if the coldness of the oxygen freezes the outlet of the reservoir. In France, liquid oxygen was started to be used by the 70s [9].

Oxygen concentrators

Oxygen concentrators supply gas enriched in oxygen by means of nitrogen absorption from the air by the use of zeolite. These electrical appliances supply gas enriched to an oxygen level of about 90% for home use.

A compressor filters room air and sends it alternately to two columns of zeolite. While one column absorbs nitrogen the other is purged of nitrogen for the next cycle. Some machines collect oxygen in a reservoir. There is the possibility of regulating flow. Most modern machines have an electronic board that allows surveillance of temperature and pressure and usage. Some machines can monitor oxygen concentration to avoid breakdown in supply. Most machines supply oxygen at 90 to 95% purity, for flow rates up to 5 liters per minute. There is a small percentage of argon that is innocuous. The gas is clean and dry, but does not fit the European definition of medical oxygen. It is rather considered as "oxygen enriched air".

The major advantage of the oxygen concentrator is the avoidance of regular delivery of oxygen and it is thereby the cheapest source of home oxygen. It allows the fabrication of oxygen as required and there are no problems of storage and reduced risk thereby.

3.2.2.2 Methods of oxygen delivery

Face masks

Face masks can be used in acute respiratory failure, and are designed to fit over the mouth and nose. High concentration masks can increase the inspired oxygen concentration to around 60%, with inspired oxygen/air flow of 6 L per minute. However patients cannot wear masks constantly over a long time because they have to be tight fitting and thereby are uncomfortable. Furthermore they have the risk of leading to carbon dioxide retention, respiratory acidosis, and ultimately death. Low concentration masks, working on a venturi principle aim to provide controlled enrichment of the inspired oxygen concentration. They allow partial relief of hypoxemia without carbon dioxide retention, but can be uncomfortable to wear over a long period.

Nasal cannulas

An alternative method of delivering oxygen is by nasal prongs, and this is the most commonly used system for prolonged oxygen delivery. They are simple, cheap and relatively well tolerated as the patient can eat, sleep, talk and expectorate without discontinuing therapy. Oxygen flow rates are well tolerated up to 3 liter/minute and do not require humidification. At greater flow rates humidification may be needed to avoid drying of the nasal mucosa, with consequent irritation and patient discomfort. Nasal prongs are visible and this may have cosmetic and psychological effects. Nasal prongs do not lead to problems of CO2 rebreathing.

The oxygen conserving cannula consists in nasal prongs with an attached, closely coupled 20ml reservoir containing a collapsible membrane and an oxygen supply line at the distal end of the reservoir on both sides. The conserving cannula stores oxygen so that during early inspiration the patient inhales a 20ml bolus of approximately 85% oxygen from the reservoir and thus one can attain satisfactory oxygenation with lower flow rates, but with the caveat that the efficiency of the system varies between patients according to the breathing pattern. Thus each individual's response has to be assessed. This device is highly visible and may be cosmetically unacceptable to many patients. They are not commonly used in Europe and tend to be replaced by phased oxygen delivery devices.

Phased oxygen delivery devices

This type of delivery is designed to conserve oxygen by using intermittent, inspiration phased O2 delivery and only oxygen delivered in the early phase of inspiration is used in gas exchange.

There are 4 basic types of demand valves [10]:

- Demand-type: demand valves deliver oxygen only during inspiration and thus eliminate wasteful oxygen delivery during exhalation.
- Pulse-type demand valves provide a bolus (pulse) of oxygen in early inspiration, which may help the oxygen enter better-ventilated lung regions. By eliminating oxygen delivery during exhalation and to dead space (from where it would be soon exhaled), pulse-type demand valves have the potential to conserve more oxygen than demand-type valves.
- Hybrid valves combine the characteristics of pulse and demand types to provide an early inspiratory bolus followed by inspiratory flow.
- Smart" valves can be programmed. Some can deliver a relatively large oxygen bolus, with each breath or during every second, third, or fourth breath. In theory, that oxygen bolus may penetrate to better ventilated lung regions and "extra" oxygen may be stored in dead space for rebreathing. Other "smart" valves can adapt to clinical responses, such as respiratory rate, and, when unable to adapt, change to continuous flow.

Most devices are valves activated by inspiratory pressure changes and thus require modified nasal prongs, which can be expensive. Unfortunately rapid respiration is common in breathless patients and this may cause practically continuous flow or inadequate oxygenation if the valve is not triggered. Thus each device needs to be tested individually.

These devices are considered useful for prolonging the time for which portable devices can be used or to reduce the intervals of liquid oxygen delivery to the home.

Continuous versus demand valves

Using a bench model, Bliss et al. [11] measured the amount of oxygen delivered through a nasal cannula by 18 commercially available demand valves, at settings that the manufacturers imply are equivalent to continuous flow. For comparison they tested the output of a conventional (continuous-flow) valve. They found that less than a third of the demand-valve measurements were truly equivalent (within 10% of the oxygen delivered by the continuous-flow valve) when tested at clinically pertinent respiratory rates. Half the demand valve measurements exceeded the equivalent continuous flow measurement, but 10% of the demand-valve measurements fell short (ie, were less than 70% of the continuous-flow measurement). The results for maximum demand-valve output (approximately 6 L/min) showed that some demand valves provided an oxygen concentration of 40%, but output dropped by nearly a third when respiratory rate was doubled to 30 breaths/min. The average resting respiratory rate of patients with stable chronic obstructive pulmonary disease is 20 breaths/min so that 40% oxygen concentration probably represents "best case" performance. Clearly, these devices must be set at a personalized level at rest and during exercise.

Concerns have been voiced, however, that, even though the newer home and portable concentrator-based devices have logical technical designs, their clinical efficacy remains uncertain. There is a particular concern that the lower oxygen concentration and lower bolus volume (ie, combining an 85–96% oxygen gas with a DODS) may cause hypoxia, especially during exercise [12].

Four DODS models were tested in subjects with stable hypoxic COPD before, during, and after functional exercise testing in a clinical setting [13]. The hypothesis was that the subjects would have similar blood oxygen saturation (measured via pulse oximetry [SpO2]) values with the 4 systems. The 4 ambulatory oxygen systems (Helios, HomeFill, FreeStyle, and a compressed-oxygen cylinder system that was regularly provided for long-term oxygen therapy) were tested with 39 subjects with stage-IV chronic stable obstructive pulmonary disease. In this randomized study, each subject performed a 6-min walk test with each oxygen system, and blood oxygen saturation was measured (via pulse oximetry [SpO2]), heart rate, and modified Borg dyspnea score were recorded and the subjects' preferences about the oxygen systems were also determined. With all 4 systems the mean pre-walk SpO2 at the prescribed pulse-dose setting was 95–96%. The mean post-walk SpO2 was 88–90% after each of the 4 walk tests. Between the 4 systems there were no statistically significant differences between the pre-walk-versus-post-walk SpO2. With each system, the pre-walk- versus post-walk SpO2 difference was between 8% and 6%. Between these 4 ambulatory oxygen systems there were no significant differences in SpO2, walking time, or walking distance, and there was no evidence of inadequate oxygenation with the 2 systems that provided a lower oxygen concentration. This finding is consistent with a similar study by Furhman et al. [14], who tested 4 DODS models and a continuous- flow oxygen system with 9 subjects performing 6-min walk tests. They found no significant SpO2 differences between the DODS and the continuous-flow oxygen systems, but some DODS models performed better than others. All 4 DODS tested provided clinically desirable prewalk (resting) SpO2 (mean: 95%). The average 6–7% pre-walk- versus post-walk difference is noteworthy. Such a substantial SpO2 drop reflects an ongoing concern, and strongly underlines the need for individualized titration and appropriate prescribing of ambulatory oxygen[15-18].

Transtracheal catheter

Transtracheal oxygen delivery involves administration of oxygen percutaneously through a catheter inserted into the suprasternal trachea. This usually improves oxygenation at flow rates that are lower than those used with nasal cannulas and also encourages continuous use of supplemental oxygen with a cosmetic advantage. This is, however an invasive procedure and there is the risk of development of mucus balls due to the drying effect of the oxygen. It is not commonly used in Europe.

3.2.2.3 Trends in new technology

Portable concentrators

Ambulatory oxygen is important in order to allow the patient to remain mobile and to be able to go out[19]. Oxygen concentrators to date have not been portable and this has lead during the last decades to use portable oxygen cylinders and portable liquid oxygen containers [19-22]. Liquid oxygen is expensive and requires regular refilling of the portable liquid container. Designed to be small enough to be carried by the patient, a portable concentrator can be powered by standard household alternating current, direct current (available in most motor vehicles), or rechargeable battery. Portable concentrators can also use the demand oxygen delivery system (DODS) technology and produce a variable oxygen percentage. Physicians, patients, and home medical equipment providers have high hopes that the most recent enhancements in portable oxygen technology will lead to greater convenience, better patient adherence to therapy, and cost savings. In recent years a number of portable oxygen concentrators have appeared on the market. All but one can only supply oxygen intermittently using economiser valves. These units are being marketed for patient mobility and travel. Currently not all airlines allow portable oxygen concentrators onboard. Addendum 8 shows the characteristics of the majority of the portable concentrators currently available on the market. This is at the cost of intermittent flow for most really portable machines or more cumbersome (rolling) machines for continuous flow.

Oxygen refilling systems

CONCENTRATOR-COMPRESSORS

The Homefill ® system, which was the first marketed system, has been developed to allow patients to fill their own high-pressure cylinders from a concentrator. The concentrator which is connected to a built-in compressor produces oxygen enriched air at (93+/-3%). Different cylinder sizes are available, for example about two hours are required to fill the M9 cylinder that gives 248 Liters of O2 for patient autonomy according to the flow rate required. Another potential advantage of these systems is that home care oxygen providers will also benefit from the virtual elimination of time-consuming and costly service calls associated with cylinder and/or liquid oxygen deliveries

Ten patients with COPD, in a stable state and previously treated with long-term domiciliary oxygen therapy performed three successive 6-min walking tests, the first test in room air and the other tests in a randomized order with either a conventional oxygen cylinder or a refilled oxygen cylinder using the Homefill® system. Mean transcutaneous oxygen saturation and mean distances were not different but significantly improved, as compared with room air with both oxygen delivery systems. Dyspnea sensations were similar for the three tests.[23].

The I-fill ® oxygen Concentrator was recently developed exclusively to fill portable oxygen bottles in the home. Two bottles containing 2 to 3 L of O2 are filled in about 45 minutes and the pressure in the filled bottles is around 175 bars.

CONCENTRATOR LIQUEFIER

This new device produces liquid oxygen with a liquefier linked to a concentrator which provides oxygen. It is being currently tested in clinical practice.

Portable liquid oxygen

The EasyMate is a portable system for liquid oxygen, that is small at 20.8 cm high and 9.2 cm diameter and weighs 1.6 Kg and can contain 30 cl of liquid oxygen and oxygen is provided by an economising demand valve.

Another system recently developed for patient mobility is the Freelox Roller (Cryopal). This can supply oxygen at variable flow rates from 0.25 to 6L/min. At 2L/min with continuous flow it allows autonomy for 7h. The pressure is at 1.45bars and the evaporation of the liquid 0.44L/jour. The filling time is less than one minute if cold and 1 minute 30 if warm. The volume of oxygen supplied is 1.2L and the empty weight is 2.8KG compared to 4.1Kg when full.

Oxygen generator

A novel system not yet in use is the Oxy-Gen Lite system that generates oxygen by the electrolysis of water, by means of a Fuel Cell technology. This involves a polymer electrolyte membrane that filters H+ ions and allows their reutilization by recombination with oxygen in the ambient air. After electrolysis there is supply of pure oxygen to the patient on the one hand and on the other hand recuperation of hydrogen ions that contribute to the electrical energy of the system and recuperation of water. The administration of oxygen will be provided by a demand valve with 7 settings and a maximum of 3,5 l/mn in constant mode with 85 % relative humidity guaranteed. The weight is likely to be 10 kg and the noise level 35dBA, with electricity consumption of 130Watts. There is also the cost of 2 to 3 litres of distilled water per week. The provisional duration of the electrodes is claimed to be five years.

3.2.2.4 Safety and materiovigilance

The multiplication of new technologies and the growing number of patients under LTOT need reinforcement of the control of equipment. ANTADIR has developed in France a materiovigilance system as a national system for gathering and analysing data of incidents relating to medical materiel in use by patients. Incidents may be any alteration of performance, any deficiency in usage instructions that could lead to danger to patients or any technical or medical problem that necessitates a systematic recall by the manufacturer. Near-incidents are also noted. This system is in compliance with European directives. By using a computerised system of transmission of information between participating centres a large number of even minor incidents can be analysed. After ten years over 2000 incidents have been recorded, and 115 required immediate notification to the French health authorities (AFSSAPS). These records largely concerned mechanical ventilators, gaseous oxygen and tracheotomy cannulas. Regarding minor events 31% of all reports led to some action by the manufacturers, such as modification of quality control procedures, or methods of fabrication or information. Regarding systems for supplying oxygen, while there are more reports concerning concentrators; 363 in 11 years versus liquid oxygen (126 incidents) and gaseous oxygen (171 reports), but there were proportionally more serious events with gaseous oxygen (26 emergency events) compared to the other systems, concentrators and liquid oxygen with 3 emergency reports each. This emphasizes the importance of patient education not only for compliance but also for safety reasons. In Belgium, those notifications should be transmitted to the Federal Agency for Medicines and Health Products (FAMHP/ FAGG/ AFMPS).

3.2.2.5 Clinical testing

There have been few comparative clinical studies of different oxygen supply systems.

As soon as 1975, Lilker and colleagues used a 10-week blinded crossover design in nine patients with resting hypoxemia. They reported improvements in minute ventilation and arterial oxygen tension, but found no change in dyspnea, subjective assessment of activity, or distance walked per day while using liquid oxygen compared with liquid air [24].

In 1989 an ANTADIR study [9]reported in 159 COPD patients the effects of portable oxygen therapy both on the daily duration of oxygen therapy and on daily activities. Patients were given two types of LTOT at random: group A (n = 75), oxygen concentrators only (OC); group B (n = 84), either small oxygen cylinders plus OC (B1 = 51) or liquid oxygen (B2 = 33). The patients were followed-up for one year by means of medical examination every three months, monthly home interviews concerning the daily duration of oxygen therapy, the utilization of the devices and the daily activities of the patients, a measurement of the daily oxygen usage. The results showed that in group B the daily use of oxygen therapy was significantly longer than in group A (17 +/- 3.5 h/day versus 14 +/- 3 h/day, $p< 0.01$) without any difference between groups B1 and B2. Outdoor walking activities were different between groups A and B, at least in those patients using oxygen more than 18 h/day. However, only 60% of patients in group B (55% of B1; 67% of B2) used their portable devices outdoors and for walking. No strict predictive criterion of this behaviour was found.

An AETMIS HTA report from Canada in 2004 [25] about portable oxygen therapy in COPD concluded that there is very limited evidence about the clinical efficacy or cost effectiveness of portable oxygen therapy. To date, only one controlled trial (completed in Québec in 2003) has been conducted with these issues in mind. According to that study, portable oxygen equipment apparently offers no benefits in terms of quality of life, compliance with treatment or exercise tolerance. It should be pointed out, however, that the sample size in this trial was too small to generalize the results to all patients.

Another AETMIS HTA report on liquid oxygen therapy at home, published in 2005[26], reports there is very limited information about the effectiveness of liquid oxygen therapy in comparison to compressed gas delivery systems in terms of enhanced patient compliance, mobility or quality of life.

Existing systematic reviews did not select the studies according to the type of devices [25]. Several devices are combined in systematic reviews about LTOT or about portable oxygen.

3.2.2.6 Compliance and Education

A prospective multi-centered study performed by the ANTADIR federation included a large number of patients (n=931) and examined the intake of medical prescription and compliance with treatment for at least 15 hours per day [27]. Only 45 % of the patients had 15 hours or more of LTOT for a day. In other studies this figure has varied from 17 to 70%. The clinical and functional severity of the patient's condition seems to be one of the determining factors for compliance. The most compliant patients are the patients with the most severe blood gas impairment and the most severe loss of capacity on spirometry. These studies reinforce the necessity to follow the defined criteria for prescription of oxygen. Putting patients on this inconvenient treatment when their complaints and disability are not severe enough to accept the treatment leads to a limited consumption of LTOT. The time of initial prescription is a crucial moment for subsequent compliance. Precise explanation of how to use oxygen is important with detailed explanation of circumstances of use and follow up education after, initiation of oxygen therapy by paramedical personnel.

Key points

- **This chapter clearly illustrates the complexity of domiciliary oxygen therapy delivery and reimbursement in Belgium.**
- **The target population of the RIZIV/INAMI-hospital convention is well defined and includes patients with severe hypoxemia. On the contrary, there is no clear description of the target population of the RIZIV/INAMI agreement with the pharmacists. This Channel of prescription should be reserved to and only to patients with acute respiratory failure requiring oxygen for a limited time. Currently, patients are allowed to use within this agreement oxygen for a long time without any interference of a pulmonologist or check-up of their oxygen level.**
- **The costs are increasing and the increase is primarily related to an increasing number of reimbursements.**
- **Within the RIZIV/INAMI-hospital convention a cost saving strategy has been made by prescribing proportionally less liquid oxygen to patients and replacing this oxygen modality by an oxygen concentrator +/- portable gaseous oxygen cylinders. Within the RIZIV/INAMI agreement with the pharmacists a steeper increase in costs is observed since there is reimbursement of an oxygen concentrator, suggesting that an increasing number of patients is started and/or is using oxygen for a long time within this agreement intended for use in the short term.**
- **Within the RIZIV/INAMI agreement with the pharmacists, only one type of concentrator is allowed. Moreover until very recently, only one company was reimbursed. This sounds at least strange, especially taking into account that within the RIZIV/INAMI- hospital convention different types of concentrators delivered by different home care companies are accepted.**
- **Within the RIZIV/INAMI –hospital convention, the use of different gaseous portable oxygen cylinders with a difference of weight ranging between 2,5 kg and about 5kg raises questions about what is really portable. Portable oxygen concentrators are available nowadays, with acceptable weight and autonomy. It is time to study their usage versus the usage of the "portable" gaseous modalities and liquid oxygen.**

Acknowledegements

We sincerely thank Mr. A. De Swaef, Ms. D. Dethier, Mr. M. DeFalleur and Mr. G. Verscuren from the RIZIV/INAMI for their data and their help in the interpretation of them.

Also thanks to Prof. JF. Muir and the other members of the Antadir task force consisting of Veale D., Couillard A., Foret D for their work on quality control of the different oxygen devices.

Chapter 2
Clinical Literature Review

1 INTRODUCTION

This chapter provides an overview of studies that aimed at evaluating home oxygen therapy (HOT) from a clinical perspective with the aim of using the results, in association with those obtained from our economic review presented in chapter 3 as input for the Belgian Economic evaluation included in chapter 4 of this Health Technology Assessment.

2 METHODS

2.1 LITERATURE SEARCH STRATEGY

The search for the clinical literature about Home Oxygen Therapy (HOT) included the consultation of electronic databases up to September 2010.

The following databases: The Cochrane Database of Systematic Reviews (CDSR), Medline, CINAHL, EMBASE and PEDro were searched to retrieve meta-analysis (MA), systematic reviews (SR), randomised controlled trials (RCTs) and cohort studies (CS) on Home Oxygen Therapy (HOT).

An overview of the search strategy is captured in appendix 1.

2.2 SELECTION CRITERIA

Table 1 summarises our selection criteria for all studies.

The population looked at included patients suffering from chronic obstructive pulmonary disease (COPD); chronic airflow limitation; chronic obstructive lung disease (COLD); hypoxaemic disease necessitating palliative care; chronic heart failure; cystic fibrosis (any age); or interstitial lung disease.

Our final selection was limited to Meta-analyses (MA), Systematic Reviews (SR) and Randomised-Controlled Trials (RCTs). Only RCTs published in full were included.

Any studies looking at hospital or acute treatment were also excluded as well as studies performed in patients younger than 18 years of age (with the only exception of cystic fibrosis patients for which we considered studies on patients of all ages).

Furthermore, patients with an acute cluster headache attack were excluded from the analysis. Likewise, patients with diseases of the chest wall or neuromuscular diseases with respiratory muscle weakness were excluded from the current review, because these pathologies are primarily managed by non-invasive or invasive positive pressure mechanical ventilation.

No language limitations were applied at this stage.

Table 1: Selection Criteria

	Inclusion	Exclusion
Population	COPD; Chronic airflow limitation; COLD; hypoxemia; interstitial lung disease; cystic fibrosis (any age); heart failure; palliative	Age<18 yrs, except in cystic fibrosis; non human Cluster headache; migraine
Intervention	Long term oxygen therapy; domiciliary; ambulatory; portable; short burst; community dwellers; institutionalized	Acute; hospital
Outcome	Survival; health related quality of life; improvements in physiological parameters (exercise capacity); patients' preference; number of avoided hospitalization days; number of gained productivity days	Other outcomes
Design	MA (RCTs); SR; RCTs	Other designs
Format	Full text articles	Abstracts and other formats

COPD = Chronic obstructive pulmonary disease
COLD = Chronic obstructive lung disease
MA = Meta-analysis
SR= Systematic review
RCT= Randomised-controlled trial

2.3 SELECTION PROCEDURE

Our study selection started by looking at titles and abstracts to exclude any studies considered not relevant for our purposes. Articles that appeared relevant or for which we had doubts were assessed by reading the full text.

Relevant titles and abstracts were selected in parallel by three reviewers. Any disagreements were discussed and a common decision and approach adopted. Following that, the studies found were split according to their indication and two reviewers evaluated the full articles.

The reference lists of the selected studies were checked for additional relevant studies that could be included in our review.

A hierarchical approach was followed by which:

Firstly, the analysis focused purely on MA and SR published up to the date of our search. Secondly, the selected evidence synthesis was updated by looking at all relevant original literature (RCTs) published after the search data of selected MA and SR and found via our search.

2.4 CRITICAL APPRAISAL

The reviewers critically appraised the SRs and MAs according to the PRISMA checklist (www.prisma-statement.org), a 27-item checklist aimed at ensuring the transparent and complete reporting of SRs and MAs.

RCTs were appraised according to:

- the JADAD score checklist [28], a simple to use 5-item checklist looking at randomization, blinding, and handling of patient withdrawals/drop-outs.
- the PEDro checklist, a 11- item scale available via the Physiotherapy Evidence Database (www.pedro.org.au), that focuses on the internal validity and the interpretability of trial quality.

No studies were excluded from our analysis on the basis of the critical appraisal results.

2.5 DATA EXTRACTION AND POOLING

The reviewers synthesised the characteristics of the studies and the available results in evidence tables.

The level of evidence was evaluated on the basis of the categories of the GRADE working group [29, 30], and classified in three different categories:

- A, representing high quality RCTs without important limitations
- B, representing moderate quality RCTs with some methodological limitations
- and C, representing low quality RCTs with important methodological limitations.

Results from the selected evidence synthesis were confronted with those from the original studies published after it. If conclusions were similar a descriptive analysis of the results from both the meta-analysis and the original studies was completed. In those cases in which the results from the original studies contradicted or added something new to the conclusions from the published evidence synthesis their results were pooled and a quantitative analysis was added to our descriptive exercise.

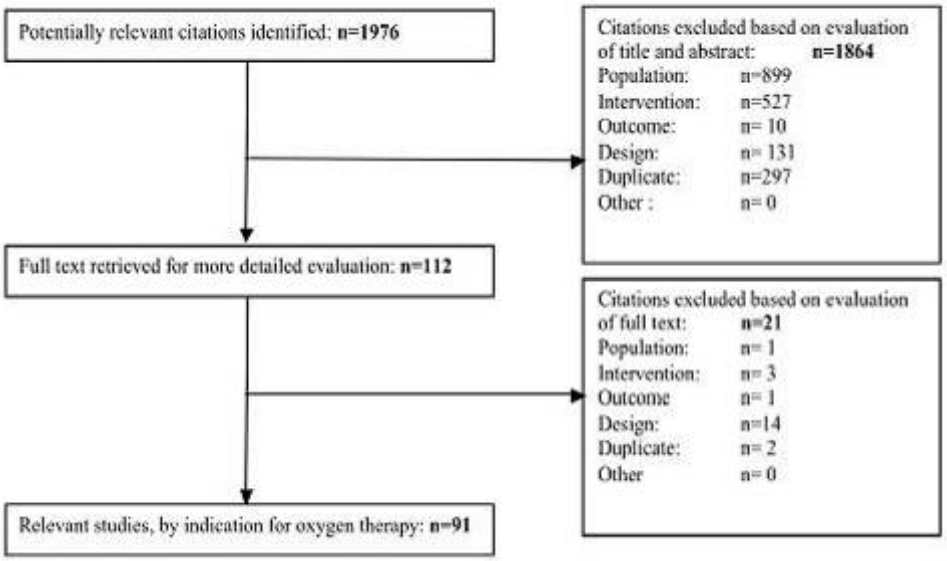
3 RESULTS

3.1 RESEARCH AND SELECTION

Figure 1 shows the flow chart of the literature selection process.

After eliminating duplicates from MEDLINE and EMBASE, searches on the previously mentioned databases listed 1976 citations. Of those, 1864 did not meet our inclusion criteria based on title or abstract or were duplicates from CINAHL, PEDro or CDSR. Of the 112 citations left, 21 were excluded from the analysis after exploring the full version of the study leaving us with a total of 91 relevant studies.

Figure 1: Flow chart of the literature selection process



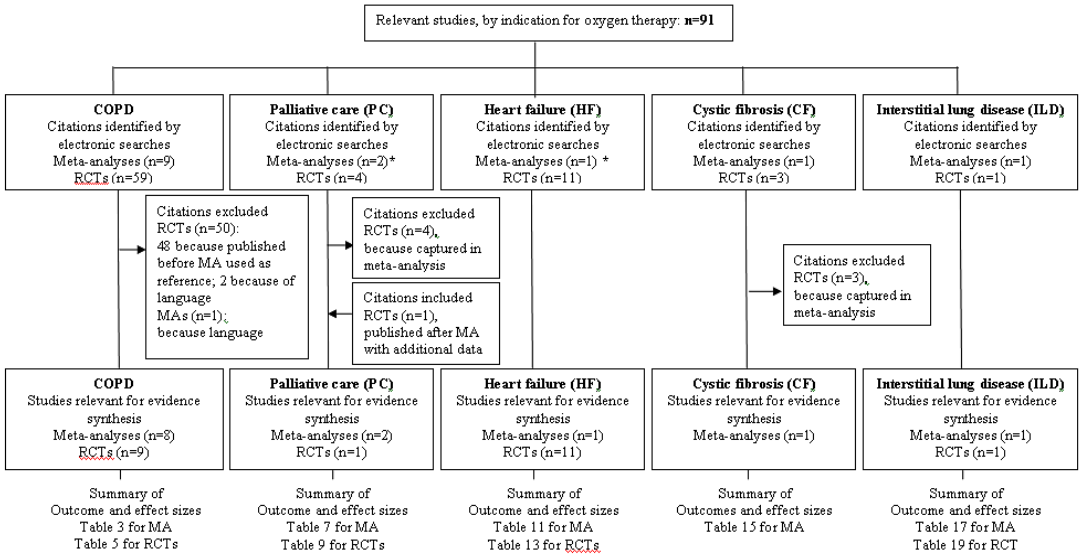
From those 91 articles, the split between indications was as follows:

- 68 on COPD, from which 9 SRs;
- 6 in palliative care (PC), from which 2 SRs;
- 12 in heart failure (HF), from which 1 SR;
- 4 in cystic fibrosis (CF), from which 1 SR;
- 2 in interstitial lung disease (ILD), from which 1 SR.

The analysis of the articles' references did not bring in any additional citations. Nevertheless, an additional (PubMed) search for papers published from September 2010 to April 2011, yielded only one additional paper with relevant information [31].

The flow chart in Figure 2 shows this split per indication.

Figure 2: Literature selection process by indication



* one Cochrane review reporting data on oxygen therapy for palliative care patients and for heart failure patients as well

Next section offers an overview of our main findings for Oxygen therapy by indication.

3.2 RESULTS BY INDICATION

Home oxygen therapy is an effective and cumbersome therapy with the patient " tethered" to the oxygen source and it plays an important role in the variation of costs[30]. Therefore, it should be prescribed to those in whom there is evidence of a benefit.

Chronic obstructive pulmonary disease (COPD) is the first condition in which HOT will be evaluated. Currently, it is the only major cause of death in the United States that is increasing[32]. By the year 2020, it is estimated that COPD will be the third-largest cause of mortality and the fifth-leading cause of disability worldwide [33, 34]. It is the most common cause of chronic hypoxemia and in Great Britain 2/3 of the patients under oxygen are COPD patients[35].

Moreover, in these patients oxygen may also be prescribed during sleep or exercise, in the latter condition, oxygen may be warranted even in those patients who do not significantly desaturate but have dyspnoea and ventilatory abnormalities.

Hypoxemia is not a disease of itself, but rather a proximate manifestation of any number of disease processes. Whether the chronic underlying condition is from pulmonary or cardiac origin, the presence of hypoxemia is a marker of the severity of the illness. However a deficit of oxygen in the blood stream is reversible merely by replacement therapy[36]. This beneficial result has lead to extend this treatment to other causes of chronic hypoxemia. Progressive cystic fibrosis and the diffuse parenchymal lung diseases (interstitial lung diseases) are two conditions that often develop chronic hypoxemia and are treated with HOT.

Sleep disordered breathing; particularly Cheyne-Stokes breathing is common among patients with heart failure. Sleep disordered breathing in patients with heart failure is important because it may independently predict mortality[37]. The use of supplemental oxygen to treat sleep disordered breathing will be assessed.

Finally, the effectiveness of palliative oxygen in relieving dyspnoea in patients with cancer will also be reviewed.

3.2.1 COPD

3.2.1.1 Meta-analyses and systematic reviews

Final selection

Our search for meta-analyses and systematic reviews for oxygen therapy in COPD identified 9 studies. From these, one[38] was written in Danish and was excluded from our analysis, leaving us with 8 relevant reviews [39-46]. No additional studies were captured by hand-checking the references.

Five reviews[39, 41, 43, 45, 46] were either Cochrane reviews published in the Cochrane library or publications in peer reviewed journals that followed a Cochrane review and therefore, made use of a similar methodology.

Another review by O'Neil et al[47] followed the criteria outlined in the QUOROM[48] statement for reporting of systematic reviews.

Two of the identified reviews[40, 44] did not specifically focus on oxygen therapy but were included in our analysis for completeness since they did look at oxygen as being one of the interventions to be included in their broader analysis.

Although one of the SRs taken into consideration[44] included other types of studies in addition to RCTs, it was included in our review since all the studies on oxygen therapy (9 in total) consisted of RCTs.

Study characteristics

A summary of the study characteristics of these reviews is presented in Table 2.

Table 2: Study characteristics for evidence synthesis - COPD

Study	Methods	Citations included	Participants	Interventions	Outcomes	Level of evidence
Bradley 2007	SR including MA RCTs only # of studies: 31	Bradley 1978, Bye 1985, Criner and Celli 1987, Davidson 1988, Dean 1992, Eaton 2002, Fujimoto 2002, Garrod 1999, Garrod 2000, Gosselin 2004, Ishimine 1995, King 1973, Knebel 2000, Kurihara 1989, Leach 1992, Leggett and Flenley 1977, Light 1989, Mannix 1992, Maltais 2001, McDonald 1995, McKeon 1988, O'Donnell 2001, O'Donnell 1997, Palange 1995, Raimondi 1970, Stein 1982, Somfay 2001, Swinburn 1984, Vyas 1971, Wadell 2001, Woodcock 1981	Stable COPD Age, mean 47 to 73 years FEV1 NA PaO2, mean 6.9 to 11.3kPa (52-85mm Hg) PaCO2 NA	Ambulatory O2 vs any control provided via similar ways. 20 studies used low-dose O2 (<or= to 4L/min), 9 used high dose O2 (>4L/min) and 2 used both	Exercise capacity (distance or time during maximal or endurance tests); HRQL: dyspnea scores (Borg scores or VAS); physiological paramaters: SaO2, minuten ventilation	A
Cranston 2008	SR including MA RCTs only # of studies: 6	Chaouat 1999, Fletcher 1992, Gorecka 1997, Haidl 2004, MRC 1981, NOTT 1980	COPD Age 40-80 FEV1 NA PaO2<55mg Hg PaO2>55mm Hg with nocturnal hypoxaemia with exercise PaCO2 NA	All forms of home LTOT vs placebo air	Survival; HRQL and improvement in physiological parameters	A
Crockett 2001	SR including MA RCTs only #of studies: 5	NOTT 1980, MRC 1981, Fletcher 1992, Gorecka 1997 and Chaouat 1999	COPD Age, range 40 to 80 years FEV1 NA PaO2<55mm Hg PaO2>55mm Hg with nocturnal hypoxaemia with exercise PaCO2 NA	All forms of home LTOT (liquid concentrators or cylinders) vs either placebo air or no specific intervention	Survival, HRQL, improvements in physiological parameters	C
Nonoyama 2009	SR including MA RCTs only # of studies: 5	Emptner 2003; Fichter 1999; Garrod 2000; Rooyackers 1997; Wadell 2001	Stable COPD patients not eligible for LTOT Age O2, range 58 to 66 years Age control, range 59 to 71.6 years FEV1 NA PaO2 NA PaCO2 NA	O2 vs placebo (room air)	Maximal exercise capacity, Maximum training level achieved during exercise; End-of-test dyspnoea scores (Borg scores or VAS) HRQoL, arterial O2 saturation post exercise	A
O, Neill 2006	SR including MA RCTs only # of studies: 8	Evans 1986; Killen 2000; Lewis 2003; Marqués-Magallanes 1998; McKeon 1988; Nandi 2003; Stevenson 2004; Woodcock 1981	COPD Age, mean 61.2 to 68.7 years FEV1, mean 27 to 68% PaO2, mean 6.8 to 9.65 kPa PaCO2 NA	Short-burst O2 vs placebo; O2 rates from 2l/min to 10l/min	Improvements in physiological parameters: breathlessness, exercise capacity, SaO2, Other ventilatory parameters (eg VE); patients' preferences	A
Puham 2004	SR including MA RCTs only # of studies: 18 (5 on oxygen)	Emptner 2003, Fichter 1999, Garrod 2000, Rooyackers 1997, Wadell 2001	COPD Age, mean 59-69 FEV1, mean 26.9 to 45.3% PaO2, mean 8.4kPa to 10.4kPa PaCO2 NA	Any supplemental intervention added to respiratory rehabilitation that included a standardised physical exercise program	HRQL, symptom scale; Exercise endurance; Physiological paramaters: cardiopulmonary exercise testing	C
Ram 2009	SR RCTs only # of studies: 2	Lilker 1975, McDonald 1995	Stable COPD Age NA FEV1 NA PaO2<7.3 kPa, 55mm Hg PaO2>7.3kPa, 55mm Hg but exercise hypoxaemia	Home LTOT vs placebo (air cylinders)	Exercise capacity HRQL; dyspnoea scores (Borg scores or VAS); physiologocal parameters: arterial O2 saturation during exercise, recovery time after exercise, lung function measurements	B
Wilt 2007	SR including MA RCTs, CT and SR # of studies: 74 (9 on OT)	Sin 2003, NOTT 1980, MRCWP 1981, Gorecka 1997, Chaouat 1999, Eaton 2002, Eaton 2006, Lacasse 2005, McDonald 1995	Stage III, IV (GOLD) COPD Age, range 48 to 73 years; FEV1, range 26% to 77% PaO2, range 51 to 75mm Hg PaCO2 NA	Inhaled therapies, pulmonary rehabilitation, disease management, and supplemental O2	Survival; HRQL; Hospitalisations; Exacerbations	B

The number of studies included per evidence synthesis ranged from a low of 2[46]to a high of 31[43].

All studies were in adult patients (reported age ranging from 40 to 80 years). FEV1 predicted, when reported, went from a low of 26% to a high of 77%. PaO2 values ranged from <55mmHg to 85mmHg.

Two studies [40, 44]; had a broader scope than the one of this review, and while Puhan et al looked at any supplementary intervention added to respiratory rehabilitation including a standardised physical exercise program, Wilt et al reviewed all different types of therapies aimed at managing COPD.

Critical appraisal

The quality assessment using the PRISMA checklist is included in appendix 2. Overall the quality of the reviews was good, with those following the Cochrane methodology meeting most of the relevant criteria.

Results

A summary of the outcomes from these reviews is presented in table 3.

MORTALITY OR MORBIDITY

Only 3 out of 8 reviews looked at the effects of oxygen therapy on survival for patients suffering from COPD [39, 41, 44].

Two studies found direct evidence of a significant longer survival in severe chronic hypoxemic COPD patients (PaO2 < 8 kPa, with disturbances of pulmonary hemodynamic and exercise capacity ranging from mild to severe) receiving long term oxygen therapy. With continuous oxygen therapy versus nocturnal oxygen therapy (1980), there was a significant improvement in mortality after 24 months (Peto odds ratio [OR] 0.45, 95% confidence interval [CI] 0.25 to 0.81; 1 trial, n=203). With domiciliary oxygen therapy versus no oxygen therapy (1981), there was a significant improvement over five years in mortality (OR 0.42, 95% CI 0.18 to 0.98; 1 trial, n=87). With nocturnal oxygen versus no oxygen therapy in patients with COPD and arterial desaturation at night, there was no difference in mortality (2 trials=114). With long-term oxygen therapy versus no oxygen therapy in COPD patients with mild to moderate hypoxaemia, there was no effect on survival for up to three years of follow up (2 trials = 163)

With regards to hospitalisation, it was not commonly covered and only one review [44] included it specifically as an outcome of focus. However, this reviewed concluded that differences in hospitalisations over a 6-12 month period did not reach statistical significance.

QUALITY OF LIFE

Health related quality of life (HRQL) measured by validated scales did not provide conclusive findings. The Chronic Respiratory Questionnaire (CRQ) and the Saint

Table 3: Summary of study results: evidence synthesis - COPD

Study ID	Mortality-Morbilidy	Quality of Life	Patient preference	Physiologcal parameters	Productivity gains
Bradley 2007	NA	Difference in breathlessness (endurance test isotimes): -1.15 Borg units (95%CI -1.65 to -0.66), p<0.05;	NA	Difference in distance (endurance test) 18.86m (95%CI 13.11-24.61), p<0.00001, Difference in time (endurance test) 2.71min (95%CI 1.96-3.46), p<0.00001) Maximal test studies confirmed these findings; Difference in SaO2 (endurance test isotime) 8.36% (95%CI 5.08-11.64%), p<0.05. Difference in PaO2 (endurance test isotime) 15.15kPa (95%CI 6.42 to 23.89 kPa), p<0.05. Difference in MV (endurance test isotime) -3.58L/min (95%CI -4.85 to -2.31L/min), p<0.05. Maximal test isotime confirmed O2 effects on PaO2; SaO2 and MV	NA
Cranston 2008	Peto odds ratio at 24 months (continuous OT vs nocturnal): 0.45, (95%CI 0.25 to 0.81), p<0.05; Peto odds ratio at 5 years (OT vs no O2 in severe hypoxaemia): 0.42, (95%CI 0.18 to 0.98), p<0.05; Peto odds ratio at 36 months (nocturnal O2 vs room air in mild to moderate hypoxaemia): 0.97 (95%CI 0.41 to 2.31), p>0.05	Non conclusive results Difference in end-exercise dyspnoea: -1.20 (95%CI -2.47 to 0.07); p=0.064	NA	Differences in endurance time (LTOT vs no O2): 2.20 (95%CI -0.73, 5.13); p=0.14 Differences in PaCO2 in 500-days survivors (LTOT vs no O2 in patients with severe hypoxaemia) -2.16 (95%CI -4.04 to -0.28), p=0.025 Differences in FEV1 in 500-days survivors (LTOT vs no O2 in severe hypoxaemia): 0.08 (0.04 to 0.12); p<0.05 Differences in PaO2 change (LTOT vs no O2 in patients with severe hypoxaemia) did not reach ss Differences in FVC change (LTOT vs no O2 in sever hypoxaemia): did not reach ss	NA
Crockett 2001	Data could not be pooled; Results from individual studies: Peto odds ratio at 24 months (continuous OT vs nocturnal): 0.45, (95%CI 0.25 to 0.81), p<0.05; Peto odds ratio at 5 years (OT vs no O2 in severe hypoxaemia): 0.42, (95%CI 0.18 to 0.98), p<0.05;	Data not pooled and no conclusive findings coming from individual studies	NA	Data not pooled and no conclusive findings	NA
Nonoyama 2009	NA	Difference in HRQL (CRQ): 0.19 (95%CI -0.21 to 0.59); p>0.05 Difference in end-of test Dyspnea score (Borg units after cycle test) -1.22 (95%CI -2.39 to -0.06) p<0.05; Difference in dyspnoea score (Borg units after shuttle test): 1.46 units (95%CI -2.72 to 0.19) p<0.05 Difference in dyspnoea score (Borg units after maximal test): not ss differences Difference in dyspnoea score (Borg units after 6MWT): not ss differences	NA	Difference in cycle endurance (exercise time in min) 2.68 (95%CI 0.07 to 5.28); p=0.044 Difference in distance (6MWT) -23.87m (95%CI -81.55 to 33.82); p>0.05 Differences in change in distance (shuttle test): uncertain Difference in SpO2 (cycle endurance, maximal test and 6MWT): no ss differences No ss differences found in FVC, PaO2, change in pack cell volume or change in weight.	NA
O, Neill 2006	NA	NA	Evidence from individual studies that patient's preference do not improve with O2 Computation of specific effect size not possible (no detail reported)	Difference in breathlessness: results could not be pooled; 4/5 studies showed no ss differences from pre-dosing with O2; Difference in rate of return to baseline breathlessness post- dosing -22.42 s, (95% CI 55.18 to 10.34), p >0.05 Difference in distance pre-dosing 5.99m (95%CI 1.11 to 10.88m), p=0.02	NA
Puham 2004	NA	Difference in HRQL (CRQ): no ss differences	NA	Difference in exercise intensity 10Watt (p<0.01) No ss differences in walking distance	NA
Ram 2009	NA	Difference dyspnoea 6MWT: -0.10 (95%CI -0.79 to 0.59); p=0.78; Difference in dyspnoea step exercise test: -0.30 (95%CI-0.98 to 0.38); p=0.39 Difference in HRQL (CRQd) 2.0 (95%CI -1.26 to 5.26); p=0.23 Difference in HRQL (CRQf) 1.0 (-1.17 to 3.17); p=0.37 Difference in HRQL (CRQe) 1.0 (-3.63 to 5.36); p=0.67 Difference in HRQL (CRQm) 1.0 (-2.0 to 4.0); p=0.51	NA	Not possible to pool results Difference in MV @ maximal exercise -11.00 L/min; (95%CI -17.53, -4.47L/min), p=0.00097. Difference in PaO2 @ rest 17.00 mmHg; (95%CI 9.13,24.87 L/min) p=0.000023. Difference in distance (walked on pedometer in miles/day) 0.32 (95% CI -0.31 to 0.95); p=0.32 Difference in distance (6MWT): 15m (95%CI -33.94 to 63.94); p=0.55	NA
Wilt 2007	Relative effect in deaths (used for 15+ hours in patients with FEV1<30% and mean resting PaO2 < = 55mm Hg): 0.61 (95% CI 0,46 to 0.82) P<0.05 Difference in mean # of hospitalisations over 6-12months 0.40 (95%CI -0.68 to 1.48), p>0.05	Difference in CRQ scores and exercise tolerance: no clinically detectable improvement Computation of specific effect size not possible (no detail reported)	NA	NA	NA

SS: Statistically significant

George Respiratory Questionnaire (SGRQ), commonly used in COPD studies, when used, did not provide statistically significant results.

PATIENT PREFERENCES

The authors of the present review acknowledge that the type of search performed was not sensitive and well targeted to capture studies focusing on patients' preferences. Nevertheless, one review [47]included it as one if its outcomes and concluded that evidence for individual studies appeared to show that such parameter did not change with oxygen use.

EXERCISE CAPACITY AND OTHER PHYSIOLOGICAL PARAMETERS

Seven reviews in total [39-41, 43, 45-47] looked at RCTs studying the effect of oxygen therapy on exercise capacity or physiological parameters such as arterial oxygen saturation, ventilatory parameters or lung function measurements. From these, two reviews reported an improvement in distance covered with oxygen versus room air;[43, 47], although three more found no statistical significant results in this area [40, 45, 46] .

Two reviews [43, 45] found a significant improvement in exercise time when using oxygen.

Other measurements where the analysed reviews favoured the use of oxygen included:

- Differences in MV [43, 46].
- Differences in exercise intensity [40] .

PRODUCTIVITY GAINS

None of the reviews found via our search captured productivity gains as one of their outcomes and thus no conclusions could be drawn.

3.2.1.2 Choice of most relevant MA for update

The review published by Cranston et al in 2008 [41] was thought to be the most up to date from those considered most relevant to answer our research question, bearing in mind that the main purpose of our review was to serve as a guide for the construction of the economic analysis in the Belgian context, for which mortality, morbidity and HRQL outcomes would be most relevant. Other reviews either did not capture mortality/morbidity outcomes or were methodological similar but outdated by the Cranston review. Therefore the latter was chosen as the starting point of our review.

However, in view of the existing reviews limiting their analysis to the measurement of exercise capacity and physiological changes in the COPD population the authors of the present review decided to also select the most methodologically sound and relevant review measuring these types of outcomes and see how its results compared with any literature published later in that field.

With this purpose in mind, the review by Bradley et al [43] was chosen as the starting point of our review of the evidence in physiological changes, in view of its quality, the number of studies included in it and the general population studied. Despite the Nonoyama review [45] scoring higher in the PRISMA checklist, it was considered to be too limiting since it excluded all patients eligible for LTOT.

3.2.1.3 Original studies (RCTs) used for the update

Final selection

Our search for original studies published in or after the search dates of the MAs chosen as point of reference (end of 2004 for Bradley et al and January 2007 for Cranston et al) identified 11 studies, two of which were written in German [49, 50] and were excluded from our analysis, leaving us with a total of 9 studies [51-59].

Study characteristics

A detailed description of the characteristics of these studies is given in table 4.

Overall the studies presented similar characteristics, with a small sample size, ranging from a low of 15 [58] to a high of 55 individuals in all cases but one [53] ,in which the sample size was 78.

Patients' age ranged from 40-86 years, with baseline FEV1 ranging from 17% to 74% predicted.

Table 4: study characteristics for primary studies – COPD

Study	Methods	Participants	Interventions	Outcomes	Level of Evidence
Bjorgen 2009	Single-blind parallel RCT; 8 weeks Randomized, n=15 Completed, n=12	Stage III (GOLD) COPD Age, range 40 to 70 years FEV1, range 30-50% PaO2: NA PaCO2: NA	100% O2 vs ambient air	Exercise endurance	GRADE C Jadad score = 2/5, poor PEDro score =4/11
Eaton 2006	Double-blind parallel RCT; 6 months Randomized, n=78 Completed, n=57	COPD patients dicharged from hospital after excerbation Age, mean 77 years FEV1, mean 44% O2 cylinder, 39% cylinder air, 45% uc	Cylinder O2 vs cylinder air vs usual care (uc)	HRQL (CRQ, 36-item Short-Form Health Survey, HAD scale); Acute healthcare utilisation	GRADE A Jadad score = 5/5, excellent PEDro score =9/11
Heraud 2008	Cross-over RCT Acute Randomized, n=25 Completed, n=25	Moderate to severe (ATS/ERS) COPD Age, mean 62 years FEV1, mean 52% PaO2, mean 67mm Hg PaCO2, mean 36mm Hg	Oxygen and room air (FiO2 20.9%)	Endurance time (cyclo-ergometer at 60% max workload), dyspnoea, ventilation (VE), breathing frequency (fb), tidal volume (Vt), cardiac output (CO), heart rate (HR) and arterio-venous difference in O2	GRADE C Jadad score = 1/5, poor PEDro score =6/11
Lacasse 2005	Double-blind cross-over RCT 1 year Randomized, n=40 Completed, n=24	Stable COPD patients (end-stage excluded) Age, mean 68 years FEV1, mean 38% PaO2, mean 53mmHg PaCO2, NA	Standard therapy (HOT + O2 concentrator) vs standard therapy + as-needed ambulatory O2 vs standard therapy + ambulatory compressed air	HRQL (CRQ), exercise capacity (6MWT)	GRADE B Jadad score = 5/5, excellent PEDro score =6/11
Nonoyama 2007	Double-blind cross-over RCT Acute (3 pairs of 2 weeks training periods) Randomized, n=38 Completed, n=27	COPD patients, severity: NA Age, mean 69 years No resting hypoxemia but desaturated on exertion PaO2: NA PaCO2: NA	O2 (2L/min) vs placebo (24% of O2; FIO2 21.2%)	HRQL (via CRQ and SGRQ); Dyspnea (Borg scale) Exercise endurance and physiological parameters after 5MWT	GRADE B Jadad score = 3/5, good PEDro score =7/11
Ozalevli 2007	Single- blind cross-over RCT; Acute Randomized, n=31 Completed, n=28	Stable stage III (GOLD) COPD Age, range 52 to 83 years FEV1, range 32-45% PaCO2, range 35.4-76.4mm Hg PaO2, range 66-87mm Hg	Room air conditions vs supplemental O2 (4L/min)	Exercise endurance (6MWT) and physiological parameters	GRADE B Jadad score = 2/5, poor PEDro score =7/11
Quantrill 2007	Double blind cross-over RCT; Acute Randomized, n=22 Completed, n=22	Stable COPD patients Age, range 56-86 years FEV1, range 17-74%, mean 38% PaO2: NA PaCO2: NA	2-4L/min of O2 via gas cylinder vs room air	Exercise endurance: Subjective and objective time to recovery	GRADE B Jadad score = 3/5, good PEDro score =7/11
Samolski 2010	Single-blind cross-over RCT; Acute Randomized, n=55 Completed, n=38	Stage IV (GOLD) COPD Age, median 68 years FEV1, median 22.4+-6.2% PaO2<60mm Hg PaCo2>50mm Hg	Daytime O2 flow rate on one night vs receiving an additional L on the alternate night	Nocturnal pulse oximetry and arterial blood gases at awakening	GRADE C Jadad score = 2/5, poor PEDro score =5/11
Sandland 2008	Double-blind, parallel RCT; 8 weeks Randomized, n=30 Completed, n=20	Stable stage III (GOLD) COPD Age, O2 mean 70.7 years; air mean 76 years FEV1, O2 mean 43.4%; air mean 43.8% Arterial O2 desaturation >4% < 90% (on standard walking test) PaO2: NA PaCO2: NA	O2 cylinder vs cylinder air @ 2L/min	Total domestic physical activity and HRQoL	GRADE B Jadad score = 5/5, excellent PEDro score =6/11

Critical appraisal

Quality assessment following the Jadad score checklist is presented in Appendix 2.

Scores on the Jadad scale were 3 or above in five cases [51-54, 57], indicating high quality studies.

While all studies were described as randomised the specific method used for randomisation was covered in detail in three cases only [52, 53, 57].

Five out of nine studies [51-54, 57] were described as double-blind but from these, one gave no details on the method used for blinding [54].

The description and explanation of drop-outs and withdrawals was appropriate in seven out of nine studies [52-55, 57-59].

These primary studies were also critically appraised following the PEDro checklist (see appendix 2 for full details). Overall the conclusions were similar to those obtained by using the JADAD score system, with most of those scoring high in the Jadad scale (3 or more), also scoring high in the PEDro scale (6 or more). There were two exceptions: Heraud et al [56] which scored only 1 in Jadad but scored 6 in the PEDro scale, and Ozalevli et al [55] that scored 2 in Jadad but 7 in the PEDro scale.

Results – Primary studies

Results are described in table 5

Table 5: Summary of study outcomes – Primary studies - COPD

	Effect size on outcome(s): O2 minus control				
Study ID	Mortality-Morbidity	Quality of Life	Patient preference	Physiologcal parameters	Productivity gains
Bjorgen 2009	NA	NA	NA	Differences in VO2 peak (one-legged cycling): increased in both training groups; differences between the groups did not reach ss Difference in VO2 peak (two-legged cycling): increased in both training groups; differences between the groups did not reach ss	NA
Eaton 2006	Difference in hospitalisations over 6-12-months (O2 vs air): 0.40 (95%CI -0.68 to 1.48), p>0.05 Difference in hospitalisations over 6-12-months (O2 vs uc): 0.80 (95%CI -0.19 to 1.79), p>0.05	No ss differences between O2 and air or O2 and uc for CRQ, SF-36 or HAD scores	NA	NA	NA
Heraud 2008	NA	Difference in Dyspnoea (VAS mm): -0.00 (-2.20 to 2.20) p>0.05 Difference in fatigue (Borg scale): -0.53 (95%CI -0.75 to -0.31) p>0.05	NA	Difference in endurance time (cyclo-ergometer): 177s (95%CI 83,54 to 270,46), p>0.05	NA
Lacasse 2005	NA	No ss differences between concentrator + ambulatory O2 vs concentrator +ambulatory air vs concentrator alone in CRQ domains	NA	Difference in distance covered (6MWT): no ss differences	NA
Nonoyama 2007	NA	Difference in CRQd: 0.22 (95%CI -0.03 to 0.47), p>0.05 Difference in CRQf: 0.14 (95%CI -0.02 to 0.31), p>0.05 Difference in CRQe: -0.01 (95%CI -0.20 to 0.18), p>0.05 Difference in CRQm: -0.10 (95%CI -0.40 to 0.19), p>0.05 Difference in SGRQs: -0.17 (95%CI -2.63 to 2.29), p>0.05 Difference in SGRQa: 0.42 (95%CI -1.59 to 2.43), p>0.05 Difference in SGRQi: -0.79 (95%CI -2.75 to 1.17), p>0.05 Difference in SGRQt: -0.32 (95%CI -1.71 to 1.06), p>0.05 Difference in dyspnea change (Borg units) -0.44 95%CI -0.86 to -0.02 p<0.05	NA	*Difference in # of steps 5MWT: 14.90 steps 95%CI 0.85 to 28.94 (p<0.05)*	NA
Ozalevli 2007	NA	Difference in severity of Dyspnoea@ end test: -2.20 (95%CI -3.31 to -1.09), p<0.05;	NA	Difference in meters (6MWT): 47.40 (95%CI 35.24 to 59.56), p<0.05; Difference in severity of leg fatigue@ end test: -1.20 (95%CI -1.63 to -0.77), p<0.05; Difference in SpO2 % : 5.40 (95%CI 2,66 to 8.14), p<0.05; Difference in heart rate (beats/min): -3.60 (95%CI -11.93 to 4.73, p<0.05	NA
Quantrill 2007	NA	NA	NA	Difference in objective recovery time:-38,(95%CI -81 to +5), p=0.08; Difference in subjective recovery time: -34, (95%CI -69 to +2), p=0.06	NA
Samolski 2010	NA	NA	NA	Difference (+1L-daytime O2) in PaO2 @awakening: 13.50 (95%CI 7.13 to 19.87), p<0.05; Difference (1+L-daytime) in overnight SpO2: 1.90 (95%CI 1.08 to 2.72), p<0.05; Difference (+1L-daytime) in PaCO2: 3.00 (95%CI -0.44 to 6.44), p>0.05; Difference (+1L-daytime) in pH: -0.02 (-0.18 to 0.14), p<0.05 Difference (+1L-daytime) in CT90: -8.90 (-15.08 to -2.72), p<0.05	NA
Sandland 2008	NA	No ss differences between O2 and air for the CRQ or the SF-36 scores Computation of specific effect size not possible (only medians reported)	NA	Difference in domestic activity (% change before and after): 15.72 (95%CI -19.76 to 51.20), p>0.05;	NA

SS: Statistically significant

Seven out of the 9 RCTs [51, 52, 54-58] focused on the use of oxygen to enhance exercise in COPD patients. From these, two [54, 55] showed statistically significant differences in the distance covered during the 6 minute walk test and a 5 min walk test respectively, with longer distances walked when using supplemental oxygen. The same authors also reported a significantly greater reduction in dyspnoea (measured in Borg units), while Ozalevli et al saw significant differences in favour of Oxygen versus room air conditions, in other parameters such as severity of leg fatigue after exercise, SpO2 % and heart rate (beats/min) following exercise.

One study by Eaton et al [53], focused on measuring HRQL and healthcare utilisation between three patient groups: patients receiving cylinder oxygen, patients receiving cylinder air and patients receiving usual care. The patient population in this study was different to that captured in all others in that it was formed by patients discharged from the hospital after being hospitalised because of an exacerbation. The authors did not capture any significant differences in either HRQL between the groups (except for the emotional domain of the CRQ) or health care utilisation over a 6-12-month period.

The remaining study [59] compared daytime oxygen rate provided overnight with an increase of 1 litre the following night in order to assess any potential benefits linked to such an increase in patients already using night oxygen. This study concluded that an additional litre of supplemental oxygen given at night significantly increased oxygenation but also increased hypercapnia and acidosis the next morning.

3.2.1.4 Results of the update

Differences in mortality, morbidity

When confronting the results reported by Cranston et al [41] in their evidence synthesis with those of the primary studies published after it, we found that no studies published during or after 2007 looked at mortality. Therefore, the authors of this review saw no added value in performing a MA to measure the effects of oxygen on that outcome.

Differences in quality of life

CHANGE IN DYSPNOEA

With regards to HRQL Cranston et al did not report conclusive results since only one of the studies included in their review with a small sample size [60] compared dyspnoea changes with LTOT versus no oxygen in patients after 1-year follow up and found no statistical significant results.

Literature published after 2007 did not find any significant results when using validated, widely used questionnaires such as the CRQ or SGRQ, but two studies (Nonoyama, Brooks et al. 2007; Ozalevli, Ozden et al. 2007) captured significant changes in Dyspnoea, measured in Borg units that favoured oxygen use. We therefore decided to perform a MA on Dyspnoea to check whether the new evidence added something new to the findings analysed by Cranston in his review.

Methods

Pooling was done using the fixed effects model. A random effects model was used to confirm the results obtained via the fixed effects model, if and when, heterogeneity, as measured by I^2, showed to be >25%.

Funnel plots were performed when more than 5 studies were available for the same measured outcome.

All analyses were performed with Review Manager version 5.0.

Results

META-ANALYSES – COPD; CHANGE IN DYSPNOEA

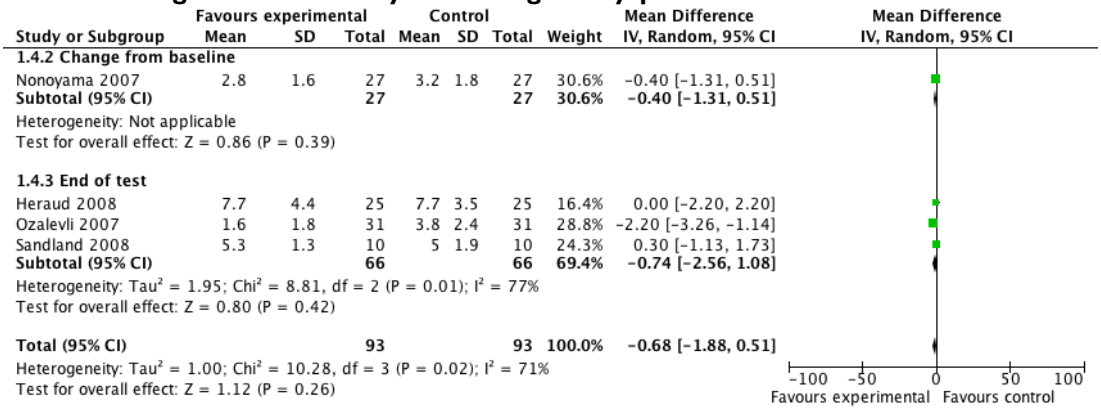
Review: Comparison of oxygen therapy versus air in COPD.

Outcome: Change in Dyspnoea (measured by Borg scale or VAS)

The results from the study by Haidl [60] included in the review by Cranston were not pooled together with the new, more recent studies, since the former measured dyspnoea scores after 1-year follow-up, while the latter did not offer a comparable follow-up period. Thus, four studies in total were pooled [54-56], involving a total of 93 patients.

The pooled estimate of the effect of oxygen, using a fixed-effects model, was statistically significant and favoured the use of oxygen. However, there was moderate heterogeneity between the trials included (I^2=31.9%). Therefore, the results were re-calculated using a random effects model (see figure 3). Using this model, the overall differences in dyspnoea did not reach statistical significance p=0.26. Therefore, no clear conclusions could be drawn from our analysis.

Figure 3: Meta-analysis – Change in Dyspnoea



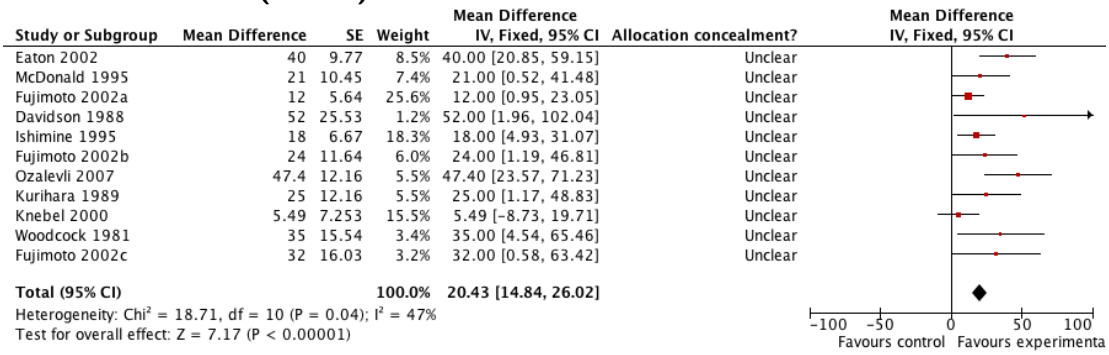
Differences in physiological outcomes

EXERCISE CAPACITY: SIX MINUTES WALK TEST

Results reported by Bradley et al in their review [43] saw statistically significant differences in favour of oxygen for distance covered during endurance tests. These results were further supported by results obtained from the literature published after the search date of this MA (end of 2004), and although the results obtained in terms of distance covered from the 6 minutes walk test (6MWT) and a 5MWT [45] did not reach the minimal important clinical difference [61], Ozalevli et al [55] did not fall far from it, taking into consideration the confidence intervals surrounding their results. Bearing this in mind, and despite the fact that the MA by Bradley and the evidence published after it, seems to show similar conclusions we decided to pool the results from Ozalevli and the original studies included in the review by Bradley et al to see how the overall results would be affected and how close or far they would stay when compared to the minimum clinical differences. The results from the Nonoyama study [45] could not be pooled since the outcomes from the 5 minute walk test used in this study would not be comparable to those obtained from the 6MWT used in all other studies. Similarly, the results from Lacase et al [52] could not be pooled since the interventions evaluated in their trial (ie concentrator alone versus concentrator added to ambulatory oxygen versus concentrator added to ambulatory compressed air) were not directly comparable to the interventions assessed in the remaining of the studies that used the 6MWT.

Figure 4 shows the results from our pooling analysis.

Figure 4 – Meta-analysis (cross-over studies) – Exercise capacity, exercise distance (6MWT)



Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Allocation concealment?
Eaton 2002	40	9.77	8.5%	40.00 [20.85, 59.15]	Unclear
McDonald 1995	21	10.45	7.4%	21.00 [0.52, 41.48]	Unclear
Fujimoto 2002a	12	5.64	25.6%	12.00 [0.95, 23.05]	Unclear
Davidson 1988	52	25.53	1.2%	52.00 [1.96, 102.04]	Unclear
Ishimine 1995	18	6.67	18.3%	18.00 [4.93, 31.07]	Unclear
Fujimoto 2002b	24	11.64	6.0%	24.00 [1.19, 46.81]	Unclear
Ozalevli 2007	47.4	12.16	5.5%	47.40 [23.57, 71.23]	Unclear
Kurihara 1989	25	12.16	5.5%	25.00 [1.17, 48.83]	Unclear
Knebel 2000	5.49	7.253	15.5%	5.49 [-8.73, 19.71]	Unclear
Woodcock 1981	35	15.54	3.4%	35.00 [4.54, 65.46]	Unclear
Fujimoto 2002c	32	16.03	3.2%	32.00 [0.58, 63.42]	Unclear
Total (95% CI)			**100.0%**	**20.43 [14.84, 26.02]**	

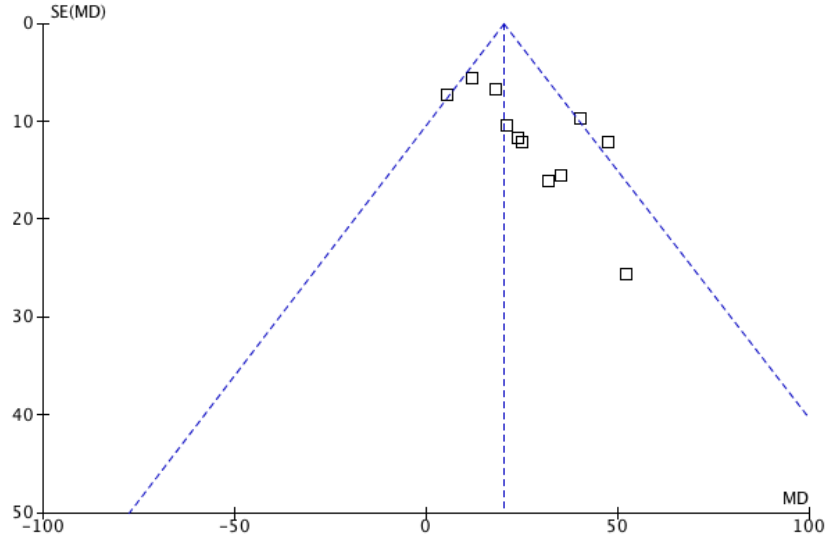
Heterogeneity: $Chi^2 = 18.71$, df = 10 (P = 0.04); $I^2 = 47\%$
Test for overall effect: Z = 7.17 (P < 0.00001)

Review: Comparison of oxygen therapy versus control in patients with COPD.
Outcome: Exercise distance, in metres.

Eleven cross-over trials involving 269 patients were included in the meta-analysis of distance covered during the 6MWT.

Using a fixed-effects model, the pooled estimate of the effect of oxygen showed a statistically significant increase in distance covered during the 6 minute walk test (6MWT), with a difference of 20.43 metres (14.84 to 26.02). There was moderate heterogeneity found between the trials (I^2=47%). Given this heterogeneity the pooled analysis was repeated using a random effects model, but the overall results did not vary (23.77 (15.44 to 32.10); p<0.00001).

Figure 5 Funnel plot– Meta-analysis (cross-over studies) – Exercise capacity, exercise distance (6MWT)

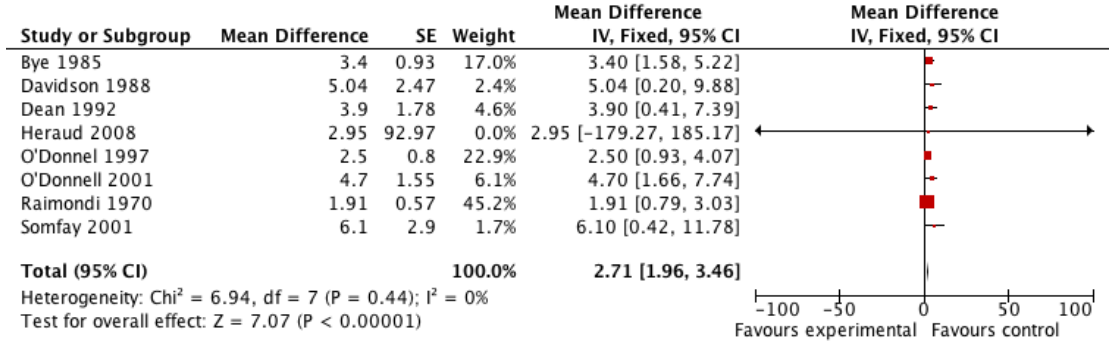


The graphical analysis of the funnel plot shows a larger number of point estimates to the right of the pooled mean difference, suggesting that we may not have captured an equivalent number of studies with a negative effect. Therefore, some cautiousness should be used before generalising our results.

EXERCISE CAPACITY: ENDURANCE TIME

Only one of the studies published after 2007 looked at endurance time (cyclo-ergometer) and found no significant results, but this result could have been affected by the small sample size: n=25 [56]. We therefore, pooled the results from this study with those of the studies grouped by Bradley et al in their review [43] to see how the overall results would be affected. The results are presented in figure 6.

Figure 6: Meta-analysis (cross-over studies) – Exercise capacity, endurance time

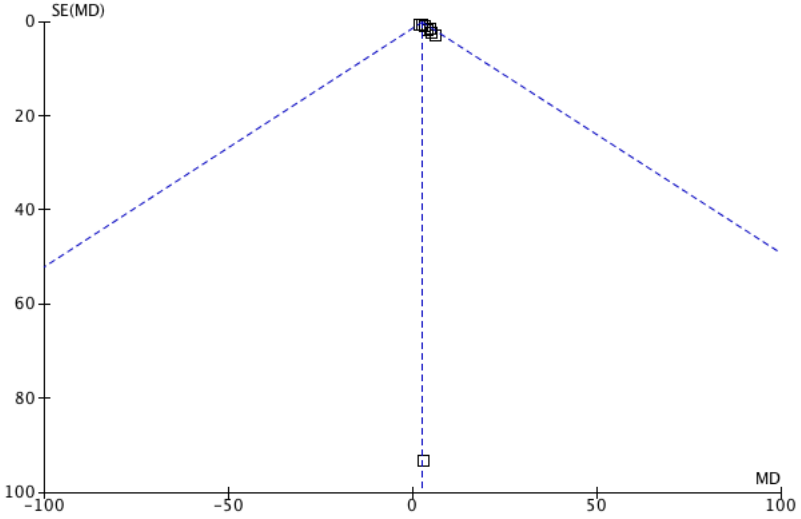


Review: Comparison of oxygen therapy versus control in patients with COPD.
Outcome: Endurance time, in minutes.

Eight cross-over trials involving 102 patients were included in the meta-analysis of endurance time.

The pooled estimate of the effect of oxygen showed a statistically significant increase in exercise time, with a difference of 2.71 minutes (95% CI 1.96 to 3.46. No statistical heterogeneity was found between the trials (I^2=0%).

Figure 7 Funnel plot– Meta-analysis (cross-over studies) – Exercise capacity, exercise time



The graphical analysis of the funnel plot shows all but one of the point estimates grouped close together around the pooled mean difference, suggesting the risk of bias to be limited.

Other outcomes

All other parameters not covered in Bradley et al 2007 [43] were described in the previous section and summarised in table 5.

3.2.1.5 Discussion and limitations

Our review has captured evidence of a benefit in using oxygen therapy versus not using it in terms of survival in COPD patients with severe airflow obstruction after 5 years and also appeared to show gains in terms of survival when using continuous oxygen versus nocturnal oxygen after a 2-year period.

The effect size on mortality of domiciliary oxygen therapy in COPD patients suffering from severe chronic hypoxemia is both statistically and clinically significant and oxygen remains, together with smoking cessation, the only available therapy demonstrated to prolong survival in these patients.

The quality of the evidence should, however, be downgraded by indirectness of evidence. Indeed, the relatively small number of participants (n=290), the young age of patients included in both studies (NOTT 1980: mean age 65.7 years in the nocturnal oxygen therapy group and 65.2 in the continuous oxygen therapy group. MRC 1981: mean age in both groups < 60 years, range (42-69)), as well as the lack of co morbidities in most of the included patients, raise concerns about today's external validity (generalization) of the probability of survival to the current clinical situation and practice with a much older patient population and different cardiovascular medications currently at hand for baseline treatment.

On the other hand, justified ethical concerns prevent new randomized studies to be performed in this kind of severe COPD patients, so conclusions need to be drawn from the limited evidence currently available which appear to support the use of oxygen in these patients.

With regards to QoL, our results are inconclusive and thus, further research in COPD patients would be needed before clear remarks can be made.

The effect on exercise capacity and other physiological parameters appear to favour the use of oxygen when looking at important outcomes such as distance covered and exercise time but whether the significant differences are also clinically meaningful is another matter and so far, the evidence seems to fail to reach minimal clinical differences. Furthermore, exercise-limiting factors are different among COPD patients, and this confounding factor was not taken into consideration in any of the selected trials.

It is important to recognise the limitations of the studies reviewed, which presented small sample populations ranging from 15 to 55 in all but one of the cases [53]. This, together with an important number of drop-outs/withdrawals in some of the revised studies: over 15% of randomized population in 2/3 of the studies [52-54, 57-59] may have contributed to the non-significance of the differences obtained for some of the outcomes.

Powering the studies with realistic assumptions on withdrawals could have helped but not all (6/9) studies performed a priori power calculations [51, 52, 54, 57].

In addition to this, there were some missing data. The diffusing capacity (DLco) which is more specific and sensitive than FEV1 to predict the development of arterial desaturation during exercise [62] was not reported by Bjorgen et al and by Eaton et al. Moreover some imbalances in the baseline characteristics between the intervention and the control groups of the three parallel RCTs were also present. Bjorgen et al [58] presenting differences in FVC measurements, as well as in FEV1/FVC ratios and Sandland et al [57] showing significant differences in vital and inspiratory capacity.The remaining parallel study Eaton, Fergusson et al. 2006; showed significant imbalances in just one aspect "living alone". These missing data and imbalances make hard the interpretations of the results.

The methods of randomisation were not well explained in all the studies, and in 4/9 there was no blinding of assessors [55, 56].

Another weakness presented by most of the studies was that due to the small sample size sub-group analyses were difficult to perform, while they could have been beneficial to evaluate potential variabilities in the patients' profile that could have affected the strength or significance of the results.

3.2.1.6 Other issues to bear in mind

Current research

The exact role of domiciliary oxygen therapy in COPD patients with mild to moderate hypoxemia remains unsolved. Likewise, the issue of different individual responses to acute oxygen supplementation, and the identification of subgroups of patients more or less likely to respond to such a therapy remains to be clarified.

An ongoing study sponsored by the Laval University (The CANOX trial, ClinicalTrials.gov identifier: NCT01044628) is recruiting COPD patients not qualifying for long-term oxygen therapy. The hypothesis of this multi-center randomized controlled study is that COPD patients who present significant nocturnal arterial oxygen desaturation (≥ 30% of the recording time with transcutaneous arterial oxygen saturation <90% on two consecutive recordings) will benefit from nocturnal oxygen therapy provided for a 3 –year period.

The primary outcome is to determine if such treatment could prolong survival or delay the requirement of long-term continuous oxygen therapy. The secondary outcome is to estimate the cost-utility ratio of such a treatment over a 3-year period.

For COPD patients who desaturate > 4% and to below 88-90% during exercise, both the BTS and the ATS guidelines recommend supplemental oxygen. However, long-term studies did not support this intervention. The effects of such an intervention will be studied during exercise in a randomized design. The studied outcomes will be: exercise tolerance, health status and exacerbation rates (NCT00592033).

(http://clinicaltrial.gov/ct2/home) Access on March 6th.

3.2.2 Diseases requiring palliative care

The duration of palliative treatment for cancer ranges from several days to a few months. At each stage of the disease the aim is to find therapies with beneficial effects largely outweighing the adverse effects. Dyspnoea in advanced cancer is the expression of multiple sensations and experiences, and not simply related to oxygen saturation [63]. Treatable and reversible causes of dyspnoea should be identified.

We reviewed studies addressing the role of oxygen in hypoxic and normoxic dyspneic patients with advanced cancer.

3.2.2.1 Systematic reviews (SR) and meta-analyses (MA)

Final selection

For the current report our final selection includes 2 meta-analyses, one published in the British Journal of Cancer [64] and one by the Cochrane library [65].

Study characteristics

Characteristics of both meta-analyses are presented in Table 6. The aim of both meta-analyses was to compare supplemental oxygen inhalation to air inhalation. Literature searches for the British Journal of Cancer meta-analysis [64] and the Cochrane review [65] were current to December 2006 and to April 2006, respectively. Even though the forest plots of these meta-analyses were based on a different number of trials (3 in the British Journal of Cancer versus 2 in the Cochrane review) and a different methodology to summarize the evidence (WMD, weighted mean difference versus SMD, standardized mean difference), both reviews reached similar conclusions regarding the effects of oxygen therapy on cancer dyspnoea.

Table 6: Study characteristics – Evidence synthesis - Palliative Care (PC)

Study	Methods	Citations included (oxygen	Participants	Interventions	Outcomes	Level of evidence
Cranston 2009	SR RCTs only # of studies: 4	Bruera 1993, Booth 1996, Ahmedzai 1998, Bruera 2003	Participants with chronic terminal illness, including cancer and heart failure (but excluding COPD) Age NA FEV1 NA PaO2 NA PaCO2 NA	Short burst or domiciliary oxygen therapy vs medical air or placebo air	Dyspnoea scores (Borg scores or VAS); Patient preferences	C
Uronis 2008	SR RCTs only # of studies: 5	Bruera 1993, Booth 1996, Bruera 2003, Booth 2004, Philip 2006	Adults with malignancy Age: adults FEV1 NA PaO2<55mm Hg	Oxygen administered by a non-invasive method was defined as oxygen delivered by nasal cannula, mouthpiece, or face mask. Placebo as comparator.	Dyspnoea scores (Borg scores or VAS); Patient preferences	C

Critical appraisal

The PRISMA checklist included in appendix 2 shows that the overall methodological quality of the reviews was very good, with a very high number of YES scores: 23 out of 27 items for the British Journal of Cancer meta-analysis [64] and 25 out of 27 items for the Cochrane review [65]. The authors of both meta-analyses clearly state that their conclusions are limited by the small volume of trials available for inclusion, the small numbers of participants, and the methods used in the trials. They also acknowledge that further study of the use of oxygen in this population is warranted given its widespread use.

Results

Results are described in table 7

Table 7: Study Outcomes – Evidence synthesis - Palliative Care

Study ID	Mortality-Morbidity	Quality of Life	Physiological parameters	Patient preference	Productivity gains
Cranston 2009	NA	The meta-analysis failed to demonstrate a significant improvement in cancer dyspnoea at rest, VAS random model effect size -12.20 (95% CI, -29.32 to +4.93).	The intensity of fatigue experienced by cancer participants during 6MWT was not reduced by the inhalation of oxygen (five litres per minute) in the single trial measuring this effect.	Participants appeared to perceive an improvement in dyspnoea through the inhalation of oxygen at rest, Peto Odds Ratio 4.94 (95% CI, 1.48 to 16.43) and during exercise, Peto Odds Ratio 2.62 (95% CI, 1.00 to 6.85).	NA
Uronis 2008	NA	Standardized mean difference in dyspnoea with oxygen inhalation (Oxygen minus Air): Modified Borg score (0-10) / VAS (0-100), SMD (Random, 95% CI): - 0.09 [-0.22, 0.04] P=0.16	One study reported a statistically significant increase in the distance with the use of oxygen (174.6m, SD 11.2) vs medical air (128.8m, SD 10.3, (P<0.01). However, a second study reported no difference in distance with oxygen (331.6m, SD 54.9) and with medical air (330.7, SD 57.6). Data not pooled for a meta-analysis. Two out of four studies reported a statistically significant still-blinded patient preference for oxygen vs air, whereas the other two found no such difference. Data not pooled for a meta-analysis.	Two out of four studies reported a statistically significant still-blinded patient preference for oxygen vs air, whereas the other two found no such difference. Data not pooled for a meta-analysis.	NA

Both meta-analyses failed to demonstrate a significant improvement in cancer dyspnoea at rest when supplemental oxygen inhalation was compared to air inhalation. Likewise, there was no overall improvement in distance walked by cancer participants with supplemental oxygen inhalation compared to air inhalation. Data on patient preference for oxygen versus air were discrepant.

3.2.2.2 Original studies (RCTs)

Final selection

Our electronic searches up to September 2010 identified 4 potentially relevant trials [66-69]. After completion of these electronic searches one additional trial was published [31]. Of these 5 potentially relevant trials, only 1 trial provided information not captured by the Uronis 2008 and the Cranston 2009 meta-analyses. More specifically, quality of life was assessed every day by use of the McGill quality of life questionnaire (MQoLQ) in the Abernethy trial [31]. Side-effects were patient-reported and measured by use of 5-point Likert-type categorical scales.

Our final selection thus includes only 1 randomised trial [31].

Study characteristics

In a double-blind, parallel-group, randomised controlled trial, Abernethy et al. [31] assessed the effectiveness of oxygen compared with room air delivered by nasal cannula for relief of breathlessness in a population of patients with life-limiting illness who were ineligible for long-term oxygen therapy. This study was conducted at five sites in Australia, two in the USA, and two in the UK, recruited patients with life-limiting illness from outpatient pulmonary, palliative care, oncology, and primary care clinics, and the results were published in The Lancet in 2010 (see Table 8).

Table 8: Study Characteristics – RCTs - Palliative Care

Study	Methods	Participants	Interventions	Outcomes	Level of evidence
Abernethy 2010	Randomized double-blind parallel-group trial; 7 days n=2497 Randomized: home oxygen therapy group 120, control group 119. Completed: home oxygen therapy group 112 (93%), control group 99 (83%).	Patients with life-limiting illness recruited from outpatient pulmonary, palliative care, oncology, and primary care clinics. Age, mean (SD): 73 (11) yrs FEV1: NA. PaO2: 10.3 (1.6) kPa SaO2: NA	Concentrated oxygen administered continuously at 2 L per min through the nasal cannula Sham control: room air	Average dyspnoea in the previous 24 h (0–10 NRS), Worst breathlessness in the previous 24 h (0–10 NRS), Relief of dyspnoea during the previous 24 h (0–10 NRS), Sleep disturbance, drowsiness, anxiety, nasal irritation, and nose bleeds. Quality of life was assessed every day by use of the McGill quality of life questionnaire (MQoLQ), which consists of 17 items and includes a single-item measure of global quality of life (0–10 NRS). Functional changes were assessed with the modified Medical Research Council (MRC) 4-point categorical dyspnoea scale and dyspnoea exertion scale.	GRADE A Jadad score = 5/5, excellent PEDro score = 11/11

Critical appraisal

Major strengths of the Abernethy trial include adequate sample size (239 participants), sufficient study duration to assess outcomes (daily measurements during a 1 week period), and patient-centred outcomes (global quality of life) that are meaningful for the target population. Quality assessment following the Jadad and PEDro score checklists is presented in Appendix 2.

Results

Results are described in table 9

In line with previously published data available from 2 meta-analyses, the primary outcome, breathlessness, did not differ between groups at any time during the study period. The findings were similar irrespective of cause of dyspnoea, performance status, opioid use and baseline oxygenation. In addition, change in quality of life did not differ between groups. There were few adverse events and no clinically meaningful difference between groups in frequency of side-effects (Table 9).

3.2.2.3 Discussion

No published survival analyses are available in this patient population, because, by implication, life expectancy of these patients is very limited ranging from several days to a few months, regardless of oxygen administration.

For all outcomes reported, no single outcome appears to favour oxygen therapy.

In particular, there are few adverse events and no clinically meaningful between group differences in frequency of side effects [31].

Quality of life assessed by the McGill quality of life questionnaire is not influenced by oxygen therapy [31]. Two meta-analyses fail to demonstrate a significant improvement in cancer dyspnoea at rest. Likewise, the intensity of fatigue experienced by cancer participants during exercise testing is not reduced by the inhalation of oxygen versus air [31, 64, 65].

Function assessed by the Medical Research Council scale is not influenced by oxygen therapy [31]. Two systematic reviews report inconclusive results for effects of oxygen on distance walked during exercise testing source [31, 64, 65].

Data on patient preference are discrepant with two trials reporting a statistically significant patient preference for oxygen versus air, and the other two trials reporting no such difference. These data were not pooled for a meta-analysis (Uronis, Currow et al. 2008).

No published data on productivity gains are available, again by implication, given the rather limited life expectancy in this target population.

In summary, no single outcome appears to favour oxygen therapy. Nevertheless, firm conclusions in patients necessitating palliative care are hampered by the limited number of trials available, the small numbers of patients included, and the lack of a priori power calculations in all but one trial [31].

Table 9: Study Outcomes – RCTs - Palliative Care

Study ID	Mortality-Morbidity	Quality of Life	Physiologcal parameters	Patient preference	Pruductivity gains
Abernethy 2010	Extreme drowsiness was reported by 12 (10%) of 116 patients assigned to receive oxygen compared with 14 (13%) of 108 patients assigned to receive room air. OR 0.78 (95% CI, 0.34 to 1.76; P=0.54) Risk Difference: -2.6% (-11.0 to +5.8%; P=0.54). Two (2%) patients in the oxygen group reported extreme symptoms of nasal irritation compared with seven (6%) in the room air group. OR 0.25 (95% CI, 0.05 to 1.25; P=0.09) Risk Difference: -4.8% (-10.0 to +0.5%; P=0.09). One patient reported an extremely troublesome nose bleed (oxygen group). OR not computable; Risk Difference: +0.4% (-1.7 to +2.5%;	Change in global QoL (0–10 NRS, numeric rating scale): 0.00 (95% CI, -0.37 to +0.36; P=0.97).Change in morning dyspnoea (0–10 NRS, numeric rating scale): -0.20 (95% CI, -0.82 to +0.42; P=0.51). Change in evening dyspnoea (0–10 NRS, numeric rating scale): +0.20 (95% CI, -0.36 to +0.42; P=0.76).	NA	NA	NA

3.2.3 Heart failure

The use of supplemental oxygen to treat Cheyne Stoke breathing (CSB) in patients with chronic heart failure is controversial. Some clinical trials have demonstrated that low flow nocturnal oxygen (2 to 3 L/min) reduces CSB and improves left ventricular function, heart failure functional class, sleep quality, and cognitive function [70, 71]. On the other hand, oxygen also increases oxidant injury and reduce cardiac function, especially in high concentrations [72]. Moreover, the role of cardiac rehabilitation is increasingly recognized as an important component of a multidisciplinary treatment strategy in cardiac patients. The effects of nocturnal oxygen therapy and supplemental oxygen therapy during exercise in patients suffering from heart failure are therefore reviewed in this section.

3.2.3.1 Published meta-analyses and systematic reviews

Final selection

Our electronic searches identified only 1 systematic review and meta-analysis providing information on patients with cardiac failure [65]. As already mentioned in section 3.2.2, this Cranston 2008 Cochrane review specifically focused on the effects of oxygen therapy on dyspnoea in patients with terminal illness, mainly cancer but also heart failure. Original studies not considering dyspnoea as an outcome were deliberately excluded a priori from this Cochrane review, leaving only 3 RCTs with patients suffering of cardiac failure [73-75] for inclusion in this Cochrane review [65].

Study characteristics

Characteristics of the Cochrane review [65] are presented in table 10. Overall, the 3 RCTs studying patients suffering of cardiac failure [73-75] included a vast majority of male participants (36 men, 2 women total), aged 31 to 78 years, with stable heart failure New York Heart Association Class II or III. No single trial described dyspnoea status at baseline.

Table 10: Study characteristics – Evidence synthesis –Heart Failure (HF)

Study ID	Methods	Citations included	Participants	Interventions	Outcomes	Level of evidence
Cranston 2009	SR RCTs only # of studies: 3	Chua 1996 Moore 1992 Restrick 1992	Participants with chronic terminal illness, including cancer and heart failure (but excluding COPD) Age NA FEV1 NA PaO2 NA PaCO2 NA	Short burst or domiciliary oxygen therapy vs medical air or placebo air	Dyspnoea scores (Borg scores or VAS) Physiological parameters	C

Table 11: Study Outcomes – Evidence synthesis - Heart Failure (HF)

Study ID	Mortality-Morbidity	Quality of life	Patients preference	Physiological parameters	Productivity gains
Cranston 2009	NA	Difference in Borg or VAS (dyspnoea) score, 0-10 units: - after 3 minutes exercise, treadmill or bicycle: -0.58 (95% CI, 0.00 to +0.84), P=0.43 - after 6 minutes exercise, treadmill or bicycle: -1.09 (95% CI, -1.74 to -0.44), P=0.001 - at peak exercise, treadmill or bicycle: -1.06 (95% CI, -3.14 to +1.02), P=0.32 Difference in Borg (fatigue) score, 0-10 units: - after 3 minutes exercise: -0.08 (95% CI, -0.95 to +0.79), P=0.86 - after 6 minutes exercise: -0.21 (95% CI, -1.37 to +0.95), P=0.72 - at peak exercise: +0.21 (95% CI, -1.33 to +1.75), P=0.79	NA	Difference in minute ventilation, peak exercise:: -6.68 (95% CI, -11.89 to -1.48), P=0.012	NA

Critical appraisal

The PRISMA checklist included in appendix 2 shows that the overall methodological quality of this review Cochrane is very good, with a YES score of 25 out of 27 items [65]. All 3 RCTs included [73-75] used a randomised cross-over design, included a similar (small) number of participants (n=12 in each trial), reported that all participants completed the study, but provided no information on allocation concealment. Outcome assessors were not blinded in 2 trials [73, 75].

Results

Somewhat surprisingly, this Cochrane review [65] included one trial [75] in the systematic review process, but not in the subsequent meta-analyses. No rationale was provided for this approach.

The results of the meta-analyses indicated that in participants with cardiac failure undergoing exercise testing there was no significant improvement in dyspnoea after 3 minutes of exercise or at peak exercise. After 6 minutes of exercise, dyspnoea was slightly but significantly reduced. Based on data from one single trial [73] there was no significant improvement in fatigue after 3 or 6 minutes of exercise, or at peak exercise (table 11).

3.2.3.2 Published original studies (RCTs)

Final selection

Our electronic searches identified 11 randomised trials providing information on oxygen therapy in patients with cardiac failure [73-83].

Studies characteristics

A detailed description of the characteristics of these 11 studies is given in table 12.

Table 12: Study Characteristics – RCTs – Heart Failure

Study	Methods	Participants	Interventions	Outcomes	Evidence level
Andreas 1996	Randomized double-blinded cross-over trial; One week n=27 Randomized: 27. Completed: 22.	Congestive heart failure and evidence of Cheyne-Stokes respiration Age, median (range): 59 (28-71) yrs FEV1: 81 (22) % of normal predicted. PaO2: NA SaO2: NA New York Heart Association Class II 3, Class III 19	Nasal nocturnal oxygen administered through nasal prongs at a flow rate of 4 L/min for seven nights Sham control, room air	Total sleep time Arousals per hour AHI, apnea-hypopnea index Sleep stage Duration of CSR Duration of CSR with apnea Oxygen desaturation during CSR	GRADE A Jadad score = 4/5, good PEDro score = 8/11
Andreas 1998	Randomized double-blinded cross-over trial; One week n=20 Randomized: 20. Completed: 20.	Congestive heart failure and evidence of Cheyne-Stokes respiration Age, mean (SD): 58 (10) yrs FEV1: 82 (22) % of normal predicted. PaO2: NA SaO2: NA New York Heart Association Class II 3, Class III 17	Nasal nocturnal oxygen administered through nasal prongs at a flow rate of 4 L/min for seven nights Sham control, room air	HCVR, hypercapnic ventilatory response End-tidal PCO2: MV, minute ventilation	GRADE A Jadad score = 4/5, good PEDro score = 8/11
Andreas 1999	Randomized double-blinded cross-over trial; One week n=17 Randomized: 17. Completed: 17.	Congestive heart failure Age, mean (SEM): 52 (4) yrs FEV1: 73 (5) % of normal predicted. PaO2: NA SaO2: NA New York Heart Association Class II 5, Class III 12	Nasal nocturnal oxygen administered through nasal prongs at a flow rate of 4 L/min for seven nights Sham control, room air	Respiratory rate O2 saturation Tc PCO2 MV, minute ventilation Systolic blood pressure Diastolic blood pressure Heart rate	GRADE A Jadad score = 4/5, good PEDro score = 7/11
Chua 1996	Randomized single-blinded cross-over trial; Treadmill cardiopulmonary exercise testing on two occasions n=12 Randomized: 12. Completed: 12.	Chronic heart failure Age (mean (standard error)): 65.5 (1.5) years FEV1: 90.5 (4.9) % predicted. PaO2: NA SaO2: 100% New York Heart Association Class II 6, Class III 6	100% oxygen via a pneumatic respiratory valve Sham control, room air	Borg (0-10) score (dyspnoea) at 3 minutes treadmill exercise Borg (0-10) score (dyspnoea) at 6 minutes treadmill exercise Borg (0-10) score (dyspnoea) at peak treadmill exercise Borg (0-10) score (fatigue) after 3 minutes treadmill exercise Borg (0-10) score (fatigue) after 6 minutes treadmill exercise Borg (0-10) score (fatigue) at peak treadmill exercise Minute ventilation (L/min) at peak treadmill exercise End-tidal CO2 (%) at peak treadmill exercise Arterial oxygen saturation (%) at peak treadmill exercise Carbon dioxide production (mL/min) at peak treadmill exercise systolic blood pressure (mm Hg) at peak treadmill exercise	GRADE B Jadad score = 2/5, poor PEDro score = 5/11
Hagenah 1996	Randomized double-blinded cross-over trial; One week n=27 Randomized: 27. Completed: 22.	Congestive heart failure and evidence of Cheyne-Stokes respiration Age, mean (SD): 57 (10) yrs FEV1: NA. PaO2: NA SaO2: NA New York Heart Association Class II 3, Class III 19	Nasal nocturnal oxygen administered through nasal prongs at a flow rate of 4 L/min for seven nights Sham control, room air	Arousals per hour Duration of CSR with apnea Ventricular ectopic beats, events during total sleep time Couplets, events during total sleep time Tachycardias, events during total sleep time	GRADE A Jadad score = 4/5, good PEDro score = 8/11
Hanly 1989	Randomized single-blinded cross-over trial; Two consecutive nights n=9 Randomized: 9. Completed: 9.	Stable congestive heart failure Age, mean (SD): 58 (7) yrs FEV1, not available PaO2: NA PaCO2: 34 (SD, 4) mmHg New York Heart Association Class III or Class IV	Oxygen at a rate of 2 to 3 L/min through a nasal cannula Sham control, compressed air	Total sleep time Arousals per hour AHI, apnea-hypopnea index Sleep stage	GRADE A Jadad score = 2/5, poor PEDro score = 6/11
Moore 1992	Randomized double-blinded cross-over trial; Exercise tests were performed on three different days n=12 Randomized: 12. Completed: 12.	Chronic heart failure Age (range): 31 to 66 years FEV1, not available FEV1: 2.88 (0.73) liters. FEV1: 78.6 (15.3) % predicted. FEV1/FVC: > 70%. SpO2: 94.6 (1.9) %. New York Heart Association class II: 7; class III: 5.	30% oxygen, and 50% oxygen-enriched air via a non-rebreathe valve Sham control, room air	Standard Borg score for perceived exertion, peak exercise VAS score dyspnoea at 6 minutes cycle ergometer exercise VAS score dyspnoea at peak cycle ergometer exercise Exercise duration Arterial oxygen saturation Minute ventilation	GRADE A Jadad score = 5/5, excellent PEDro score = 7/11
Restrick 1992	Randomized double-blinded cross-over trial; Five six-minute walks over one day and four endurance walks over a second day n=12 Randomized: 12. Completed: 12.	Stable chronic heart failure Age (range): 28 to 74 yrs FEV1: 2.4 (0.6) liters. FEV1: 81.5 (13.4)% of normal predicted. PaO2: 11.8 (1.5) kPa. SaO2: 94.4 (3.7)%. Heart failure: New York Heart Association class III: all 12 (stable chronic heart failure)	portable oxygen, 2 L/min and 4 L/min via a nasal cannula Sham control, room air	Borg score for perceived exertion (0-10), six-minutes walks Borg score for perceived exertion (0-10), endurance walks VAS (0-10) score dyspnoea, six-minutes walks VAS (0-10) score dyspnoea, endurance walks SaO2 (%),six-minutes walks SaO2 (%), endurance walks	GRADE A Jadad score = 4/5, good PEDro score = 7/11
Russel 1999	Randomized double-blinded cross-over trial; Acute, a symptom-limited cycle ergometry test (total exercise time: 600 seconds, SD 181 seconds) n=17 Randomized: 17. Completed: 16.	Men with New York Heart Association functional class II to III heart failure symptoms and severe left ventricular dysfunction Age, mean (SD): 56 (9) yrs FEV1, mean (SD): 2.91 (0.59) L; 80 % of normal predicted. PaO2: NA SaO2: NA New York Heart Association Class: not stated	60% humidified oxygen through a mouthpiece Sham control, 21% humidified oxygen	Exercise time Respiratory rate Ventilation Carbon dioxide production Mean blood pressure Heart rate Arterial lactate	GRADE A Jadad score = 4/5, good PEDro score = 8/11
Sasayama 2009	Randomized double-blinded parallel-group trial; One year n=52 Randomized: home oxygen therapy group 26, control group 26. Completed: home oxygen therapy group 26, control group 25.	Chronic heart failure Age, mean (SD): 68 (10) yrs FEV1: NA. PaO2: 37 (5) mmHg SaO2: NA New York Heart Association Class II 36, Class III 15	92% oxygen at a rate of 3 L/min through a nasal cannula Control: room air, usual breathing (No nasal cannula)	All-cause mortality Cardiac events AHI, apnea-hypopnea index CAI, central apnea index Mean SpO2, percutaneous arterial oxygen saturation SAS, Specific Activity Scale, Mets Change in NYHA, New York Heart Association class	GRADE B Jadad score = 3/5, good PEDro score = 6/11
Staniforth 1998	Randomized double-blinded cross-over trial; Four weeks n=12 Randomized: 12. Completed: 11.	Stable heart failure and documented Cheyne-Stokes respiration during sleep Age, mean (SD): 68 (7) yrs FEV1: 86 (17) % of normal predicted. PaO2: 10.7 (1.1) kPa SaO2: 4.4 (0.6) kPa New York Heart Association Class: not stated	overnight oxygen and air at a rate of 2 L/min via nasal cannulae. Sham control, room air	Quality of life score (max 240) ESS, Epworth sleepiness scale Steer Clear driving simulator, objects hit Total sleep time Arousals per hour AHI, apnea-hypopnea index Central apnoea index periodic breathing time	GRADE A Jadad score = 4/5, good PEDro score = 8/11

Overall the studies were characterised by a very small sample size, with only 9 [76] to 52 patients included [83].

The reported mean age was over 50 years in all trials, even though patient's age varied widely (from 28 to 74 years). FEV1 predicted ranged from 73 to 86%.

Only one trial used a parallel group design [78], all others a cross-over design. Seven trials focused on respiration and sleep failure [76-81, 83].

Four trials on exercise performance and tolerance failure [73-75, 82]. Interestingly, one research group managed to publish results on the same population in 4 different papers, mainly because each paper reported on different outcomes [77-79, 81].

Critical appraisal

Quality assessments according to the Jadad and PEDro score checklists are presented in appendix 2.

Overall, the JADAD score was rated as excellent for 1 trial [74], good for 8 trials [75, 77-83] and poor for 2 trials [73, 76]. Likewise, the overall PEDro ratings showed that the methodological quality was high for all trials. Yet, according to the individual items of the PEDro, no single report stated that allocation was concealed, no single report stated that outcome was analysed by "intention to treat", and only one study reported results of between-group statistical comparisons for key outcomes. No single report provided power and sample size calculations, or explicitly defined a primary outcome measure [80].

Results of individual trials

Results of each individual trial are described in table 13

Data on mortality and morbidity were reported only in the parallel group trial. This single trial found that long-term oxygen therapy (52 weeks) did not improve survival and did no decrease cardiac events compared with no oxygen therapy in patients with heart failure [83].

For quality of life measured by a validated instrument, two studies reported a statistically significant improvement in quality of life with the use of oxygen [74,83]. However, three other studies reported no difference [73, 75, 80].

Physiological parameters available from all 11 trials also give contrasting results depending on the study and the physiological outcome of interest.

No data on patient preference is available in patients with heart failure.

Finally, no data on productivity gains is available in patients with heart failure.

Table 13: Study outcomes – RCTs – Heart Failure

Study ID	Mortality- Morbidity	Quality of life	Physiologcal parameters	Patient preferences	Pruductivity gains
Hanly 1989	NA	NA	Difference in total sleep time, minutes: +49.29 (+9.20 to +89.40, P=0.016) Difference in arousals per hour: -16.57 (-24.53 to -8.61, P<0.001) Difference in AHI, apnea-hypopnea index, events per hour during total sleep time: -11.10 (-15.98 to -6.22, P<0.001)	NA	NA
Moore 1992	NA	Difference in VAS score dyspnoea at 6 minutes cycle ergometer exercise: -1.57 (95% CI, -2.70 to -0.44, P=0.007). Difference in VAS score dyspnoea at peak cycle ergometer exercise: -2.05 (95% CI, -3.25 to -0.85, P<0.001). Difference in standard Borg score for perceived exertion, peak exercise: -2.40 (-3.93 to -0.87, P=0.002	Within-patient changes in exercise duration (seconds): +52.00 (95% CI, +36.69 to +67.31, P<0.001) Difference in arterial oxygen saturation (%): + 2.90 (+2.15 to +3.65; P<0.001) Difference in minute ventilation (L/min), peak exercise: -8.00 (95% CI, -13.62 to -2.38, P=0.005).	NA	NA
Restrick 1992	NA	Difference in VAS (0-10) score dyspnoea, six-minutes walks: -0.05 (-1.4 to +1.3; P=0.95) Difference in VAS (0-10) score dyspnoea, endurance walks: +0.6 (-0.1 to +1.3; P=0.09) Difference in Borg score for perceived exertion (0-10), six-minutes walks: -1.0 (-2.5 to -0.5; P=0.17) Difference in Borg score for perceived exertion (0-10), endurance walks:+0.25 (-0.5 to +1.0; P=0.47)	Difference in SaO2 (%),six-minutes walks: +2.80 (+1.39 to +4.21; P<0.001) Difference in SaO2 (%), endurance walks: +1.20 (+0.21 to +2.19; P=0.018)	NA	NA
Andreas 1996	NA	NA	Difference in total sleep time, minutes: -3.0 (-24.4 to +18.4; p=0.78) Difference in arousals per hour: -5.0 (-8.3 to -1.7; P=0.003) Difference in duration of CSR: % of total sleep time computation of effect size not possible (only medians available). Difference in duration of CSR with apnea: % of total sleep time computation of effect size not possible (only medians available). Difference in oxygen desaturation during CSR: -7.00% (-8.51 to -5.49%; P<0.001) Difference in AHI, apnea-hypopnea index, events per hour during total sleep time: -16.0 (-21.4 to -10.6; P<0.001)	NA	NA
Chua 1996	NA	Difference in Borg (0-10) score (dyspnoea) at 3 minutes treadmill exercise (100% oxygen minus air): +0.16 (95% CI, -0.67 to +0.99, P=0.71). Difference in Borg (0-10) score (dyspnoea) at 6 minutes treadmill exercise: -0.85 (95% CI, -1.64 to -0.06, P=0.036). Difference in Borg (0-10) score (dyspnoea) at peak treadmill exercise: +0.08 (95% CI, -1.56 to +1.72, P=0.92). Difference in Borg (0-10) score (fatigue) after 3 minutes treadmill exercise (100% oxygen minus air): -0.08 (95% CI, -0.95 to +0.79, P=0.86). Difference in Borg (0-10) score (fatigue) after 6 minutes treadmill exercise: -0.21 (95% CI, -1.37 to -0.95, P=0.72). Difference in Borg (0-10) score (fatigue) at peak treadmill exercise: +0.21 (95% CI, -1.33 to +1.75, P=0.79).	Difference in minute ventilation (L/min) at peak treadmill exercise: +1.26 (95% CI, -12.54 to +15.06). Difference in end-tidal CO2 (%) at peak treadmill exercise: -0.69 (-1.01 to -0.37; P<0.001) Difference in carbon dioxide production (mL/min) at peak treadmill exercise: -163.0 (-275.0 to -51.0; P=0.004) Difference in systolic blood pressure (mm Hg) at peak treadmill exercise: -15.0 (-25.49 to -4.51; P=0.005)	NA	NA
Hagenah 1996	NA	NA	Difference in duration of CSR with apnea: % of total sleep time:: -74.0 (-111.0 to -36.9; P<0.001) Difference in arousals per hour: -6.0 (-9.3 to -2.7; P<0.001) Difference in couplets, events during total sleep time: -5.3 (-13.8 to +3.2; P=0.22) Difference in tachycardias, events during total sleep time: -1.4 (-2.9 to +0.1; P=0.07)	NA	NA

Andreas 1998	NA	NA	Difference in HCVR, hypercapnic ventilatory response: L/min/mmHg: -0.29 (-0.52 to -0.06; P=.013) Difference in End-tidal PCO2: mmHg: +0.70 (-1.21 to +2.61; P=0.47) Difference in MV, minute ventilation, L/min -030 (-1.68 to +1.08; P=0.67)	NA	NA
Staniforth 1998	NA	Difference in quality of life score (max 240): +2.0 (-10.6 to +14.6; P=0.76) Difference in ESS, Epworth sleepiness scale: -0.60 (-3.26 to +2.06; P=0.66)	Difference in Steer Cleer driving simulator, objects hit: +34.0 (-14.7 to +82.7; P=0.17) Difference in total sleep time, minutes: +27.0 (-19.2 to +73.2; P=0.25) Difference in arousal index: events per hour total sleep time: -1.80 (-4.10 to +0.50; P=0.12) Difference in oxygen desaturation index: per total recording time: -20.8 (-25.3 to -16.27; P<0.001) Difference in Min SaO2: %: +8.7 (+7.2 to +10.2; P<0.001) Difference in AHI, apnea-hypopnea index, events per hour actual sleep time:: -12.9 (-20.0 to -5.8; P<0.001) Difference in central apnoea index, events per hour actual sleep time: -14.6 (-19.6 to -9.7; P<0.001) Difference in periodic breathing time, % of actual sleep time: -22.9 (-31.7 to -14.1; P<0.001)	NA	NA
Andreas 1999	NA	NA	Difference in Respiratory rate: per min: +0.34 (-0.28 to +.097; P=0.29) Difference in Tidal volume: L. Difference in MV, minute ventilation, L/min -0.40 (-1.01 to +0.21; P=0.23) Difference in O2 saturation, minute ventilation: %: +2.80 (+2.21 to +3.39; P<0.001) Difference in Tc PCO2: mmHg: +1.50 (+0.52 to +2.48; P=0.003) Difference in systolic blood pressure: mmHg: +1.80 (-0.55 to +4.15; P=0.14) Difference in diastolic blood pressure: mmHg: -0.03 (-1.99 to +1.93; P=0.98) Difference in heart rate: beats per min: -2.30 (-3.28 to -1.32; P<0.001)	NA	NA
Russel 1999	NA	NA	Difference in exercise time, minutes: +7.0 (-55.4 to +69.4; P=0.82) Difference in Heart rate (beats/min): -1.0 (-7.4 to +5.3; P=0.76) Difference in Mean blood pressure (mm Hg): +6.0 (-0.4 to +12.4; p=0.07) Difference in Arterial lactate (mmol/L): -0.50 (-0.96 to -0.04; P=0.034) Ventilatory responses: Difference in Ventilation (L/min): -1.8 (-5.3 to +1.7; P:0.32) Difference in Respiratory rate (breaths/min): -1.0 (-2.5 to +0.5; P=0.18) Difference in Carbon dioxide production (L/min): +11.0 (-90.3 to +112.3; P=0.83)	NA	NA
Sasayama 2009	Survival: Odds ratio for all-cause mortality: 0.790 (0.246 to 2.537; P=0.69) Relative Risk for all-cause mortality: 0.855 (0.392 to 1.861) Difference in all-cause mortality: -5.2% (-31.3 to +20.6%) Cardiac events: Odds ratio for cardiac events: 0.938 (0.305 to 2.886; P=0.91) Relative Hazard for for cardiac events: 0.78 (0.30 to 2.05; P=0.62) Difference in cardiac events: -1.5% (-28.3 to +25.3%).	Difference in SAS, Specific Activity Scale, Mets: +0.93 (+0.34 to +1.52; P=0.002) Change in NYHA, New York Heart Association class (% improved) OR (95% CI; P value): 17.6 (2.058 to 150.550; P=0.019) RR: 10.577 (1.472 to 76.010) Risk Difference: 38.3 (17.8 to 58.8) % improved NNT 3 (2 to 6)	Difference in AHI, apnea-hypopnea index, events/hour: -10.8 (-17.4 to -4.2; P<0.001) Difference in CAI, central apnea index: -7.7 (-12.8 to -2.6; P=0.003) Difference in Mean SpO2, percutaneous arterial oxygen saturation, %; +3.6 (+2.6 to +4.6; P<0.001)	NA	NA

3.2.3.3 *Updated and additional meta-analyses*

Methods

For the current report commissioned by the KCE we decided to perform an updated systematic review and meta-analysis based on all trials currently available for the target population of patients with cardiac failure.

Four trials reported on the effects of oxygen therapy on exercise capacity in patients with chronic, stable heart failure [73-75, 82].

Seven trials investigated the effects of oxygen therapy on respiration and sleep quality in patients with chronic (stable) heart failure [76-81, 83].

Updated meta-analyses were performed for quality of life parameters: dyspnoea at 3 minutes exercise, dyspnoea at 6 minutes exercise, dyspnoea at peak exercise, fatigue at peak exercise, and total exercise time.

Additional meta-analyses were also performed for physiological parameters: total sleep time, arousal index, apnoea-hypopnoea index (AHI), central apnoea index (CAI), sleep stage 1, sleep stage 2, sleep stages 3-4 (slow wave sleep), REM (rapid eye movement) sleep, minute ventilation (MV), and arterial oxygen saturation (SaO2).

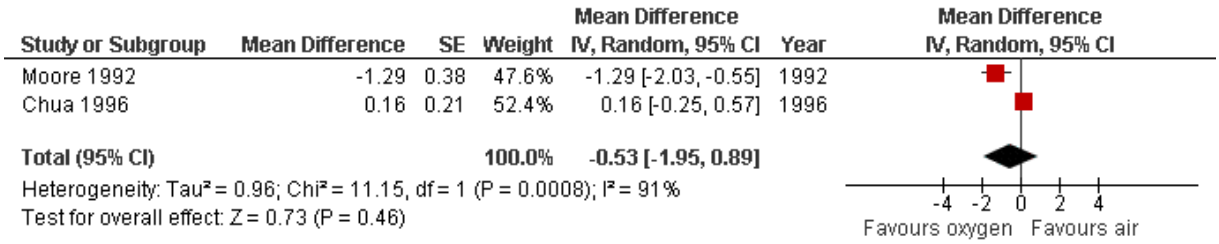
Estimates of the effect of oxygen therapy on each outcome of interest (effect size) were calculated for each individual trial. Pooled estimates of the mean effect of oxygen therapy on each outcome of interest and the corresponding 95% CIs were determined using RevMan 5.1 beta software. Since we anticipated heterogeneity, we report only random effects analyses that incorporate both between- and within-study variation (providing more conservative estimates). Effect sizes are presented as mean difference (MD) with standard error (SE) and 95% confidence intervals (CIs).

Results

QUALITY OF LIFE

Dyspnoea at 3 minutes

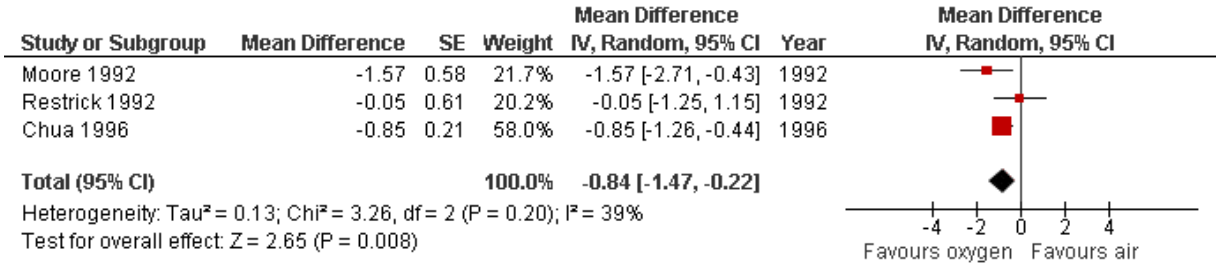
Figure 8: Meta-analysis - Dyspnoea at 3 minutes exercise, VAS/Borg (0-10) scale



Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: Dyspnoea at 3 minutes exercise, VAS/Borg (0-10) scale.
Number of participants: randomised 24; completed 24.

Dyspnoea at 6 minutes exercise

Figure 9: Meta-analysis - Dyspnoea at 6 minutes exercise, VAS/Borg (0-10) scale



Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: Dyspnoea at 6 minutes exercise, VAS/Borg (0-10) scale.
Number of participants: randomised 36; completed 36.

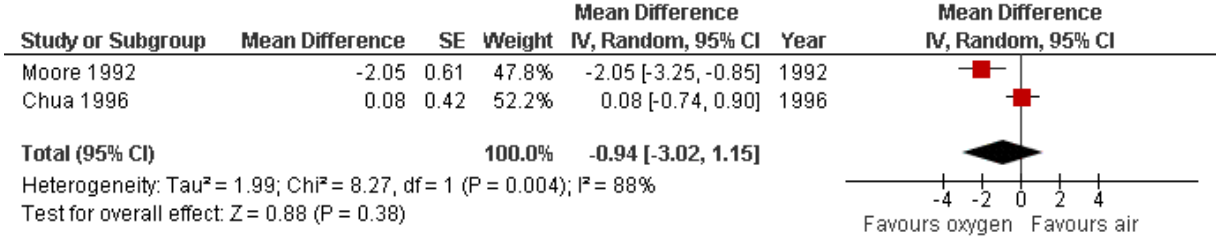
Overall, in patients with chronic and stable heart failure undergoing exercise testing, meta-analysis found that there was no improvement in dyspnoea at 3 minutes exercise, dyspnoea at peak exercise, fatigue at peak exercise, total exercise time, minute ventilation (MV), and arterial oxygen saturation (SaO2). A major limitation of these meta-analyses is the very small number of trials available for inclusion. In addition, each individual trial had a very small sample size.

Despite these limitations, dyspnoea at 6 minutes exercise was significantly reduced in favour of oxygen, with an effect size of -0.84 (-1.47, -0.22) on a 0-10 point scale.

Heterogeneity was moderate (I^2=39%). This finding should be interpreted with some caution when considering the problem of multiple hypothesis testing.

Dyspnoea at peak exercise

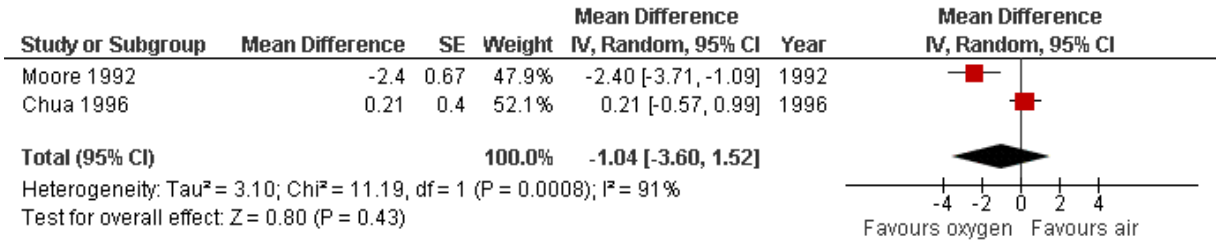
Figure 10: Meta-analysis - Dyspnoea at peak exercise, VAS/Borg (0-10) scale



Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: Dyspnoea at peak exercise, VAS/Borg (0-10) scale.
Number of participants: randomised 24; completed 24.

Fatigue at peak exercise

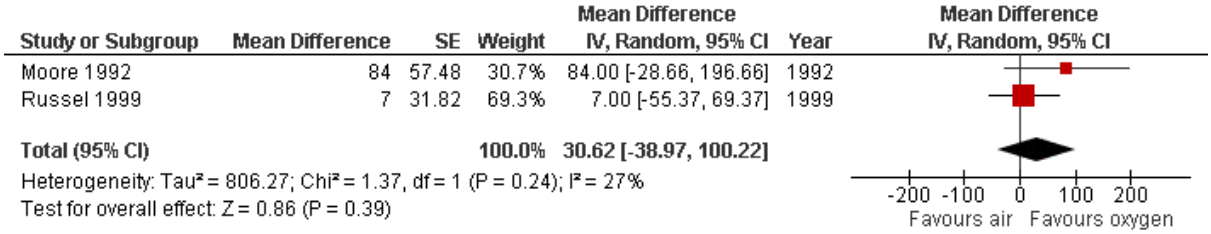
Figure 11: Meta-analysis - Fatigue at peak exercise, VAS/Borg (0-10) scale



Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: Fatigue at peak exercise, VAS/Borg (0-10) scale.
Number of participants: randomised 24; completed 24.

Total exercise

Figure 12: Meta-analysis - Total exercise time, seconds

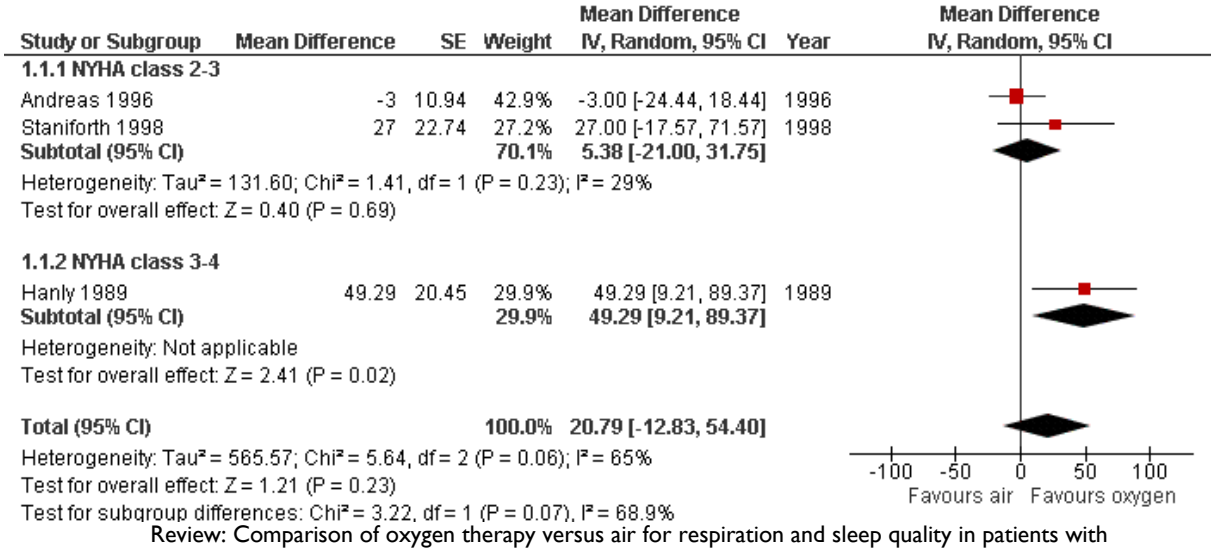


Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: Total exercise time, seconds.
Number of participants: randomised 29; completed 28.

PHYSIOLOGICAL PARAMETERS

Total sleep time

Figure 13: Meta-analysis - Total sleep time

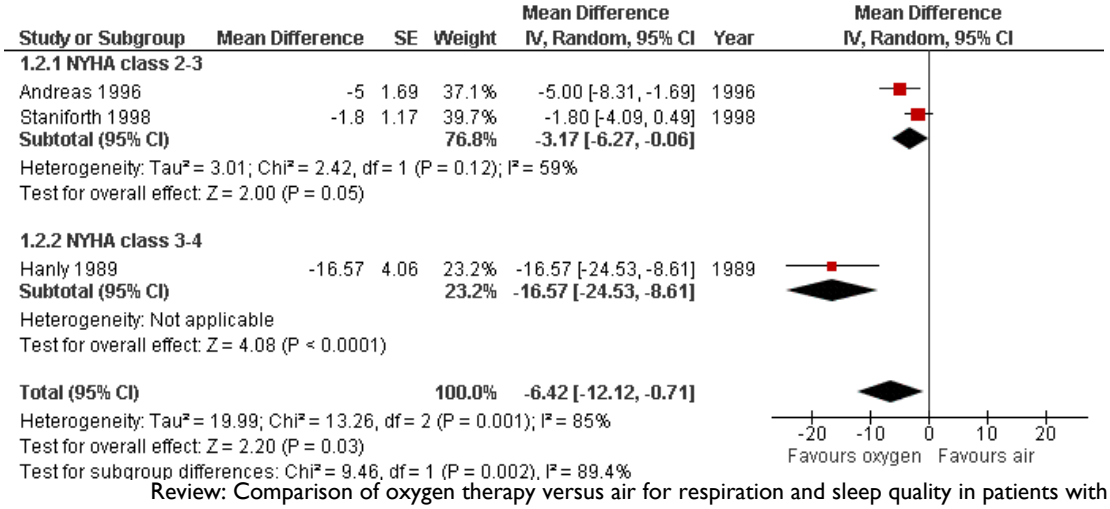


Review: Comparison of oxygen therapy versus air for respiration and sleep quality in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for respiration and sleep quality in patients with chronic, stable heart failure.
Outcome: total sleep time, minutes.
Number of participants: randomised 48; completed 42.

Three cross-over trials involving 42 patients were included in the meta-analysis of total sleep time. Two of these trials, conducted in patients with NYHA class 2-3, found no difference in duration of total sleep time. Total sleep time was significantly longer with oxygen among patients with NYHA class 3-4. The pooled estimate of the effect of oxygen was a statistically not significant increase in total sleep time, Statistical heterogeneity between the trials was high (I^2=65%). After stratification according to the degree of heart failure the test for subgroup differences suggested a trend towards increased total sleep time with oxygen among patients with more severe heart failure (P=0.07).

Arousal index

Figure 14: Meta-analysis - Arousal index



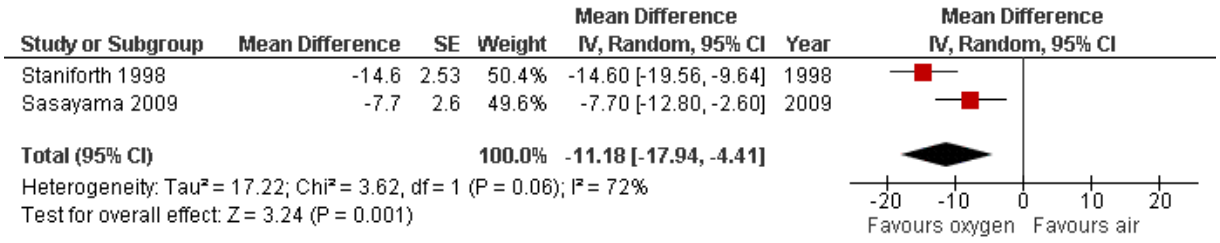
Review: Comparison of oxygen therapy versus air for respiration and sleep quality in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for respiration and sleep quality in patients with chronic, stable heart failure, with subgroup analysis according to NYHA class.
Outcome: arousal index, events per hour.
Number of participants: randomised 48; completed 42.

Three trials involving the same 42 patients were included in the meta-analysis of arousal index, the number of arousal events per hour.

Only one of these trials, conducted in patients with NYHA class 2-3, found no difference in arousal index. The number of arousal events per hour was significantly less in the both other trials. The pooled estimate of the effect of oxygen was a statistically significant decrease in number of arousal events, with a difference of -6.45 (-12.12, -0.71) in favour of oxygen. Statistical heterogeneity between the trials was very high (I^2 =85%). Stratification according to the degree of heart failure indicated that the decrease in number of arousals with oxygen was associated with a more severe degree of heart failure (test for subgroup differences P=0.03).

Central apnoea index

Figure 15: Meta-analysis - CAI, central apnoea index

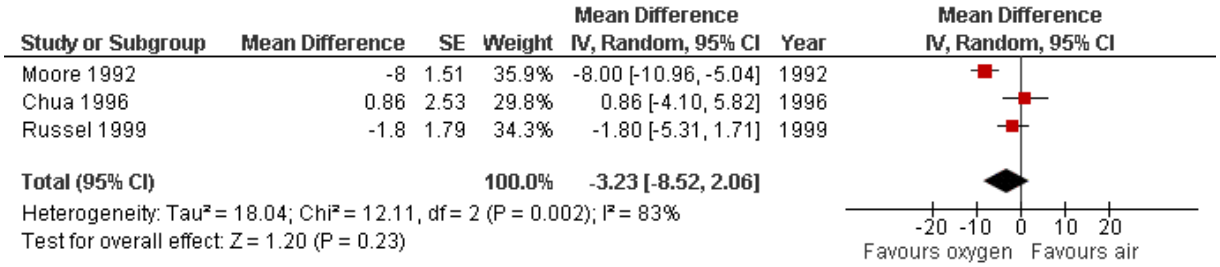


Review: Comparison of oxygen therapy versus air for respiration and sleep quality in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for respiration and sleep quality in patients with chronic, stable heart failure.
Outcome: CAI, central apnoea index, events per hour.
Number of participants: randomised 63; completed 62.

Both trials documenting the effects of oxygen therapy on central apnoea index (CAI) found a statistically decrease in central apnoea index (CAI). The number of central apnoea events was significantly less in both trials. The pooled estimate of the effect of oxygen was a statistically significant decrease in AHI, with a difference of -11.18 (-17.94, -4.41) - central apnoea events in favour of oxygen. Statistical heterogeneity between the trials was a high (I^2 =72%). The Staniforth and Sasayama trials were clinically heterogeneous with respect to publication year (1998 versus 2009), study design (cross-over versus parallel group design), number of patients included (11 versus 52), duration of treatment and follow-up (4 versus 52 weeks), country and ethnicity (United Kingdom versus Japan).

Minute ventilation

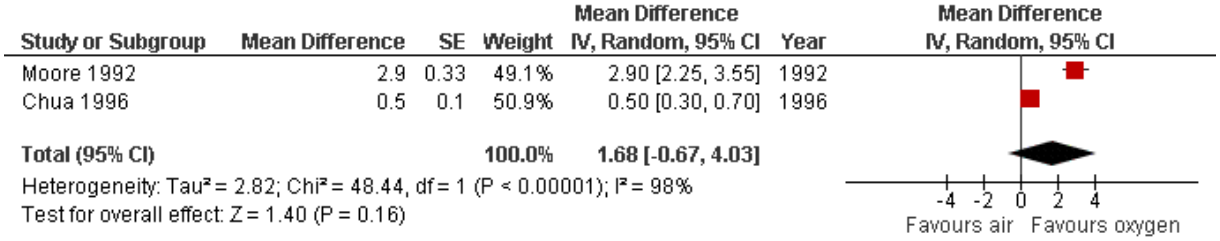
Figure 16: Meta-analysis - MV, minute ventilation, L/min



Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: MV, minute ventilation, L/min.
Number of participants: randomised 41; completed 40.

SaO2 arterial oxygen saturation

Figure 17: Meta-analysis - SaO2, arterial oxygen saturation, %



Review: Comparison of oxygen therapy versus air for exercise capacity in patients with chronic, stable heart failure.
Comparison: Supplemental oxygen inhalation versus air inhalation for exercise capacity in patients with chronic, stable heart failure
Outcome: SaO2, arterial oxygen saturation, %
Number of participants: randomised 24; completed 24.

Results and forest plots of the meta-analyses performed for other physiological parameters including apnoea-hypopnoea index (AHI), sleep stage 1, sleep stage 2, sleep stages 3-4 (slow wave sleep), and REM (rapid eye movement) sleep, are listed in Appendix 2.4.

Sensitivity analyses

Initially, we planned to consider the following characteristics for (a priori defined) subgroup and meta-regression analyses: gender; disease severity; level of hypoxemia; storage method of oxygen delivery; dose, duration, and period of oxygen delivered; study quality; calendar year for conduction and publication of study. These analyses were not meaningful for comparing the effects of oxygen therapy versus air on exercise capacity, respiration and sleep quality in patients with chronic heart failure, given the very small number of trials available in this population of interest.

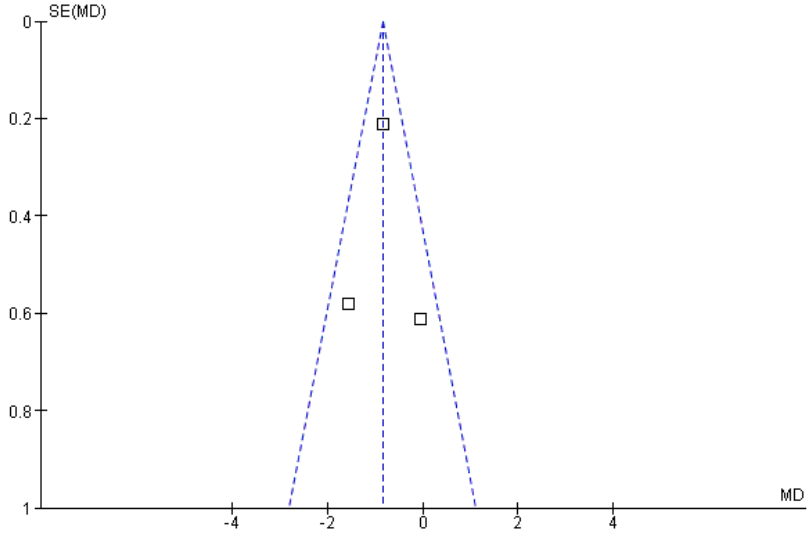
Stratified analyses based on severity of heart failure and study design have been presented in the previous paragraphs.

Publication bias

We explored potential publication bias by funnel plot, and assessed the potential implications for our results by the trim-and-fill and the fail-safe N method. These procedures were generated only for outcomes reported in at least 3 trials. The fail-safe N method was applied only for meta-analyses with a statistically significant pooled estimate.

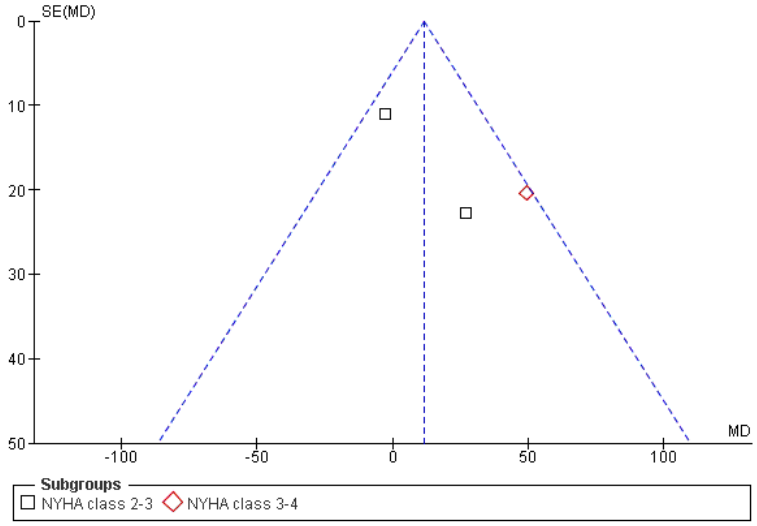
Egger's test for detecting publication bias was not applied as this test is likely underpowered if the number of available studies is less than 10.

Figure 18: Funnel plot - Dyspnoea at 6 minutes exercise



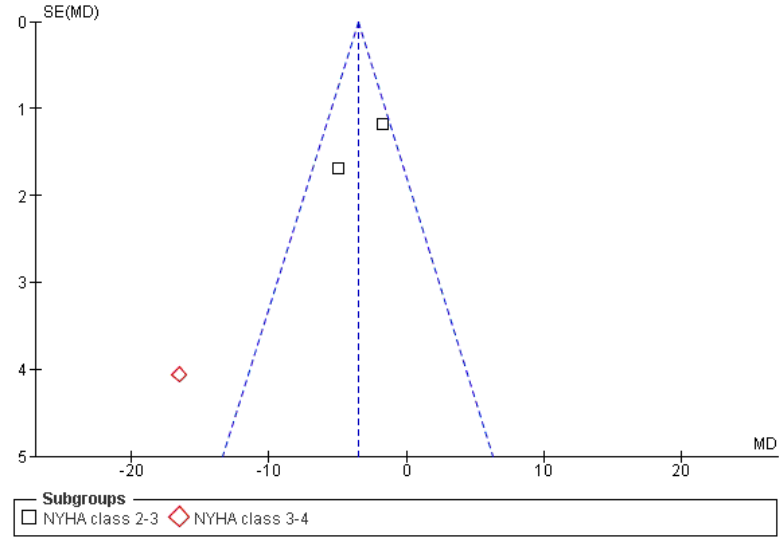
The funnel plot for dyspnoea at 6 minutes exercise shows no asymmetry, and the trim and fill computations indicate that the imputed pooled estimate is identical to our random effects model pooled estimate and its 95% confidence interval. The fail-safe N method indicates that the number of missing studies that would render our pooled estimate non significant is 10. Publication bias is thus very unlikely to affect our conclusions for dyspnoea at 6 minutes exercise.

Figure 19: Funnel plot - Total sleep time



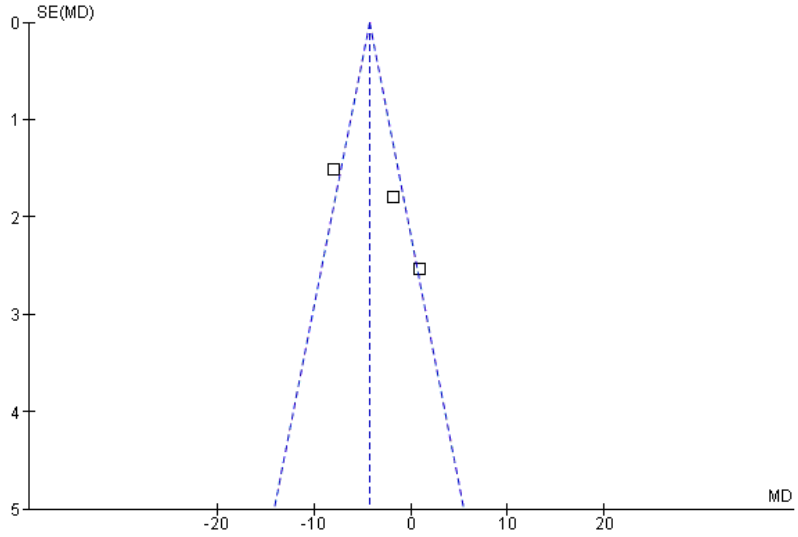
The funnel plot for total sleep time was slightly asymmetric. The trim-and-fill method indicated that publication bias might have occurred due to our inability to find or the absence of two small studies on the left of the summary estimate. Under a random effects model we computed a pooled estimate and 95% confidence interval for the included trials of 20.79 (-12.83, 54.40). Using trim and fill methodology the imputed point estimate is -3.00 (-36.34, 30.34). These overlapping confidence intervals indicate that publication bias is unlikely to change our conclusions.

Figure 20: Funnel plot - Arousal index



Visual inspection of the funnel plot for arousal index suggests asymmetry due to the absence of small studies on the right of the summary estimate. Yet, the trim-and-fill computations indicate that publication bias is very unlikely. Under a random effects model we computed a pooled estimate and 95% confidence interval for the included trials of -6.42 (-12.12, -0.71). Using trim and fill methodology the imputed poled estimate is identical. Likewise, the fail-safe N method indicates that the number of missing studies that would render our pooled estimate non significant is 17, indicating that publication bias is very unlikely to affect the findings of our meta-analysis.

Figure 21: Funnel plot - MV, minute ventilation, L/min



The funnel plot for minute ventilation suggests asymmetry due to the absence of small studies on the left of the summary estimate. Yet, the trim-and-fill computations indicate that publication bias is unlikely, as the imputed pooled estimate is identical to our random effects model pooled estimate and its 95% confidence interval.

Funnel plots for other physiological parameters including apnoea-hyppnoea index (AHI), sleep stage 1, sleep stage 2, and REM (rapid eye movement) sleep, are shown in Appendix 2.5.

DISCUSSION

The only trial assessing mortality and/or morbidity among patients with chronic heart failure treated with oxygen found no significant differences for all-cause mortality or cardiac events during the 52 weeks of oxygen therapy versus air [83]. This trial is very likely to be underpowered given the very small sample size and the very small number of clinically relevant (mortality and morbidity) events.

Quality of life data available from one single trial showed statistically significant improvements in quality of life scores, as measured by SAS (Specific Activity Scale), ESS (Epworth sleepiness scale), and NYHA (York Heart Association class) in favour of oxygen therapy versus air. In line with the Cochrane meta-analysis [65], our updated meta-analyses confirm a statistically significant change in dyspnoea at 6 minutes exercise testing in favour of oxygen therapy, but no differences in dyspnoea at 3 minutes or peak exercise testing [83]; updated meta-analyses presented in the current KCE report).

One trial found no differences in cognitive function.

Our additional meta-analyses exploring the potential effects of oxygen therapy on a variety of physiological parameters showed statistically significant changes in arousal index, apnoea-hypopnoea index (AHI), central apnoea index (CAI), sleep stage 1, sleep stage 2, and REM (rapid eye movement) sleep in favour of oxygen therapy, but no differences in total sleep time, minute ventilation or arterial oxygen saturation

The vast majority of these trials focus on physiological parameters, rather than clinically relevant and patient oriented outcomes. Very few trials report power and sample size calculations or explicitly define a primary outcome measure, and no single trial provides information on how to address the problem of multiple testing. Despite these limitations, several statistically significant and clinically relevant effects in favour of oxygen were observed, especially for quality of life.

The effects of improved physiological parameters observed with oxygen therapy on quality of life, morbidity and mortality, on the other hand, are not always well established. Patients suffering from heart failure and Cheyne Stokes breathing (CSB) have a worse prognosis than patients without CSB [37]. The Apnoea-hypopnoea index is the best predictor of cardiac mortality [37]. Currently however, it is not clear if the observed association between CSB and increased cardiac mortality is causal or not, as CSB might be a marker of more severe heart failure or a comorbidity worsening heart failure (or both). There is no clear association between Cheyne-Stokes respiration and health-related quality of life, daytime sleepiness or nocturnal dyspnea among patients stabilized following treatment for congestive heart failure. There is not always a clear relationship between AHI and daytime sleepiness. Generic quality of life or disease-specific quality of life were not related to AHI. As a general rule, almost all trials are likely to be underpowered for detecting associations between physiological parameters and clinically relevant outcomes.

No published data is available for the effects of oxygen therapy versus air on patient preference or productivity gains.

In summary, the meta-analyses and publication bias procedures presented here are likely to be hampered by the small number of trials available and several intrinsic limitations of these trials. Despite these limitations, meta-analyses yield statistically significant effects in favour of oxygen therapy for several outcomes, mainly related to quality of life, respiration and sleep disorders in patients with chronic, stable heart failure. Publication bias is very unlikely to affect these statistically significant findings.

3.2.4 Cystic fibrosis

Cystic fibrosis (CF), an autosomal recessive disease is one of the most common lethal genetic diseases among Caucasians. Although abnormalities occur in the hepatic, gastrointestinal, and male reproductive systems, lung disease is the major cause of morbidity and mortality [84]. Most individuals with CF develop obstructive lung disease associated with chronic infection that leads to progressive loss of pulmonary function. The rationale of supplemental oxygen breathing in children with respiratory disease is quite similar to adults. The aims are to reduce the work of breathing resulting in fewer respiratory symptoms; relax the pulmonary vasculature, decreasing the potential for pulmonary hypertension and congestive heart failure; and improve feeding [85]. Enhanced understanding of the genetics and pathophysiology of the disease and well-designed clinical trials are responsible for a substantial portion of the improved patient survival. Lung transplantation provides an additional management option. The 3-year survival rate following transplantation for cystic fibrosis is about 55%. Currently, the life expectancy of patients with cystic fibrosis is increasing and the median survival age is over 35 years [86].

3.2.4.1 Meta-analyses and systematic reviews

Final selection

Our electronic searches identified 1 meta-analysis [87] relevant in patients with cystic fibrosis.

This Cochrane review [87] published in 2009 is up to date and provides relevant information to answer our research question.

Study characteristics

This Elphic 2009 Cochrane review captured all available trials from the Cystic Fibrosis Trials Register, compiled from electronic searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and the prospective handsearching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. The trials included in the Cochrane review were published from 1984 to 2006.

As the individual trials included a very limited number of patients, the Elphic 2009 Cochrane review is based on 172 participants, of which only 28 received long-term oxygen therapy. The individual trials report a mean age of 22 to 26 years for their participants (see Table 14).

Table 14: Study Characteristics – Evidence synthesis – Cystic Fibrosis

Study	Methods	Citations included (oxygen vs control)	Participants	Interventions	Outcomes	Level of evidence
Elphic 2009	SR RCTs only # of studies: 11	Nixon 1990, Marcus 1992, Parsons 1996, Shah 1997, Gozal 1997, Barker 1998, Spier 1984, Zinman 1989, Milross 2001, McKone 2002, Falk 2006	Children and adults with cystic fibrosis (CF) diagnosed clinically and by sweat or genetic testing including all ages and all degrees of severity. Age NA FEV1, 29 to 62 %predicted PaO2 < 70 mmHg PaCO2 > 45 mmHg	Therapy with oxygen supplementation in which outcomes are compared with air.	Survival Exercise capacity Physiologocal parameters Regular attendance at school or work	A

Critical appraisal

The quality assessment using the PRISMA checklist is included in appendix 2. Overall the methodological quality of the review by Elphic [87] Cochrane review is very good, with 25 out of the 27 items of the PRISMA checklist marked as YES.

Results

Results are described in table 15

The authors conclude (quote): "Short-term oxygen therapy during sleep and exercise improves oxygenation but is associated with modest and probably clinically inconsequential hypercapnia. There are improvements in exercise duration, time to fall asleep and regular attendance at school or work. There is a need for larger, well-designed clinical trials to assess the benefits of long-term oxygen therapy in people with CF administered continuously or during exercise or sleep or both."

Table 15: Study outcomes – Evidence synthesis – Cystic Fibrosis

Study ID	Mortality-Morbidity	Quality of Life	Physiological parameters	Patients preference	Productivity gains
Elphic 2009	There was no statistically significant improvement in survival in one single trial measuring this effect: Deaths at 36 months: Odds Ratio (M-H, Fixed, 95% CI) 1.00 [0.19, 5.15]	One study reported an improvement in regular attendance at school or work in those receiving oxygen therapy at 6 and 12 months. at 6 months: Odds Ratio (M-H, Fixed, 95% CI) 9.17 [1.63, 51.43] at 12 months: Odds Ratio (M-H, Fixed, 95% CI) 40.00 [3.05, 524.83]	After sub-maximal exercise there was a significant improvement in SaO2 levels with administration of supplementary oxygen, MD 2.11 (95% CI 1.54 to 2.68, P < 0.00001). There was no significant difference in post-exercise end-tidal CO2 tension (PET CO2, MD 0.11, 95% CI -2.14 to 2.36). During maximal exercise and the use of supplementary oxygen during maximal	NA	One study reported an improvement in regular attendance at school or work in those receiving oxygen therapy at 6 and 12 months. at 6 months: Odds Ratio (M-H, Fixed, 95% CI) 9.17 [1.63, 51.43] at 12 months: Odds Ratio (M-H, Fixed, 95% CI) 40.00 [3.05, 524.83]

3.2.4.2 Original studies (RCTs)

Final selection

Our electronic searches identified 3 randomised trials potentially relevant in patients with cystic fibrosis [88-90].

The Cochrane review [87] is based on a literature search current to November 2008 and 10 original trials including the 3 trials identified by our electronic searches. Our search for original studies identified no additional cystic fibrosis trials published in or after 2008.

Our final selection includes no additional trials on patients with cystic fibrosis.

Studies characteristics

Not applicable as our final selection includes no randomised trials in patients with cystic fibrosis.

Critical appraisal

Not applicable as our final selection includes no randomised trials in patients with cystic fibrosis.

Results

Not applicable as our final selection includes no randomised trials in patients with cystic fibrosis.

3.2.4.3 Discussion

There is no statistically significant improvement in survival, lung function, or cardiac health in the single trial measuring this effect [87].

For quality of life no published data is available.

By contrast, ample information is available on the effects of oxygen on several physiological parameters. These results are clearly described and summarised in an uptodate, methodologically sound Cochrane review for a variety of physiological parameters. The percentage of total sleep time spent in REM sleep is significantly reduced and arterial oxygen saturation (SaO2) during REM sleep significantly improved with oxygen therapy. Total sleep time and arousal index are not significantly different between room air and oxygen therapy. Patients are able to exercise for a significantly longer duration with oxygen therapy, even though there are no significant differences for oxygen consumption, CO2 production, minute ventilation, and heart rate source [87].

For patient preference, again, no published data is available.

For productivity gains, only one single trial reports an improvement in regular attendance at school or work at 6 and 12 months in patients receiving oxygen therapy [87].

Although this Cochrane review [87] published in 2009 is up to date and provides relevant information to answer our research question, the authors acknowledge several potential limitations, including the limited number of patients (the Elphic 2009 Cochrane review is based on 172 participants, of which only 28 received long-term oxygen therapy), and emphasize the need for additional adequately powered trials evaluating the effects of long-term oxygen treatment. The vast majority of trials focus on physiological parameters, rather than clinically relevant and patient oriented outcomes. Almost all trials are likely to be underpowered given their very small sample size and the very small number of clinically relevant (mortality and morbidity) events. Moreover, the association between physiological parameters and health-related quality of life or clinically relevant (mortality and morbidity) events remains unknown.

3.2.5 Interstitial lung disease

Interstitial lung diseases (ILD) are nonmalignant disorders and are not caused by identified infectious agents. Although there are multiple initiating agent(s) of injury, the immunopathogenic responses of lung tissue are limited. The two major histopathologic patterns are a granulomatous pattern and a pattern in which inflammation and fibrosis predominate.The course of ILD is variable, progression is common and often insidious. Virtually all patients with IPF will eventually require supplemental oxygen, initially just with exertion and then continuously [91]. This section covers supplemental oxygen in patients suffering from ILD.

3.2.5.1 Meta-analyses and systematic reviews

Final selection

Our electronic searches for the effects of oxygen therapy in patients with interstitial lung disease (ILD) identified only one potentially relevant Cochrane review [92].

Study characteristics

This Cochrane review aimed to evaluate the effect of domiciliary long-term oxygen therapy on survival and quality of life in patients with ILD.

No other outcomes were considered.

Only one (unpublished) randomized controlled trial with survival data over 4 years was identified. Inclusion criteria included a total lung capacity (TLC) <80% predicted and an arterial oxygen tension (PaO2) of 45-60 mm Hg (see Table 16).

Table 16: Study outcomes – Evidence synthesis – ILD

Study ID	Survival	Hospitalisations	HRQL	Patients preference	Physiological parameters	Productivity gains
Crockett 2010	Mortality at 12 months, Peto Odds Ratio (Peto, Fixed, 95% CI): 0.50 [0.15, 1.61] P=0.24 Mortality at 24 months, Peto Odds Ratio (Peto, Fixed, 95% CI): 1.76 [0.64, 4.86] P=0.27 Mortality at 36 months, Peto Odds Ratio (Peto, Fixed, 95% CI): 0.99 [0.16, 6.26] P=0.99	NA	NA	NA	NA	NA

Critical appraisal

The quality assessment using the PRISMA checklist is included in appendix 2. Overall the methodological quality of this Cochrane review [92] is very good, with 24 out of the 27 items of the PRISMA checklist marked as YES.

By contrast, the method of randomisation for the individual multi-centre trial, started in 1988, was not stated. The method of blinding was not described. The results are not available through a peer-reviewed journal.

Results

Results are described in table 17.

This unpublished study reported that long-term oxygen therapy did not improve survival compared with no oxygen therapy in patients with ILD. No data on quality of life was available.

Table 17: Study outcomes – Evidence synthesis – ILD

Study ID	Survival	Hospitalisations	HRQL	Patients preference	Physiological parameters	Productivity gains
Crockett 2010	Mortality at 12 months, Peto Odds Ratio (Peto, Fixed, 95% CI): 0.50 [0.15, 1.61] P=0.24 Mortality at 24 months, Peto Odds Ratio (Peto, Fixed, 95% CI): 1.76 [0.64, 4.86] P=0.27 Mortality at 36 months, Peto Odds Ratio (Peto, Fixed, 95% CI): 0.99 [0.16, 6.26] P=0.99	NA	NA	NA	NA	NA

3.2.5.2 Original studies (RCTs)

Final selection

Our electronic searches for the effects of oxygen therapy in patients with interstitial lung disease (ILD) identified only one randomised trial [93].

The focus of the Cochrane review does not capture the information on exercise performance reported in the Harris-Eze trial [93].

The focus of the Harris-Eze trial [93] is on exercise performance and does not capture the information reported in the Cochrane review.

Studies characteristics

Patients with clinical, radiographic and pulmonary evidence of interstitial lung disease, clinically stable for at least two months before the study were included. Major exclusion criteria were: pleural disease, chest wall abnormality, respiratory muscle weakness, disease that could impair exercise tolerance.

The trial considers only physiological parameters during exercise performance in patients with ILD (see Table 18).

Table 18: Study characteristics – RCTs – ILD

Study	Methods	Participants	Interventions	Outcomes	Level of evidence
Harris-Eze1994	Randomized double-blinded cross-over trial; Acute exercise test n=7 Randomized: 7 patients. Completed: 7 patients.	Interstitial lung disease, clinically stable for at least two months before the study Age, mean (SEM): 49 (6) yrs FEV1: 2.55 (SEM 0.24). PaO2: NA SaO2: NA	oxygen of 60% (FiO2) or room air via a mouth peace Sham control: room air	VO2, oxygen uptake VCO2, carbon dioxide output HR, heart rate, beats/min HR, heart rate, beats/min VT, tidal volume Respiratory frequency	GRADE A Jadad score = 4/5, good PEDro score = 8/11

Critical appraisal

Despite good overall JADAD and PEDro scores (appendix 2), it is not clear if allocation was concealed and if analysis was by "intention to treat". The results are not reported as between-group statistical comparisons.

Results

Results are described in table 19

Breathing 60%oxygen during exercise resulted in a significant increase in oxygen uptake, exercise duration, and maximal work load. There was no difference in maximal minute ventilation.

3.2.5.3 Discussion

Outcome data on the effects of oxygen therapy in patients with ILD are rather scarce, with data available from only two trials, one unpublished.

Only one (unpublished) trial documents similar survival rates after 12, 24 and 36 months of oxygen therapy [92].

Likewise, one trial reports significant differences in oxygen uptake (VO2), carbon dioxide output (VCO2), and oxygen saturation (SaO2) in favour of oxygen. There are no differences in heart rate, tidal volume (Vt), and respiratory frequency [93].

For quality of life, patient preference, or productivity gains no published data are available.

The results reported here are likely to be hampered by the very small number of trials available and the intrinsic limitations of these trials. The unpublished trial is likely to be underpowered given the very small sample size and the very small number of clinically relevant (mortality) events. The clinical relevance of trial focusing on physiological parameters only remains unclear, as the association between physiological parameters and health-related quality of life or clinically relevant (mortality and morbidity) events is unknown.

Table 19: Study outcomes – RCTs – Interstitial lung disease

Study ID	Mortality-Morbidity	Quality of Life	Physiologcal parameters	Patient preferences	Pruductivity gains
Harris-Eze 1994	NA	NA	Difference in VO2, oxygen uptake, L/min: +0.26 (95% CI, +0.17 to 0.35; P<0.001) Difference in VCO2, carbon dioxide output, L/min: +0.11 (95% CI, +0.01 to 0.21; P=0.025) Difference in SaO2, oxygen saturation, %:+15.0 (95% CI, +13.0 to 17.0; P<0.001) Difference in HR, heart rate, beats/min: -2.0 (95% CI, -6.5 to -2.5; P=0.39)	NA	NA

Key points – clinical effectiveness of oxygen therapy versus air

COPD

Mortality/morbidity:

- **Published evidence coming primarily from two trials supports that, in patients with severe hypoxaemia (paO2 ≤55mm Hg or PaO2 < 60 mmHg with disturbances of pulmonary hemodynamic,right heart failure or erythrocytosis), oxygen therapy significantly improves mortality at 5 years (Peto odds ratio 0.42, 95%CI 0.18 to 0.98) if compared with no oxygen (B). In patients with severe hypoxaemia, continuous oxygen therapy significantly improves mortality at 2 years (Peto odds ratio 0.45, 95%CI 0.25 to 0.81) if compared with nocturnal oxygen therapy (B).**
- **Evidence is limited to relatively young population (mean age less than 66 years) in both studies.**
- **In patients with mild or moderate hypoxaemia, or who desaturate only at night, the effect of continuous oxygen on mortality remains unclear today and may be clarified by currently ongoing studies.**

Quality of life:

- **Health related quality of life measured by validated scales provide inconclusive findings (B).**
- **Although some recent evidence from small studies have shown significant results in dyspnoea change in favour of oxygen therapy versus no oxygen, our meta-analysis of the results obtained so far with regards to this outcome are inconclusive (B).**

Physiological parameters:

- **Exercise capacity**
  - **Our meta-analyses show that oxygen therapy improves both exercise time (2.71 minutes more for patients on oxygen, 95%CI 1.96 to 3.46) and distance (20.43 meters more for patients on oxygen, 95% CI 14;84 to 26.02), although these differences might not be clinically relevant (B).**
- **Other parameters**
  - **Other physiological parameters such as SaO2, or VE (minute ventilation), as well as exercise intensity, may also be positively affected by the use of oxygen. However, the clinical relevance of this evidence remains to be clarified. (B).**

Patient preference:

- **Our search does not provide clear conclusions about this outcome.**

Productivity gains:

- **No studies focus on productivity gains and therefore no conclusions can be drawn from our review.**

Patients necessitating palliative care (PC)

Mortality/morbidity:

- **Our search does not yield published data on survival.**
- **There are few adverse events and no clinically meaningful difference between groups in frequency of side-effects (C).**

Quality of life:

- **One trial reports no difference in global quality of life (McGill questionnaire) (B).**
- **Two meta-analyses fail to demonstrate a significant improvement in cancer dyspnoea at rest (A).**
- **The intensity of fatigue experienced by cancer participants during exercise testing is not reduced by the inhalation of oxygen versus air (B).**

Physiological parameters:

- **Exercise capacity**
  - **Two systematic reviews report inconclusive results for effects of oxygen on distance walked during exercise (B).**
- **Other parameters:**
  - **One trial reports no difference in daily activity function (Medical Research Council scale) (B).**

Patient preference:

- **There are conflicting results between studies: two out of four trials report a statistically significant patient preference for oxygen versus air; the other two trials found no such difference (B).**

Productivity gains:

- **Our search does not yield published data.**

Heart failure (HF)

Mortality/morbidity:

- **One trial reports no significant differences for all-cause mortality or cardiac events during the 52 weeks of oxygen therapy versus air (B).**

Quality of life:

- **Health related quality of life measured by validated scales do not provide conclusive findings due to conflicting results between trials (B).**

Physiological parameters:

- **Exercise capacity**
  - **Our meta-analyses suggest a statistically significant improvement in dyspnoea at 6 minutes exercise testing (-0.84 [-1.26, -0.22] VAS/Borg (0-10) scale) in favour of oxygen therapy. There are no differences in dyspnoea at 3 minutes or peak exercise testing (B).**
- **Other parameters**
  - **Our meta-analyses suggest statistically significant changes in arousal index, apnoea-hypopnoea index (AHI), central apnoea index (CAI), sleep stage 1, sleep stage 2, and REM (rapid eye movement) sleep in favour of oxygen therapy, but no differences in total sleep time (A).**

Patient preference:

- **Our search does not yield published data.**

Productivity gains:

- **Our search does not yield published data.**

Cystic fibrosis (CF)

Mortality/morbidity:

- **There is no statistically significant improvement in survival in one single trial measuring this effect (B).**

Quality of life:

- **Our search does not yield published data (see also productivity gains: attendance at school or work).**

Physiological parameters:

- **Exercise capacity**
  - **Patients are able to exercise for a significantly longer duration with oxygen therapy (MD 1.03 minutes [0.11-1.95]) during maximal exercise, even though there are no significant differences for oxygen consumption, CO2 production, minute ventilation, and heart rate (A).**
- **Other parameters**
  - **The percentage of total sleep time spent in REM sleep is significantly reduced and arterial oxygen saturation (SaO2) during REM sleep significantly improved with oxygen therapy. Total sleep time and arousal index are not significantly different between room air and oxygen therapy (A).**

Patient preference:

- **Our search does not yield published data.**

Productivity gains:

- **One trial reports an improvement in regular attendance at school or work at 6 and 12 months in patients receiving oxygen therapy (B).**

Interstitial lung disease (ILD)

Mortality/morbidity:

- **One trial documents similar survival rates after 12, 24 and 36 months of oxygen therapy (C)**

Quality of life:

- **Our search does not yield published data.**

Physiological parameters:

- **Exercise capacity**
  - **Our search does not yield published data**
- **Other parameters**
  - **One trial reports significant differences in oxygen uptake (VO2), carbon dioxide output (VCO2), and oxygen saturation (SaO2) in favour of oxygen. There are no differences in heart rate, tidal volume (Vt), and respiratory frequency (B).**

Patient preference:

- **Our search does not yield published data.**

Productivity gains:

- **Our search does not yield published data.**

Chapter 3
Economic Literature Review

1 INTRODUCTION

This chapter provides an overview of studies that aimed at evaluating home oxygen therapy (HOT) from a health economic perspective. The purpose is threefold:

- to obtain an estimate of the order of magnitude and the variability in the cost of HOT
- to obtain an insight in the value for money of HOT as such, and of different HOT modalities compared to each other.
- to provide an overview of methodological approaches in these analyses, which can serve as an inspiration for our own health economic evaluation (see Deliverable 4).

2 METHODS

2.1 LITERATURE SEARCH STRATEGY

The search for the economic literature about Home Oxygen Therapy (HOT) included the consultation of electronic databases from 1995 up to mid April 2010. Economic literature published before 1995 was thought to be too old in the field to bring in valuable results.

The HTA (CRD) database, and the websites of Health Technology Assessment (HTA) institutes listed on the INAHTA (International Network of Agencies for Health Technology Assessment) website, as well as the evidence database of NICE (www.nice.org.uk) were consulted to retrieve HTA reports on this topic. Medline (PUBMED), EMBASE, CINAHL, PeDro, Clinicaltrials.gov, Econlit and Web of Sciences were searched to retrieve cost descriptive studies (studies only looking at costs) and full economic evaluations (studies looking at competing alternatives from both a cost and an outcome perspective) on Home Oxygen Therapy (HOT). An overview of the search strategy is captured in appendix 1.

2.2 SELECTION PROCEDURE AND CRITERIA

In order to select the relevant studies we used a hierarchical approach by which first titles were looked at in order to exclude any obvious studies that did not respond to our needs. Any articles that seemed relevant or for which we had doubts were evaluated by reading their abstracts (when available). Once more, any studies that seemed relevant or for which there were some doubts, as well as those with no abstract available, were assessed by reading the full text.

The first 300 titles were selected in parallel by two reviewers. Any disagreements were discussed and a common decision and approach was adopted. Following that the remaining studies were split between the two reviewers.

The reference lists of the selected studies were checked for additional relevant studies that could be included in our review.

All studies included in our review were critically evaluated using the checklist developed by Drummond et al [94] and, if the studies were based on modelling techniques, using the ISPOR guidelines by Weinstein et al. [95]. Their summaries were presented in a table format (see appendix 2).

2.3 ECONOMIC EVALUATION SELECTION CRITERIA

Studies that did not cover costs or did not look at use of oxygen at home were excluded from the review. Similarly, studies with an extremely small sample size (less than 10 patients), letters, individual case studies or any descriptive analysis that did not show any quantitative results were also excluded. Articles published in Dutch, English, French, German, Italian, Portuguese or Spanish were included. No other limitations were imposed.

Consultation of HTA websites was done with the purpose of extending the potential list of relevant studies.

Table 1: Economic Evaluation Selection Criteria

	Inclusion	Exclusion
Population	Patients receiving or eligible for HOT	Studies with less than 10 patients
Objective	Clear focus on oxygen therapy and its costs	Focus on other interventions/diseases
Intervention	Oxygen Therapy	Others
Setting	Home	Hospital/ residential care
Design	Economic evaluations Cost studies Descriptive studies with an economic component	Case studies Descriptive studies with no quantitative analysis Studies displayed on a letter format
Language	Dutch, English, French, German, Italian, Portuguese, Spanish	All others.

HOT = Home Oxygen Therapy

3 RESULTS

Figure 1 shows the flow chart of the literature selection process. The searches on the databases and local HTA websites returned 2294 citations. After exclusion of 463 duplicates, 1831 unique citations were left. Of those, 1362 did not meet our inclusion criteria based on title. Of the 469 citations left, 320 were excluded from the analysis after exploring their abstracts leaving us with 149 citations for full-text assessment. After reading the full texts, 20 studies were considered relevant.

The analysis of the articles' references and the HTA websites did bring in an additional citation, giving us a total of 21 relevant studies for inclusion in our review.

There were no significant discordances on the articles selected by the first and second reviewers.

Table 2 provides a summary overview of the selected studies.

Figure 1: Flow chart of the literature selection process

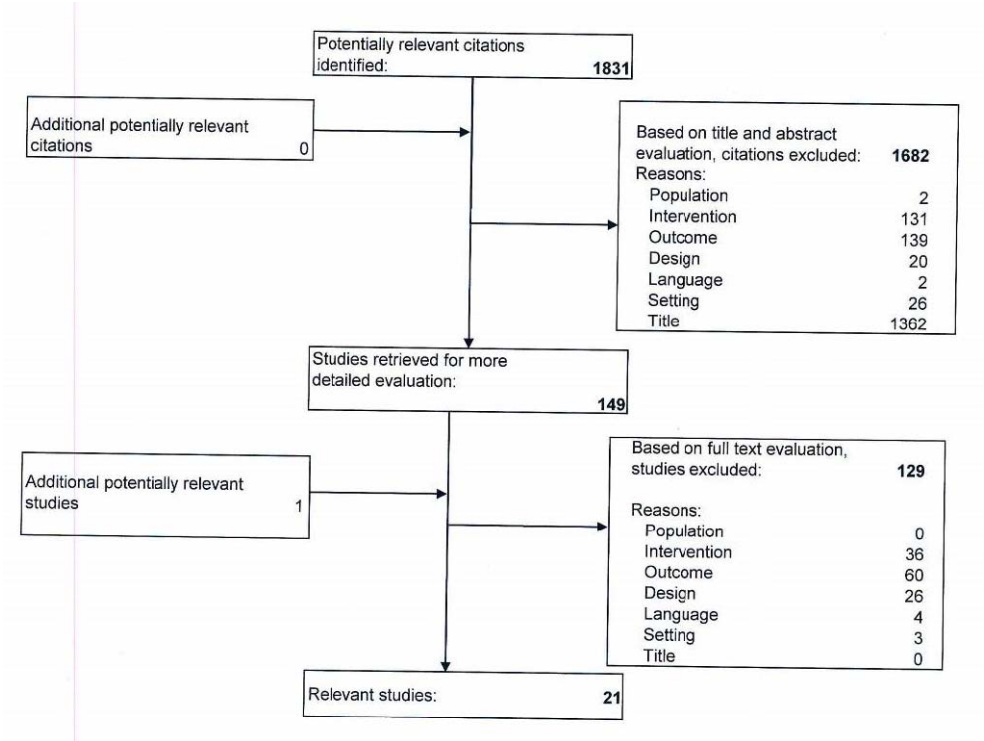


Table 2: Overview of cost studies on home oxygen therapy included in our analysis

Author	Year	Country	Type of analysis	Time horizon	Discount rate	Perspective
Oba	2009	USA	Markov model	5 years	3%	Third party payer
Serginson	2009	Australia	Retrospective observational study	1 year	NA	Government perspective
Mapel	2008	USA	Retrospective comparative study	36 months	Not specified	Healthcare system
Jones	2007	Australia	Retrospective observational study	1 year	NA	Healthcare system
Seino	2007	Japan	RCT	6 months	NA	Health insurance
Cavassa	2005	Italy	Retrospective case review	9 months	NA	Healthcare system
Guyatt	2005	Canada	RCT	1 year	NA	Third party payer
O'Neill	2005	UK	Descriptive comparative study (survey based)	8 months	NA	Healthcare system
Greenough	2004	UK	Retrospective comparative study	2 years	Not specified	Health care system
Farrero	2001	Spain	RCT	1 year	NA	Hospital
Maquilón	2001	Chile	Retrospective comparative analysis	1 year	NA	Healthcare system
Zinman	2000	South Africa	Retrospective case review	10 months	NA	Healthcare system
Heaney	1999	Northern Ireland	Hypothetical cost study	1 year	NA	Health insurance
Andersson	1998	Sweden	RCT	6 months	NA	Healthcare system
Bertrand	1998	Chile	Retrospective comparative case review	4 years	Not specified	Health care system
Jackson	1998	UK	Cross-over study	6 months	NA	Health insurance
Montner	1998	USA	RCT	2 years	Not specified	Third party payer
Pelletier-Fleury	1997	France	Retrospective comparative case review	1 year	NA	National Health insurance
Pelletier-Fleury	1996	France	Retrospective comparative case review	1 year	NA	Health insurance
Hallam	1996	UK	Retrospective comparative analysis	Until weaned off oxygen	5%	Health services and parents perspectives
Cottrell	1995	USA	RCT	1 year	NA	Third party payer

RCT (Randomised controlled trial)

3.1 STUDY DESIGN

In total, we evaluated 21 studies (see table 2) from which 12 were published after 1999. Among them, 10 were case reviews which included an economic component: 3 non-comparative [96-98], and 7 comparative [30, 99-104]. In all these case reviews the analysis was done retrospectively. There were 6 randomized controlled trials [105-110] with an economic component, and one cross-over study [111]. The remaining 4 studies included a Markov model [112], two hypothetical costs analyses [113, 114], where costs were calculated for theoretical scenarios and not based on hard data or evidence and one descriptive analysis based on a survey [115].

3.2 TYPE OF COST STUDY

Twenty of the 21 articles included in our evaluation consisted of cost analyses, and only one [112] was designed as a cost-utility analysis. Three studies were presented as cost-minimisation analysis [107, 113, 115], but neither of them presented evidence or proof of equivalent effectiveness when looking at the two compared treatment alternatives.

One more study [105] was presented as a cost-benefit study but did not truly assigned money values to health outcomes.

3.3 TIME FRAME OF STUDY

Only 5 studies looked at a timeframe of more than one year [99, 101, 103, 109, 112], with Oba (2009) presenting the largest – projected – time frame of 5 years. The latter explicitly applied discount rates in order to facilitate the comparison of both costs and outcomes captured in different time periods. One more study by Hallam et al followed infants until weaned off oxygen and did mention a discount rate of 5%. No other paper explained the methodology used to make the necessary time adjustments.

Six other studies had time frames shorter than a year [96, 97, 105, 108, 111, 115].

Although one year may be long enough to capture certain factors such as exacerbations, hospitalisations and GP visits, ideally a study in patients requiring long-term oxygen therapy, due to the chronicity of its nature, should be undertaken over a longer period of time and ideally it would cover a patient's lifetime or in the case of infants, the overall period during which the therapy is considered necessary (until weaned off). Only one paper [114] did follow infants over such a period.

3.4 PERSPECTIVE

All studies included in our review focused on costs to the hospital, the health care system or to the insurer and only included in their calculations direct costs.

In some instances, [112] it was argued that the cost of absenteeism is not that important in patients with severe pulmonary insufficiency since they tend to be elderly and therefore, usually retired or suffering from disabilities that would not allow them to work. Although such an argument may be plausible for the majority of patients, there is still a minority of them that do continue working. The argument does not either reflect the reality of patients with cystic fibrosis who are young and could be productive, if on better heath. Furthermore, even in those cases in which productivity losses and absenteeism may not be that relevant for patients it may still occur in the family or carers. These factors were not taken into consideration in the calculation of any of the studies analysed.

Table 3 summarizes the sample size for the studies included in our review as well as the comparator included.

3.5 POPULATION

Not all studies specified a population, since some of them evaluated the costs of specific HOT programs and did not focus on the number of patients covered by such programs. For population-based studies, the number of patients varied from a low of 26 COPD patients [111] to a high of 2725 COPD patients [99]. From the 13 population based studies only 4 had a sample size of over 100 patients [99, 101, 106, 107], and as many as 9 had populations of less than 70 patients [30, 102-105, 108, 110, 111, 114].

Table 3: Population and intervention data from relevant studies

Author	Year	Country	Population	Comparison
Oba	2009	USA	COPD patients with SRH and those with ND	Continuous or nocturnal (9hrs/day) oxygen therapy versus no oxygen
Serginson	2009	Australia	NA	Not comparative
Mapel	2008	USA	2725 COPD patients	Light-weight portable oxygen versus E-cylinder (i.e. 682 litre-cylinder) systems
Jones	2007	Australia	All patients receiving government funded HOT in Tasmania between Dec 2002-Apr 2004	Impact of a specialist oxygen clinic versus no specialist clinic
Seino	2007	Japan	56 ambulatory patients with CHF	HOT at a rate of 3 L/min versus room air
Cavassa	2005	Italy	NA	Not comparative
Guyatt	2005	Canada	546 applicants for HOT	Alternative strategies for assessing eligibility for HOT
O'Neill	2005	UK	100 patients with COPD receiving short burst oxygen therapy	Oxygen cylinders versus oxygen concentrators
Greenough	2004	UK	235 neonates born at <32 weeks of gestational age	Centres with high use of HOT versus centres with low use of HOT
Farrero	2001	Spain	122 COPD patients on HOT	Conventional care versus a special home care program (HCP)
Maquilón	2001	Chile	34 patients with COPD and PaO2 values < or = to 55mmHg, receiving HOT	Patients in HOT versus patients on waiting list
Zinman	2000	South Africa	NA	Non comparative
Heaney	1999	Northern Ireland	Costs extrapolated to the whole population of Northern Ireland (2927)	Oxygen concentrators versus oxygen cylinders
Andersson	1998	Sweden	51 patients with pulmonary disease eligible for liquid oxygen	Oxygen cylinders versus liquid oxygen
Bertrand	1998	Chile	55 patients receiving HOT	Costs of patients receiving oxygen therapy at the hospital versus patients receiving it at home
Jackson	1998	UK	26 patients with COPD	Oxygen concentrators versus oxygen cylinders
Montner	1998	USA	NA. Only the costs of the programme evaluated.	A new programme for HOT compared to the old one
Pelletier-Fleury	1996, 1997	France	61 patients with COPD receiving HOT	oxygen delivered at home: non for profit sector versus for-profit sector
Hallam	1996	UK	55 infants discharged home on oxygen between 1988 and 1992	Costs of caring for infants at home versus costs of caring for them at the hospital
Cottrell	1995	USA	50 patients on a stable HOT regimen	2 versus 6 month re-evaluation intervals in patients requiring continuous HOT

HOT (Home Oxygen Therapy), COPD (Chronic Obstructive Pulmonary Disease), SRH (Severe Resting Hypoxemia), ND (Nocturnal Desaturation), CHF (Chronic Heart Failure)

3.6 COMPARATOR

Due to the inclusion criteria used for our review, which included all articles that mentioned costs of Oxygen therapy there were a number of relevant but non-comparative descriptive cost studies [96-98].

We will come back to these later.

The remaining studies included in the review showed important variations in terms of the comparators used and could be split into two separate groups:

3.6.1 Studies comparing different interventions

Eight studies in total focused their comparisons on interventions. From those:

- three studies compared home oxygen therapy versus no oxygen [102, 105, 112];
- three other analyses focused on comparisons between oxygen cylinders versus oxygen concentrators [111, 113, 115];
- Anderson et al [108] compared oxygen cylinders versus liquid oxygen;
- Finally, Mapel et al [99] focused on comparisons between lightweight portable oxygen versus oxygen cylinders.

3.6.2 Studies comparing processes

Ten studies looked at processes and the impact that any changes could have on costs. From those:

- Bertrand et al [103] and Hallam et al [114] compared the costs of treating a patient with oxygen in the hospital setting versus the home setting;
- Cottrell et al [110] and Guyatt et al [106] compared the impact that more frequent re-evaluations of patients eligible for home oxygen therapy could have versus less frequent re-evaluations;
- Jones et al [100] looked at the impact that setting up a specialist oxygen clinic could have on costs and service provision;
- Greenough [101] compared high use oxygen therapy centres (described as centres treating more than 50% of chronic lung disease infants with oxygen) with low use of oxygen therapy centres (described as centres treating less than 20% of chronic lung disease infants with oxygen) in neonates.
- Montner et al [109] evaluated and compared a new program for long term oxygen therapy, which incorporated numerous changes such as the establishment of a new position of home oxygen co-ordinator, with the original program in which responsibilities where not clearly assigned;
- Farrero [107] looked at the impact of a home-based care program consisting of a monthly telephone call, home visits every three months and home or hospital visits on a demand basis versus conventional care in patients receiving long-term oxygen therapy at home.
- Pelletier-Fleury et al [30],[104] looked at the impact that delivering the oxygen services via the not-for profit sector could have versus having the oxygen delivered via the for profit sector in two studies.

3.7 COSTS AND OUTCOMES

3.7.1 Studies Comparing interventions

Table 4 summarizes the overall results for the 8 studies comparing different interventions.

Costs were presented as cost per patient per year to facilitate the comparison of interventions between the studies. To improve this comparability, original costs were standardized in common € of the year 2009 using Consumer Price Indices and exchange rates quoted by the OECD (www.oecd.org).

Costs included in such studies were of a varied nature and while some articles only covered oxygen costs, others looked also at resource utilisation costs (hospitalisations, visits to doctors, nurses and specialists, home visits, physiotherapy, transport costs, etc).

In all cases the analysis was limited to direct costs.

With regards to outcomes, not all studies captured them since two of them [113, 115] just looked at costs.

Two studies [99, 102], only included health care utilisation rates (eg hospitalisation, GP visits, etc) and only 4 others [105, 108, 111, 112] captured health related quality of life measures.

In the following section, for the individual study analysis the original costs are reported.

Table 4: Studies comparing interventions

Author	Country	Sample size	Interventions	Costs captured	Outcomes captured	Total cost of interventions /patient/yr in 2009 €	Difference	P value
Mapel 08	USA	2725	Lightweight portable O2 systems versus E-cylinders	OT Health care utilisation costs	No health outcomes captured but utilisation rates such as hospitalisations rates were included in the study	E-cylinder: 10823 Lightweight: 8147	2676 in favour of lightweight	p>0.05
Seino 07	Japan	56	HOT (using a concetrator) versus no O2	Hospitalisations ER visits Outpatient visits HOT	QoL measures	With oxygen:13701 w/o oxygen: 27968	14267 in favour of the oxygen group	NA
O'Neill 05	UK	100	O2 cylinders versus O2 concetrators	Installation, rental, servicing and electricity, ingredient costs, dispensing fee, delivery and flow head rental	Only costs captured since it was purely a cost-descriptive analysis	Cylinders: from 684 to 2575 Concentrators from 485 to 508	From 199 to 2067 (depending on cylinder use) in favor of concentrators	NA
Maquilón 01	Chile	21	HOT versus no O2	Health care utilisation costs O2	No health outcomes captured but hospitalisations and emergency consultations included	Oxygen: 1267 Waiting list: 1424	157 in favor of oxygen	p=0.83
Heaney 99	UK	NA	O2 concentrators versus O2 cylinders	Installation costs, oxygen consumption and electricity	No health outcomes captured since it was purely a cost descriptive analysis	Transferring some patients to concentrators: from 106 to 483 Cylinders: 490	From 7 to 384 depending on consumption. In favour of transferring tc concentrators	NA
Andersson 98	Sweden	51	O2 cylinders versus liquid O2	O2 and equipment, transport and medical or technical services	HRQL via the SIP and EuroQoL questionnaires	Concentrator: 2582 Liquid: 9756	7174 in favor of concentrator	NA

NA: not available

3.7.1.1 Oxygen Therapy versus No Oxygen

Oba et al [112] performed a cost-utility study in the USA from a third party payer perspective using a Markov model, comparing oxygen therapy versus no oxygen in COPD patients with severe resting hypoxemia (SRH) and patients with nocturnal desaturation (ND). Input data was derived from published literature.

The overall time window was set to 5 years. The authors argued that expanding it further was unnecessary, since there was up to that date (study published in 2009) no data available of the efficacy of HOT beyond the 5 years point. Considering the aim of the study, to evaluate the cost-utility and not just the efficacy of HOT, a time horizon extended in this case over a longer time period (ideally patients' lifetime) would have been preferred.

Both costs and outcomes were captured and published literature was used to fill in the model inputs and calculate incremental cost-effectiveness ratios. Only direct costs of nocturnal and continuous oxygen therapy were looked at and a discount of 3% was applied for both costs and outcomes.

Incremental cost-effectiveness ratios (ICER) were presented for nocturnal and continuous oxygen therapy (for patients with severe resting hypoxaemia and patients with nocturnal desaturation respectively). For patients with severe resting hypoxaemia (SRH) oxygen was assumed to be continuous (>16hrs/day), while the assumption in the nocturnal group was 9hrs/day. Appendix 2 gives more information on the stages used to build the model.

The results (in 2007 US$) show an ICER for continuous therapy versus no oxygen therapy of $16 124 for a 5-year time horizon, while the ICER was $ 306,356 for nocturnal oxygen therapy versus no oxygen therapy.

A sensitivity analysis was performed which confirmed the robustness of the findings obtained for continuous oxygen therapy but showed sensitivity to variations in the mortality rate for ICERs obtained for nocturnal oxygen therapy.

A more detailed description and validation of the modelling techniques used in this study is provided under section "Modelling".

Seino et al [105] conducted a cost analysis alongside an RCT to evaluate the cost as well as the clinical efficacy of nocturnal HOT (at a rate of 3L/min through nasal cannulas) in 56 ambulatory patients over 20years of age, with central sleep apnea caused by chronic heart failure (CHF). More details on patients'characteristics are given in appendix 2.

The analysis was performed from a health insurance perspective and cost calculations were looked at over a 6-month period. Only direct costs were considered and in addition to HOT costs of other healthcare utilisation were included in the calculations.

Results showed that despite the additional charge of HOT there was an expected cost reduction of 1,854,175 in 2003 Yens (14,267 in 2009 €) per patient per year. A sensitivity test was performed modifying the hospitalisation period. This sensitivity test supported the robustness of the main results.

Maquilón et al [102] undertook a retrospective comparative analysis to compare healthcare costs for COPD patients in a home oxygen therapy program to those of a similar group of patients in a waiting list. Patients presented PaO2<or=55mmHg while breathing room air and were free from hospitalisations for at least a month prior to the start of the study.

Costs included direct HOT costs and resource utilisation costs (i.e. hospitalisations, ambulatory visits, emergency consultations and pharmaceuticals consumed).

No health outcomes were captured, although hospitalisation rates and emergency consultations were taken into consideration for the cost calculations.

The results show that although the ambulatory costs of the HOT group were higher this was compensated by lower hospitalisation and emergency consultation costs.

No sensitivity analysis was performed.

The study presented two further drawbacks: the patient sample for which a complete analysis was done included only 21 patients and the baseline characteristics of the populations compared were statistically different with regards to the patients' age.

3.7.1.2 Oxygen Cylinders versus Oxygen Concentrators

The three studies that compared oxygen cylinders to oxygen concentrators seemed to favour the use of concentrators over that of the cylinders. Results were, as expected, more or less favourable depending on usage levels of oxygen cylinders.

O'Neill et al [115] performed a cost analysis with the aim of evaluating patient's use of short burst oxygen therapy (SBOT) and any potential savings that moving from cylinders to concentrators could bring in the UK. The analysis was performed in 100 COPD patients already receiving SBOT for at least three months prior to the study. Patients meeting the criteria for long term oxygen therapy (LTOT) were excluded from the study.

The results in 2003 pound prices showed estimated savings from moving from cylinders to concentrators per patient over the mean time period oxygen was used by the respective groups that ranged from £530.73 to £3682.54 depending on cylinder usage (number of cylinders consumed per month based on a cylinder size of 1360L and a flow rate of 2 l/min). No sensitivity test was performed.

Outcomes were not captured in this study and the source of costs was not clearly revealed. There was no randomisation of patients.

Heaney et al [113] undertook a cost study to determine the level of oxygen cylinder use (based on a cylinder size of 1360 litres) at which it becomes cheaper to move to a concentrator. The study was done from a public health insurance perspective and the setting was the home of the patient, while the time horizon was limited to a year.

Only direct costs of providing oxygen were included in the analysis. No outcomes were captured since it was purely a cost study.

Only hypothetical cost savings based on assumptions with regards to the number of cylinders provided per patient were presented (not a patient-based study). The results conclude that if more than 3 cylinders per month were being used, independent of flow rate or duration of prescription, it was always cheaper to prescribe a concentrator. To cover for uncertainty, the authors calculated a minimum and maximum savings scenario based on the assumptions made around values that particular variables (minutes of oxygen used per day, overall duration of therapy and flow rate) were likely to take. The potential savings for Northern Ireland of moving patients already on home oxygen therapy (HOT) from cylinders to concentrators (when using more than 22 cylinders per year) were estimated to be between £13 363 and £794 798 (1996 values). The main limitation of the study was that it consisted on a hypothetical costing exercise limited to the provision of oxygen via cylinders or concentrators. The calculations were based on pre-determined scenarios and not on hard data. It was undertaken in view of the reimbursement situation at the time in Northern Ireland to influence a revision of prescribing and reimbursement guidelines and therefore its findings cannot be easily generalized to other populations.

On the other hand, this methodology is useful when the purpose of the analysis is a threshold analysis aiming at optimal efficiency in the delivery of HOT.

Finally, Jackson et al [111], undertook a cross-over study for the UK where 26 patients, who were already authorised O2 cylinder users, were treated with one type of oxygen (either cylinders or concentrators) and after 3 months changed to the other (concentrators or cylinders).

For the costing an assumption was made that patients consumed 2 l/min of oxygen and patients included in the study used oxygen for relatively short periods (from 1 to 8 hours per day). The perspective was that of the public health insurance and only direct

oxygen costs were considered. Outcomes captured included measurements of FEV1, FVC and PEF.

While there were no significant differences made apparent with regards to FEV1, FVC or PEF measurements, both groups of patients declared an improvement in QoL when receiving oxygen from a concentrator ($p<0.05$). In addition to this, the cost of supplying oxygen via a concentrator seemed to be cheaper than supplying oxygen with cylinders, for patients who used oxygen above an average time as short as 1.4hours/day. One-way sensitivity testing was performed with regards to patient survival but did not change much the cross-over point.

The main limitation of the study, came from the small sample size. The fact that it was a cross-over study may have also introduced some bias.

The size of the cylinders was not made explicit in this study. However, given it was published only one year earlier than Heaney's and that they both refer to the UK, the size it refers to is likely to be 1360 litres as well.

Despite their limitations these three UK-based studies will be revisited in chapter 5 to facilitate comparisons of the organisation of home oxygen therapy between the UK and Belgium, given that the UK was one of the countries selected to be included in our international comparison exercise.

3.7.1.3 Lightweight/liquid Oxygen versus Oxygen cylinders

Mapel [99] undertook a retrospective comparative study aimed at measuring the costs of patients with COPD using lightweight portable oxygen systems to those using E-cylinder (i.e. 682 litre-cylinders) from a healthcare system perspective. The overall time frame for the study was 36 months and it concerned 2725 patients with COPD, with 40-89 years of age and who had had over 11 fills over a 12-month interval prior to the study. In addition to costs of oxygen, healthcare utilisation costs were also considered.

No health outcomes were captured, but health care utilisation rates were included in the analysis.

Hospitalisation rates favoured the lightweight oxygen group ($p<0.05$), but median total differences costs in the first year did not reach statistical significance, ($6,515 per year with the lightweight versus $9,503 per year with E-cylinders). The cost difference remained non-significant after adjustment for clinical factors.

No sensitivity analysis was performed.

Similarly, Andersson et al [108] performed a cost analysis based on an RCT to compare concentrators in addition to small oxygen cylinders for deambulation, versus liquid oxygen at home in 51 COPD patients with chronic hypoxaemia, eligible for liquid oxygen and able to use the equipment outdoors. The study run over a six-month period. Only direct costs were considered and the study was performed from a health care system perspective. Health related quality of life (HRQL) was captured during the study. Cost calculations were based on only 48 patients for whom satisfactory data was collected. The mean total cost per patient for the 6-month period in the concentrator group was US$1,310, while it was US$4 950 for liquid oxygen (in 1996 US$). However, although HRQL measured via the SIP questionnaire seemed to favour patients on liquid oxygen, these significant differences were not confirmed by the data captured via the EuroQoL questionnaire.

No sensitivity test was performed. Other limitations of this study include an overall short time horizon (only 6 months) and the fact that it may not truly capture all relevant costs (technical services may not all be captured in such a short time horizon). The conflicting results in terms of HRQL depending on what instrument was used also posed some questions regarding the validity of its findings. There was no incremental analysis of costs and consequences, which were reported and analysed separately.

3.7.2 Studies Comparing processes

Table 5 summarises the overall results of all studies comparing different processes. Because of the heterogeneity of the processes analysed no attempt to standardize the overall costs was made in this case. However, where reported, costs are given in 2009 €s to facilitate interpretation. For that purpose, in those cases where the year of costing was not made explicit in the study it was assumed to be two years before the publication date.

Most of the studies 9/10, recorded healthcare utilisation rates in the form of either hospitalisation, nursing services, physiotherapy or ambulatory visits. Only Jones et al [100] focused purely on oxygen costs.

In all cases the analysis was limited to direct costs.

With regards to outcomes, Jones et al [100] was the only study that did not capture any, while Greenough [101], Hallam [114] and Pelletier-Fleury [30] did not capture health outcomes but did look into healthcare resource utilisation. The latter did capture survival in a similar study published in 1997 [104].

Bertrand et al [103] captured prognosis measures based on the original diagnosis and Cottrell et al [110] and Guyatt et al [106] captured HRQL. Farrero et al [107] captured survival, HRQL and resource use. Finally, Montner [109] captured data on patient's satisfaction.

Table 5: Studies comparing processes

Author	Year	Country	Comparaisons	Costs captured	Outcomes captured	Results (costs in C2009)	Sensitivity analysis
Jones A	2007	Australia	Costs of HOT before and after setting up a specialist oxygen clinic	Equipment Delivery charges Ambulatory Oxygen supplies	None captured	With the oxygen clinic the prescription rate fell to 1.82 per 100 000/month compared with 5.26 per 100,000 in previous months Costs after the establishment of the clinic decreased from €14008 in December 2002 to €8410 in April 2004	No sensitivity analysis performed
Guyatt	2005	Canada	New approach to eligibility for HOT versus the original process	Assessment and appeal costs HOT costs Hospitalisations	HRQL via chronic respiratory questionnaire (CQR) and the Health Utilities Index (HUI) Mortality	The HUI3 results show that both groups tend to improve their scores over time. The results from the CRQ confirm this finding. Mortality was similar in both groups. Costs not significantly different (€4923 for the new approach versus 4949 with the original approach; p=0.98)	Costs in each arm of the study were also calculated using cost estimates for the US
Greenough	2004	UK	Two high use centres of HOT (>50% of chronic lung disease infants) versus two low usage centres (<20% of chronic lung disease infants)	Hospital admissions Outpatient visits Visits of health personnel at home Pharmaceuticals Oxygen consumed	No health outcomes captured but utilisation rates such as hospitalisations rates or health visits were included in the study	Overall cost of care lower for the high use centres: C39117 versus C58820 in low-use centres (p<0.0001). Differences primarily due to an earlier discharge from the neonatal unit in the high-use centres (p<0.001)	No sensitivity analysis performed
Farrero	2001	Spain	Conventional medical care versus home care in patients already receiving LTOT	Staffing costs Costs of routine examinations Drugs Cost of home care program (HCP)	Survival and QoL (via the chronic respiratory questionnaire) FEV1, FVC and arterial blood gases Resource use	No significant differences in survival or QoL between the two groups Significant reduction in resource use per patient: emergency department visits (-1,13); hospital admissions (-0,79); days of hospitalisation (-10,77) Cost savings with HCP: €55422	No sensitivity analysis performed
Bertrand	1998	Chile	HOT versus oxygen therapy at the hospital	Cardiorespiratory monitors Nebulizers Physiotherapy Nursing costs Oxygen	Prognosis depending on diagnosis was captured	Costs of treating a patient at the hospital: €29628 /year vs €7153 for those treated at home (when the patient received 1 l/min). Neonatal distress and broncho-pulmonary dysplasia had the best prognosis with oxygen discontinued at 4 and 5.7 months respectively	No sensitivity
Montner	1998	USA	New HOT programme (1995) versus original programme (1994)	Initial set up Equipment costs Oxygen costs Respiratory therapist visits	No health outcomes captured. However, referrals and oxygen prescriptions as well as patient satisfaction were included	Total costs per patient diminish from €1533 to a €939 despite an increase in the number of patients of 43.9% Referrals, patient satisfaction and oxygen prescription all improved significantly under the new programme	No sensitivity analysis performed
Pelletier-Fleury	1997	France	Delivery of oxygen at home by the non-for-profit sector versus the for-profit sector	Physician visits Tests Drugs Physiotherapy Oxygen therapy Transport	Survival	No significant differences in survival between the two groups. Statistically significant difference in costs between the two different provision modes (C2247 in the for-profit versus C1875 in the non-for-profit). A consequence of the less expensive cost of oxygen in the latter.	No sensitivity analysis performed
Pelletier-Fleury	1996	France	Delivery of oxygen at home by the non-for-profit sector versus the for-profit sector	Physician visits Tests Drugs Physiotherapy Oxygen therapy Hospitalisations Transport	No health outcomes captured, but health care utilisation in the form of GP visits, chest specialists and hospitalisations were included	No significant differences in health care utilisation. Total ambulatory costs per pedent per year were: C5629 in the for-profit sector versus C4791 in the not for profit.	No sensitivity analysis performed
Hellam	1996	UK	HOT versus oxygen therapy at the hospital (in infants)	Equipment Training Health services use Travel costs	No health outcomes captured, but health care utilisation in the form of GP visits, chest specialists and hospitalisations were included	Estimated cost differences between the costs of caring for oxygen dependent babies at home versus at the hospital ranged from €74883 to €22874 per baby, depending on nursing time and cylinder consumption	No sensitivity analysis performed
Cottrell	1995	USA	Identical re-evaluations of patients requiring continuous HOT at 2 versus 6 months	Healthcare resource costs Oxygen costs	Pulmonary function testing, arterial blood gas analysis, pulsoximetry, visual analogue scale for dyspnea (VAS), 34 sickness impact profile (SIP) and exercise tolerance	While outcome results were similar in both groups, cost differences showed an advantage for the 6-month evaluation group versus the 2-month evaluation group of €218	No sensitivity analysis performed

3.7.2.1 More or less frequent patient evaluations

Guyatt et al [106] looked at Canadian costs as part of a 546 patient RCT that compared alternative strategies for assessing eligibility for HOT. The study included all first time applicants for HTOof over 18years of age. The time horizon of the study was 1 year and it was undertaken from a third party payer perspective. Only direct costs were included and in addition to oxygen costs, health care utilisation costs and assessment costs were included in the calculations. Both mortality and HRQL were captured in the analysis.

The results showed that oxygen costs were lower with an alternative strategy consisting on re-assessing those patients that had been eligible at the initial assessment after two months of stability. Thus the costs of oxygen were reduced from Can$3097 to Can$2501 (p=0.0002) in 2004 Canadian $, although the overall costs seemed to be similar in both arms with a minimal reduction from $5982 to $5627. Both QoL and mortality rates showed similar results under both strategies.

The authors concluded that re-assessment of originally eligible candidates for HOT could reduce costs while not having a negative impact on mortality or QoL.

The calculations were repeated using US costs providing similar results.

There was randomisation of patients and the sample size made this study interesting, although not all patients accepted to fill in the QoL questionnaire and thus QoL measurements were completed in a smaller sample size (101 in the conventional arm versus 99 in the alternative arm).

Cottrell et al [110] assessed in an RCT the impact on costs and outcomes of 2 versus 6-month re-evaluation intervals in 50 patients on a stable HOT regimen (see appendix 2 for more details) requiring continuous oxygen therapy. The study was undertaken from a public payer perspective and patients were followed-up for a year. There were no statistically significant differences between the baseline characteristics of both groups (including oxygen flow rates) indicating that randomisation was adequate.

Only direct costs were looked at and in addition to oxygen costs, hospitalisation and medical visit costs were included in the calculations. The year of costing was not made explicit.

There was no detailed explanation on protocols regarding eligibility of patients for HOT, since the study focused primarily on the programme and the process followed to identify its problems and address its needs.

Cottrell found that while outcomes were not significantly affected, total costs were higher (although not significantly higher) in the 2-month group versus the 6-month group. Not surprisingly, there was a significant difference in terms of evaluation costs (p=0.001) and thus the authors concluded that patients on HTO should not be routinely evaluated more frequently than every 6 months.

No sensitivity analysis was performed to account for uncertainty.

The limited sample size makes it not advisable to generalize these findings. In addition to this, compliance was not controlled or captured during the study, which could account for some of the cost differences.

3.7.2.2 *Oxygen at home versus Oxygen at the hospital* In a retrospective case review by Bertrand et al [103] aimed at assessing the impact on costs of treating hypoxaemic children (3 weeks to 11 years of age) at home versus treating them at the hospital. Data for a total of 55 patients were analysed between January 1993 and December 1996. The perspective was that of the healthcare services and only direct costs were looked at. Costs included in the study were: costs of cardiorespiratory monitor, nebulizers, physiotherapy services, nursing costs and oxygen costs. The costing year was not made explicit.

The study also included the analysis of different diagnoses in order to assess which one presented better prognosis.

Results showed that the overall costs of treating a patient at the hospital were pesos 1 200 000 (€2469 in 2009) per month versus pesos 254 030 (€523 in 2009) per month for the patient treated at home (when patient received 0,25l/min) or pesos 289 730 (€ 596 in 2009) (when patient received 1 l/min). No statistical analysis was performed for the cost side of the analysis and therefore no p values were reported. Furthermore, no sensitivity test was performed.

The study had a relatively small patient population, which makes it risky to generalize its findings.

Similarly, Hallam et al [114] compared the costs of treating infants with oxygen at home versus treating them at the hospital. The analysis was done from both a health service perspective and parents' perspective. Information was captured via interviews and hospital records regarding 55 babies who had been discharged home on oxygen between 1988 and 1993 in the Oxford region. Their costs were compared with a hypothetical scenario in which they would have stayed at the hospital (there was no control group).

Costs measured included training and equipment costs health services use and travel cost to and from the hospital.

No health outcomes were captured since it was purely a cost analysis but health care utilisation was measured and taken into consideration in the cost calculations.

The estimated cost savings from caring for an infant on oxygen at home versus caring for him at the hospital ranged between pounds15378 to pounds 50343 (adjusted to 1994 pounds) depending on the number of oxygen cylinders consumed per week and the nursing time used.

No sensitivity analysis was performed.

A further limitation of this study was that cost measures were taken retrospectively via interviews, which could have introduced some bias.

This UK- based study will be revisited in chapter 5 to assess whether it does provide some valuable information for our international comparison exercise.

3.7.2.3 *Other comparisons on processes*

Jones et al [100] performed in 2007 a retrospective observational study based on the records of all Tasmanians receiving government funded HTO, from a health care system perspective. The aim was to assess the use of domiciliary oxygen and the impact of establishing a new specialist oxygen clinic in Tasmania. The overall time horizon for the study was 1 year, and only direct costs of equipment, delivery and ambulatory oxygen supplies were included. Prescribed quantities of oxygen varied depending on the diagnosis and ranged from a median in COPD patients of 19.5 hours per day compared with 8.6 hours for overnight use and 8.0 hours for symptom relief.

No health outcomes were looked at. After the establishment of the oxygen clinic, the prescription rate fell to 1.82 per 100 000 per month, compared to a rate of 5.26 per 100 000 in previous months. This translated into savings of $7559 (comparing costs in December 2002, before the establishment of the clinic, to cost in April 2004, after the establishment of the clinic).

No sensitivity analysis was performed and there was no explicit mention of time adjustment techniques used for the calculations. The costs of the establishment of the clinic did not appear to be included in the calculations, although this was difficult to confirm since the description of the costs included and the calculations performed were not detailed enough.

Montner et al [109] undertook a randomized controlled trial, published in 2008 to evaluate the effect of a new multidisciplinary total quality improvement team, established to re-organise and improve the long-term oxygen therapy programme at the Albuquerque Veterans Affairs Medical Centre.

The study was performed from a third party payer perspective and compared the original plan available in 1994 with the new programme established in 1995.

Costs included are the initial set up, any equipment costs, oxygen costs and respiratory therapist visits. No health care utilisation costs were captured.

Other than costs, referrals and oxygen prescriptions were also analysed and a patients' satisfaction survey was used to take into consideration patients' perceptions.

The results show that the overall costs diminish by 9.5% to a total of $546 586 despite an increase in the number of patients of 43.9%.

The cost per patient in 1995 with the new program was $926, which meant a reduction of 37.1% . No sensitivity test was undertaken.

Greenough et al [101] performed a retrospective case review looking for potential differences in terms of costs between two medical centres with high use of home oxygen therapy (>50% of chronic lung disease infants) versus two medical centres with low use of home oxygen therapy (<20% of chronic lung disease infants). Data from 235 neonates born at less than 32 weeks of gestational age admitted during their first week to the ICU and developing chronic lung disease was analysed and direct costs of oxygen and resource consumption (i.e. hospitalisations, outpatient visits, visits of health personnel at home, pharmaceuticals) were considered in the calculations over a two year follow-up period. The results expressed in 1999 pounds showed a significantly $p<0.0001$ lower overall cost of care for the high oxygen use centres (£28965) versus the low oxygen use centres (£43555). The difference found was due to lower costs at the neonatal unit following birth, and specifically to an earlier discharge of infants in the high home oxygen use centres.

No health outcomes were captured during the study and no sensitivity test was carried out. However, the most important limitation of the analysis is the direct comparison of 4 centres, which makes it hard to know whether the differences found were purely due to the higher or lower use of home oxygen services or whether they were a reflection of differences in terms of protocols or general care between the neonatal units of the different centres.

This study will be re-assessed later on in chapter 5 in order to evaluate whether it adds helpful information on the organisation of home oxygen therapy in the UK, that could be used for comparisons with the Belgian context.

Farrero et al [107] undertook a RCT in Spain aimed at measuring the influence of a hospital based home-care program (HCP) on the management of COPD patients already on HOT.

A total of 122 patients were enrolled from which 94 completed the 1-year follow-up period (see Appendix 2 for more details on patient characteristics).

Only direct hospital costs were taken into consideration. These included: staffing costs, costs of routine evaluations, any medications required by the patient as well as the additional costs of the HCP (administrative costs, costs of home visits and costs of additional hospital visits).

Survival and QoL were looked at during the analysis, but QoL was only captured for the first 40 patients enrolled in the study. There was no cost-effectiveness analysis and costs and outcomes were looked at separately.

No statistically significant differences were found in survival - with a median of 20 months in both groups (p=0,79) – or QoL.

There was a significant reduction in resource use given in the form of:

Reduction in visits to the emergency department per patient: 0,45 versus 1,58 in the control group (conventional care); p=0,0001.

Reduction in the number of hospital admissions per patients: 0,5 versus 1,29 in the control group; p=0,001)

Reduction in days spent at the hospital: 7,43 versus 18,20 for the control group; p=0,01.

In terms of costs there was an overall reduction in total costs incurred in for patients on the HCP versus the control group: US$90121versus US$136944 in the control group. A saving of US$46823.

There was no sensitivity analysis performed and compliance with both programs was not looked at.

Pelletier-Fleury et al published in 1997 a retrospective case review [104] in which they used regression techniques to compare the costs of COPD patients (see appendix 2 for more on paitents'characteristics) having their HOT delivered via the not-for-profit sector versus patients having it delivered via the for profit sector. The study followed 61 patients in total and the analysis was performed from a national health insurance perspective, having a time horizon of a year.

Costs captured in 1994 FF included physician's visits, tests, drugs, physiotherapy and oxygen therapy, as well as transportation costs.

Outcomes were also captured in the form of survival.

The results showed that while there were no significant differences in terms of survival between the two groups analysed, there was a statistically significant difference in costs between the two groups in favour of the not for profit sector (FF2065,2) versus the for profit sector (FF2474). The results are a reflection of the less expensive cost of oxygen in the not for profit sector (mainly using concentrators) when compared to the for profit sector (mainly using gas cylinders).

No sensitivity test was performed.

The overall aim of the study as well as the question to be answered is not well defined since it mixes way of delivery (not for profit versus for profit) and different modes of administration (concentrators versus cylinders).

The sample size was relatively low but the results achieved statistical significance.

The group on the non-for profit arm was not picked randomly since there was a limited number of records showing patients who were alive at the end of the study period.

The same authors published a similar study in 1996 [30] that estimated the annual costs for respiratory care in the same patient population over the same period of time. The study which compared the costs of those receiving HOT, via two different delivery modes (for profit versus not-for profit) was done from a national health insurance perspective, over a 1-year time horizon.

Costs captured included medical visits, tests, drugs, physiotherapy, oxygen therapy, hospitalisations and transport. No health outcomes were captured this time but health care utilisation was included in the cost calculations.

Although health care utilisation did not present statistically significant differences between the two study groups (p>0.05), the total ambulatory costs per patient per year for patients having their oxygen delivered by the not for profit sector was lower (US$4596) than ambulatory costs for patients having their oxygen delivered by the for profit sector (US$5399).

Once more the overall objective of the analysis was not well defined, since it mixed way of delivery and oxygen administration mode.

Another limitation of the study was the lack of sensitivity analysis, as well as the small sample size (61 patients in total).

The research by Pelletier-Fleury would be re-asessed later on in chapter 5 to try and draw any valuable conclusions regarding the organisation of home oxygen therapy in France that could serve as an example for the Belgian situation.

3.8 OTHER RELEVANT STUDIES

Sergison et al [98] published in 2009 the results from a retrospective observational study to measure, amongst other things, the total cost of government- funded domiciliary oxygen therapy in Australia from a government's perspective. The study looked at costs for one financial year (2004-2005).

Costs included equipment and administrative costs only and no indirect cost were captured. The items included in the cost calculations were not explained in enough detail and costs of 2005 were not available for all jurisdictions, so in few cases 2003 costs were used instead. For those cases there was no explanation as to how the authors adjusted for the different time periods.

No outcomes were included in the analysis.

The results showed that the cost per patient per year varied fourfold between the different sources of funding: the Department of Veteran Affairs ($842) and the Department of Health and Ageing ($3189).

No sensitivity analysis was performed.

Zinman et al [96] studied in a retrospective case review, published in 2000, the direct costs savings brought for an oxygen clinic in South Africa through an assessment of patients to clearly define and separate those eligible for oxygen therapy versus those non eligible. The analysis was done from a government perspective. The records of 679 patients attending a newly established oxygen clinic were analysed. Only direct oxygen costs were included in the analysis. There was no explicit explanation regarding the source of the costs, while outcomes (FEV1 and PaO2 measurements) were captured during the study.

The study showed that there were statistically significant differences between the FEV1 and PaO2 measurements between patients who were given oxygen versus those for which oxygen was denied.

With regards to the potential cost savings calculated, the authors mentioned savings to the state from oxygen not prescribed (in those cases where the patient was not eligible) of 125000 South African Rand per month in 1996. This study highlights the importance of clearly identifying the right patients most likely to benefit from O2. However, no sensitivity analysis was performed and there was no incremental analysis of costs and consequences performed.

3.9 MODELLING

Oba [112] estimated the clinical effects and costs in the USA of HOT in patients with COPD, using a cost-utility model (Markov-model). Two cohorts were analyzed: patients with severe resting hypoxemia (SRH) and patients with significant nocturnal desaturation but without SRH (ND).

Table 6 shows the study baseline results over a 5-year horizon, with an acceptable ICER for continuous oxygen therapy (COT) compared to no oxygen therapy in the SRH cohort ($16124/QALY) and a non cost-effective result for NOT (nocturnal oxygen therapy) compared to no oxygen therapy in the ND cohort ($306356/QALY). The probabilistic sensitivity analysis for the ND cohort also shows that in a large portion of the 95% CI of the ICER of NOT compared with no oxygen therapy, the estimated ICER was more than $100000/QALY. For the SRH cohort, the 95% CI of the estimated ICER of COT was entirely below $50000/QALY.

Heterogeneity was taken into account by using 2 different cohorts in the modelled population. A clear description was given of the competing interventions (HOT and the absence of any oxygen strategy) and assumptions were made explicit.

The third-party payer's perspective is narrower than a societal perspective, but the report reflects that indirect costs such as absence from work, are probably irrelevant because only a small portion of patients with COPD have a paid job. Both costs and health outcomes reflect the chosen perspective.

Table 6: Baseline results over a 5-year horizon

	Incremental cost ($)	QALY's	Incremental QALY's	ICER ($/QALY)
SRH cohort				
Control	-	2.07	-	-
COT	9517	2.66	0.59	16124
ND cohort				
Control	-	2.68	-	-
NOT	8615	2.70	0.0281	306356

COT: continuous oxygen therapy; NOT: nocturnal oxygen therapy

The model design is simple and transparent. The structure of the model is clearly defined and simple. Incorporating a relation in the model between different parameters or not, is justified with available evidence.

The model handles a cycle length of 3 months to capture disease progression. The time horizon however is limited to 5 years because of insufficient data on the efficacy of HOT beyond this time horizon. A lifetime horizon would be better to capture all relevant costs and health effects.

Identification, modelling and incorporation of data is clearly presented. Literature research has been done in bibliographic databases for key model inputs (hospitalisations, progression of the disease, effect of HOT on hospitalisation).

The author scored the methodological quality of the used studies for input data. All sources of used data (QALY's, mortality rates, costs, …) are presented.

Assumptions of the division of the cohorts in the different disease stages and of estimating the progression probabilities are well described and provided with scientific evidence. The calculation of transitional probabilities of death, corresponding to the time interval used in the model, is well explained and sources of methods or literature input are mentioned. A discount rate of 3% is used for costs and health benefits and inflation is not taken into account. Data input and assumptions are tested in extensive sensitivity analyses (deterministic 1-way and probabilistic). For the cohort simulation, a second-order Monte Carlo simulation was used. Using a half cycle correction was justified and the used software was mentioned (Tree-Age Pro).

The internal validation of the study is poor because there are no definite data on the effect of HOT on HRQL from which appropriate estimates could be drawn, and the efficacy data taken from the literature are over 30 years old. The possibility of adapting the model to new evidence is however a strength and shows a good external validity. When additional data from clinical trials are available, the precision of estimates may be improved.

This modelling paper is of good quality. Recommendations for future research are the use of a societal perspective, a longer time horizon and a stronger internal validation of the study.

3.10 UNCERTAINTY ANALYSIS

Uncertainty in estimating costs and consequences in economic studies is an important factor that should not be overseen but rather accounted for and handled in statistical analyses, sensitivity analyses and in the conclusions of the study.

When patient-level data on costs or consequences are available, appropriate statistical analyses should be performed. In seven studies [100, 105, 109, 111, 112, 114, 115] it was either mentioned that statistical analyses were performed, but without mentioning which tests, or there was nothing mentioned about statistical analyses. Seven studies [30, 96, 101, 102, 108, 110] shortly described which analytical tests were used in the analyses of the data. Only Farrero [107], Guyatt et al [106], Pelletier-Fleury et al [104], Mapel et al [99] and Serginson et al [98], described in detail the appropriate analyses performed in the study.

Sensitivity analyses were performed in only 5 of the 18 comparative studies included in our review.

The analysis of uncertainty in Heaney et al [113] was limited to a sensitivity analysis where the results of a best- and worst-case scenario (maximum and minimum savings scenarios) were presented based around values of key.

In both Seino et al [105] and Jackson et al [111] a one-way sensitivity test was performed varying the hospital period for the former and the survival rate for the latter. Guyatt et al [106] repeated their original calculations using US costing, which seemed to confirm their findings.

Only Oba et al [112] performed both 1-way and probabilistic sensitivity analysis.

4 DISCUSSION AND CONCLUSIONS

The literature review on the cost effectiveness of home oxygen therapy (HOT) did not show conclusive results, primarily due to the flaws found in most published studies. Focusing only on the comparative studies since non-comparative studies, although informative, would not offer an insight into potential cost-effectiveness of the therapy, HOT appeared to present a relatively low incremental cost effectiveness ratio in comparison to no oxygen in the case of continuous oxygen therapy, while this was not the case for nocturnal oxygen. The study did not cover the patient's life period and only included direct costs but sensitivity analysis confirmed the robustness of its findings [112].

Two more studies [102, 105] compared oxygen versus no oxygen, suggesting net savings for those on oxygen, but both presented small sample sizes.

All of the three studies that compared HOT provided by cylinders to HOT provided by concentrators showed that concentrators were cheaper for as long as a minimum of oxygen was consumed per day or month: 1.4 hrs per day in Jacksson et al [111] and two cylinders per month for a year in Heaney et al [113], but from them only one captured health outcomes and these were analysed separately from costs. Thus, no incremental analysis was performed. Further limitations of that study included its nature, being a cross-over study in a small number of patients, which is likely to introduce some biases in the final results.

The two studies that compared lightweight or liquid oxygen to oxygen cylinders did not show a consistent picture and while Mapel et al [99] concluded that the type of oxygen system did not significantly affect the overall cost of COPD patients on HOT, Andersson et al [108] did show higher costs for the liquid oxygen group, but did also mention a benefit for the liquid oxygen group in the form of HRQL. In addition to the conflicting results, none of the studies performed a sensitivity analysis and there was no incremental analysis of costs and consequences.

Two studies analysed the potential savings that could be derived from more or less frequent patient evaluations but failed to show statistically significant savings derived from more frequent re-assessments [106, 110].

Two small studies (55 patients in both) compared treating patients with oxygen at home versus treating them at the hospital and concluded that treating the patients at home resulted in savings. However, in addition to the small sample size they presented other important limitations, since none of the two studies performed a sensitivity analysis, and no p values were reported [103, 114].

Studies looking at processes such as the establishment of a new specialist oxygen clinic in Tasmania or the effect of a new multidisciplinary total quality improvement team did not give p values and failed to perform a sensitivity analysis [100, 109].

Farrero [107] investigated the impact that a home care programme could have when compared to conventional medical care and proved that despite the additional costs of implementing the home care program savings could be met primarily due to the reduction in emergency visits, hospital admissions and hospital length of stay. No sensitivity analysis was performed and costs and outcomes were looked at and analysed separately.

Pelletier-Fleury [104,30] looked at the cost differences of having the oxygen delivered by the for profit sector as opposed to the not-for profit sector and did show a significant benefit in favour of the not-for profit sector.

However, the study included only 61 patients and the overall objective was not well defined, mixing the route of delivery with the route of administration, (concentrators more common in the not for profit sector versus cylinders more common in the for profit sector).

We can conclude that all of the studies did present some important limitations since:

- Practically all studies were purely cost descriptive or cost analyses; with the only exception of one cost-utility [112]
- In most cases there was no consideration of uncertainties surrounding all costing exercise.
- The sample size was less than 100 in almost three quarters of the population based studies analysed.
- No study included indirect costs.
- Appropriate statistical analysis was not always present, and when present it was very rarely well covered and explained.
- No discount rates were made explicit in most of the studies with a time horizon of over a year (only 2 of a total of 5).
- Not all studies offered a detailed description of patients' characteristics, which is imperative at the time of interpreting the validity of their results.
- The specific amount of oxygen used and the period over which it was used was not always reported.

In view of those limitations, more robust studies should be performed to assess the cost-effectiveness of HOT.

Chapter 4
Health Economic Evaluation

1 INTRODUCTION & OBJECTIVES

This chapter describes the health economic evaluation of long-term oxygen therapy (LTOT). We decided to focus on LTOT in COPD, which is the most frequent indication for LTOT. The systematic economic literature review in Chapter II revealed that only a few studies investigated the cost dimension of LTOT, and a limited number captured the impact on health related quality of life (HRQoL). Only 1 study was a cost-utility study (Oba, 2009), expressing results in cost per QALY. Other studies were purely cost descriptions or cost analyses.

Most of the studies had small sample sizes and a lot of them did not perform a so called incremental analysis of the costs and the health-related outcomes (meaning that they did not consider the differences between different treatment options). Uncertainty around cost data was often not taken into account and appropriate statistical analyses were not always presented.

The objectives of the current economic evaluation of LTOT in Belgium were twofold:

6. to compare the costs and health effects of LTOT in COPD to no LTOT in COPD, with health effects expressed in Life Years and in QALYs.
7. to compare the different modalities of LTOT in terms of costs.

2 METHODS

2.1 MODEL

To compare the costs and health effects between LTOT and no LTOT in patients with COPD a Markov model was constructed in Excel. The model is based upon the effect of LTOT on hospitalisation rates and its effect on mortality. It should be noted that no proven effect of LTOT on exacerbations was found in the clinical literature. Regarding hospitalisation rates, the reported meta-analysis [44] could not identify a decreased rate. However, an observational study did show an effect of LTOT on hospitalisation rates[116]. Our model is therefore programmed to account for such an effect. In the basecase analysis we do not assume an effect on hospitalisation, while in a secondary analysis we do account for this effect.

The Markov model includes the following 5 disease/management states:

- State 1: COPD without hospitalisation
- State 2: hospitalisation
- State 3: 1st month post-hospitalised
- State 4: COPD post-hospitalisation
- State 5: death

This means that at any point in time, a patient can be in one of these mutually exclusive states.

A cycle length of 1 month (meaning that each month a patient can move from one state to another) and a time horizon of 5 years (hence a total of 5 x 12 = 60 cycles) was chosen for this analysis. A discount rate of 3% and 1.5% for respectively future costs and health effects is used, according to the Belgian guidelines for pharmaco-economic evaluations[117].

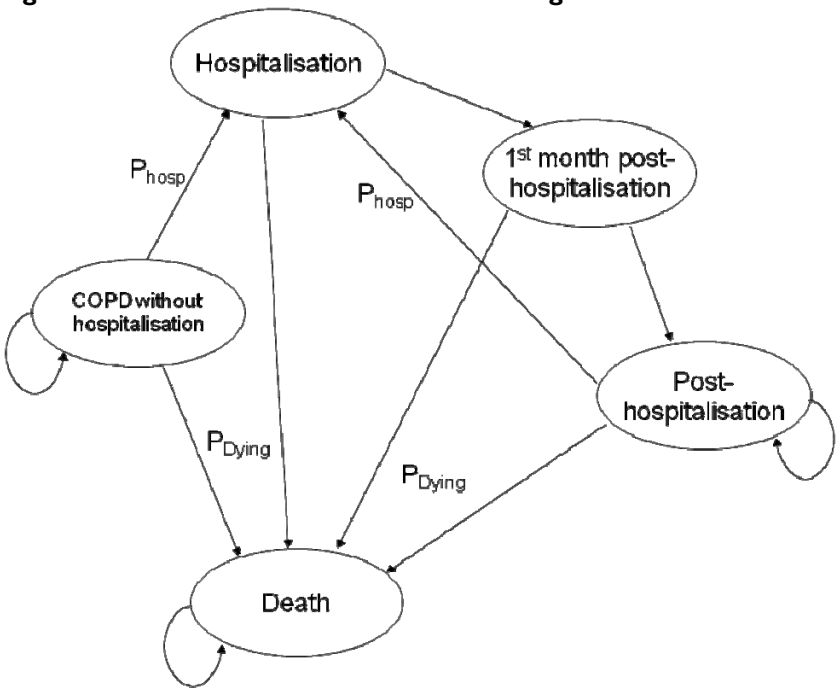
2.2 PERSPECTIVE

The study is undertaken from the health care payers' perspective, i.e. the RIZIV-INAMI plus the patient.

2.3 TRANSITION PROBABILITIES

After every cycle of one month, patients can move from one state to another according to the arrows shown in the figure below (Figure 1).

Figure 1: Health economic model LTOT Belgium



One-month mortality probabilities (PDying) for patients on LTOT are derived from the Belgian EPS database. Based on the clinical literature a relative risk of LTOT versus no LTOT is applied. The probabilities for hospitalisation per cycle (Phosp) in case of LTOR are again derived from the EPS database. In the basecase there is no difference between LTOT and no LTOT with regard to hospitalisation rates, while in the secondary analysis the relative risk of LTOT versus no LTOT is taken from Ringbaek et al. (2002). We assume the same transition probability for patients moving from 'COPD without hospitalisation' to 'Hospitalisation' as for patients moving from 'COPD post-hospitalisation' to 'Hospitalisation'.

After hospitalisation, patients who survive move automatically to the state '1st month post-hospitalisation'. After that month, they move to 'COPD post-hospitalisation'.

Mortality rates and hospital admission rates were converted to 1-month probabilities.

Table 1: Literature results for transition probabilities (basecase)

	Without LTOT	With LTOT	RRR (+/- St Err)	Source
Mortality COPD patients / 3months (%)	0.0523	0.0270	48.3% (39.23%- 57.43%)	EPS & Oba (2009), based on NOTT (1980) & MRC (1981)
Hospital admission rate COPD patients over 10 months (SD)	0.0945	0.0720	23.8%* (17.13%- 30.49%)	EPS & Ringbaek et al. (2002)

* only in the secondary analysis

Since the meta-analysis by Wilt et al did not find a significant effect of LTOT on hospitalisation rates, a secondary analysis assumed no difference in hospitalisation rates and applied the LTOT rate for all patients.

2.4 HEALTH RELATED QUALITY OF LIFE

Mean health related quality of life (HRQoL) and utility values were derived from the literature. For states 1 and 4, when COPD patients are not hospitalised, the utility values from the study of Rutten-van Mölken et al. (2006) for patients in stage III and IV (following the Gold-criteria) during stable phases were used (0.734, SD: 0.212). HRQoL is assumed to decline when patients are hospitalised. For this purpose, utility values reported by O'Reilly (2007) were applied. Utility values represent the absolute value of HRQoL on a scale from 0 (death) to 1 (perfect health). In case of very severe conditions the value can be below 0 ("worse than death"). O'Reilly et al reported utility values of hospitalized patients upon admission (-0.084, SD: 0.382) and discharge (0.578, SD: 0.325). These values together with the average length of a hospital stay of COPD patients (12 days, obtained from the Belgian tct database – www.tct.fgov.be, APR-DRG 140), were used to calculate the utility loss associated with a hospitalization. For the 1st month post-hospitalisation, the mean value of the utilities during and post-hospitalisation, is used.

Table 2 shows the applied utility values for each state:

Table 2: Utility values per model state

State	Utility value	95% CI
COPD	0.734	CI 0.718 ; 0.751
hospitalisation	0.575	CI 0.565 ; 0.586
posthosp 1	0.655	CI 0.641 ; 0.668
COPD posthosp	0.734	CI 0.718 ; 0.751
death	0	

2.5 COSTS & RESOURCE USE

2.5.1 Data source

For this health economic evaluation in Belgium, the EPS release 5 (EPSR5) is used. EPSR5 is a representative sample of all compulsory health insurance reimbursements of the Belgian population between 2002 and 2009, (see appendix to this chapter for a more detailed account on EPS).

2.5.2 Analysis sample

From the EPSR5, all patients with at least one reimbursement for oxygen therapy or for oxygen as a drug are selected for research. The selection is based on respectively the RIZIV-INAMI nomenclature codes for the different RIZIV-INAMI conventions and the public pharmacy CNK numbers (both lists can be found in the appendix to this chapter). Only the hospital convention and the pharmacist convention were taken into account (see Chapter 1 for a full description of the different conventions). The cystic fibrosis convention and the mechanical ventilation convention were not taken into account because of the relative few patients with reimbursements in the EPSR5 (both less than 60 patients). As a result, 5487 patients were selected between 2002 and 2009. From these, a number of patients were excluded for several reasons (see Table 3). Eventually, we retained 1956 patients for further analysis.

Table 3 Exclusion criteria overview

Exclusion rule	Motivation	Number of patients concerned
All reimbursements of a patient are on a single date.	Not considered chronic therapy.	1960 (35.8%)
All reimbursements of a patient are on two dates.	Not considered chronic therapy.	785 (14.3%)
Reimbursements concern oxygen only and there are no convention reimbursements.	Considered out of scope.	175 (3.19%)
Reimbursements concern pharmacy convention nomenclature only and there are no oxygen reimbursements).	Considered out of scope.	212 (3.9%)
Reimbursements concern hospital and pharmacy convention reimbursements intertwined.	Oxygen and other reimbursements could not be uniquely attributed to a single convention.	317 (5.8%)
Self-employed patients with health insurance for major risks but without health insurance for minor risks prior to 2008.	Oxygen reimbursements are insured as minor risk. Hence no data are available for these patients prior to 2008.	82 (1.5%)

For each patient, an oxygen therapy episode is defined based on start and end date of the convention or oxygen reimbursements. Only reimbursements within this episode are considered for analysis.

Based on the RIZIV-INAMI convention reimbursement, each patient is categorized as being reimbursed either under the hospital convention (N=509, 26%) or under the pharmacy convention (N=1447, 74%). Likewise, each patient's episode is attributed an oxygen therapy type (see Table 4).

Table 3: Oxygen therapy modalities

Oxygen therapy type	Number of patients	% of patients
Gaseous	1434	73.3%
Concentrator	232	11.9%
Gaseous + concentrator	143	7.3%
Liquid	65	3.3%
Gaseous + liquid	44	2.2%
Gaseous + liquid + concentrator	23	1.2%
Liquid + concentrator	15	0.8%

2.5.3 Descriptive statistics of the analysis sample

The mean age at the onset of oxygen therapy is 74.9 years (SD=11.6, Median=76). Patients in the hospital convention are somewhat younger than patients in the pharmacy convention (respectively M=72.4, SD=9.7, Median=73; and M=75.8, SD=12.1, Median=78). The age descriptive statistics for oxygen therapy modalities are shown in Table 4.

There are more male patients in the sample than female patients (respectively 56.34% and 43.6%). This difference is larger in the hospital convention (61.7% male, 38.3% female) than in the pharmacy convention (54.5% male, 45.5% female). The gender descriptive statistics for oxygen therapy modalities are shown in Table 4.

Table 4 Age and gender descriptive statistics by oxygen therapy modalities

Modality	Age			Gender	
	Mean	SD	Median	% Male	% Female
Gaseous	75.8	12.1	78	45.5%	54.5%
Concentrator	74.0	9.1	74.5	41.8%	58.2%
Gaseous + concentrator	71.8	9.7	73	35.7%	64.3%
Liquid	70.2	11.5	73	24.6%	75.4%
Gaseous + liquid	71.6	11.8	74	50.0%	50.0%
Gaseous + liquid + concentrator	69.7	7.1	71	34.8%	65.2%
Liquid + concentrator	71.6	7.1	71	46.7%	53.3%

2.5.4 Cost calculations

For each convention type and for each oxygen therapy modality, the following costs are calculated (see details of calculation in the appendix to this chapter):

- Mean of total costs per month
- Mean of total ambulatory costs per month (excluding all hospital reimbursements)
- Mean of all RIZIV-INAMI convention nomenclature and oxygen CNK costs per month

Each item includes both the RIZIV-INAMI reimbursements and the patient's co-payments (but without supplements) within the oxygen therapy episode.

To calculate the health care costs for COPD patients without LTOT, we subtract the costs of LTOT from the total monthly costs of patients with LTOT, thereby assuming that patients with LTOT do not have extra consultations with the pneumologist as compared to patients without LTOT. Expert opinion supported this assumption.

To compare the different oxygen therapy modalities for LTOT in terms of costs and effects (research question 2), a direct comparison of costs between the modalities (liquid, gas, concentrator) was conducted.

The table below shows the obtained costs per month from the EPS database:

The EPS analysis reported the following monthly costs (Table 5):

Table 5 Oxygen therapy modalities

	All patients (€)			Hospital convention			Pharmacist convention		
Total cost per month	**N**	**Mean**	**st ERR**	**N**	**Mean**	**st ERR**	**N**	**Mean**	**st ERR**
Total cost all patients on oxygen	1956	€ 2,259	€ 60	509	€ 2,306	€ 168	1447	€ 2,242	€ 55
Total cost excluding hospitalisation	1956	€ 1,263	€ 26	509	€ 1,113	€ 33	1447	€ 1,316	€ 33
Oxygen plus equipment cost	1956	€ 222	€ 8	509	€ 350	€ 11	1447	€ 177	€ 9
Estimated cost without oxygen excluding hospitalization (line 2 minus line 3)	1956	€ 1,041	€ 27	509	€ 764	€ 35	1447	€ 1,139	€ 34
Estimated cost without oxygen (line 1 minus line 3)	1956	€ 2,037	€ 60	509	€ 1,956	€ 168	1447	€ 2,066	€ 56

There are no important differences in cost between the two types of convention, with exception of the monthly cost of oxygen itself which is higher in the hospital convention group. This is not surprising since it can be expected that patients in the hospital convention group use oxygen on average more intensively.

2.6 ICER

The Markov-model generates the total discounted costs and effectiveness of the different strategies (LTOT and no LTOT) over 5 years. By dividing the incremental cost of the most costly strategy by the incremental effectiveness of that strategy, the ICER is calculated.

2.7 SENSITIVITY ANALYSIS

One-way sensitivity analysis is performed for assessing the impact of uncertainty in a number of variables on the estimated ICER. This is done by running the model first with the lower boundary and then with the upper boundary of the 95% confidence intervals. The variables for which a one-way sensitivity analysis is performed:

- Mortality probability in patients with LTOT
- Hospitalisation rate in patients with LTOT
- Utility value of COPD patients without hospitalisation
- Utility decrement of COPD patients at hospital admission
- Utility value of COPD patients at discharge
- Days hospitalised
- Costs of oxygen and monthly cost of care

In addition to the one-way sensitivity analyses, a probabilistic sensitivity analysis is performed by varying all parameters at the same time using their probability distributions. Beta distributions were defined for mortality and hospitalisation rates, and for utility values of COPD patients without hospitalisation and at discharge of hospitalisation.. A normal distribution was applied for the negative utility value at hospital admission and for the hospitalisation rate. A gamma distribution was applied for costs. Five thousand simulations were performed, leading to 5000 estimates for the ICER.

2.8 SCENARIO ANALYSIS

Next to the base case scenario, which is in accordance with the findings of the meta-analysis from the clinical literature review (Chapter 2). a second scenario was elaborated. In this second scenario, LTOT is assumed to have an effect on hospitalisation rates in COPD patients, as reported by Ringbaek et al (2002). Hence, in this scenario, the lower hospital admission rate for patients with LTOT is used.

3 RESULTS

3.1 BASE CASE SCENARIO

Table 6 shows the basecase result of this health economic evaluation.

Table 6: basecase scenario incremental cost effectiveness analysis

	LYs	Incr. LYs	QALYs	Incr. QALYs	Costs (€)	Incr. costs (€)	ICER (€/LY)	ICER (€/QALY)
without O2	1.457		1.048		18372			
with O2	2.326	0.869	1.674	0.626	34504	16,133	18555	25783

A total discounted cost of €18,372 is predicted without LTOT and € 34,504 with LTOT, i.e. a difference of € 16,133 over a period of 5 years.

Because of the reduced mortality the number of LYs with LTOT amount to 2.326 at 5 years as compared to 1.457 without LTOT i.e. a benefit of 0.869 LYs on 5 years time per average patient. The number of QALYs with LTOT amount to 1.674 at 5 years as compared to 1.048 without LTOT i.e. a benefit of 0.625 QALYs on 5 years time per average patient.

The estimated mean ICER of LTOT vs no LTOT equals €18,555 per LY gained (95% Credibility Interval (CrI): €14318- €22404) and € 25,783 per QALY gained (95% Credibility Interval (CrI): €19510 -€31259).

3.2 ALTERNATIVE SCENARIO

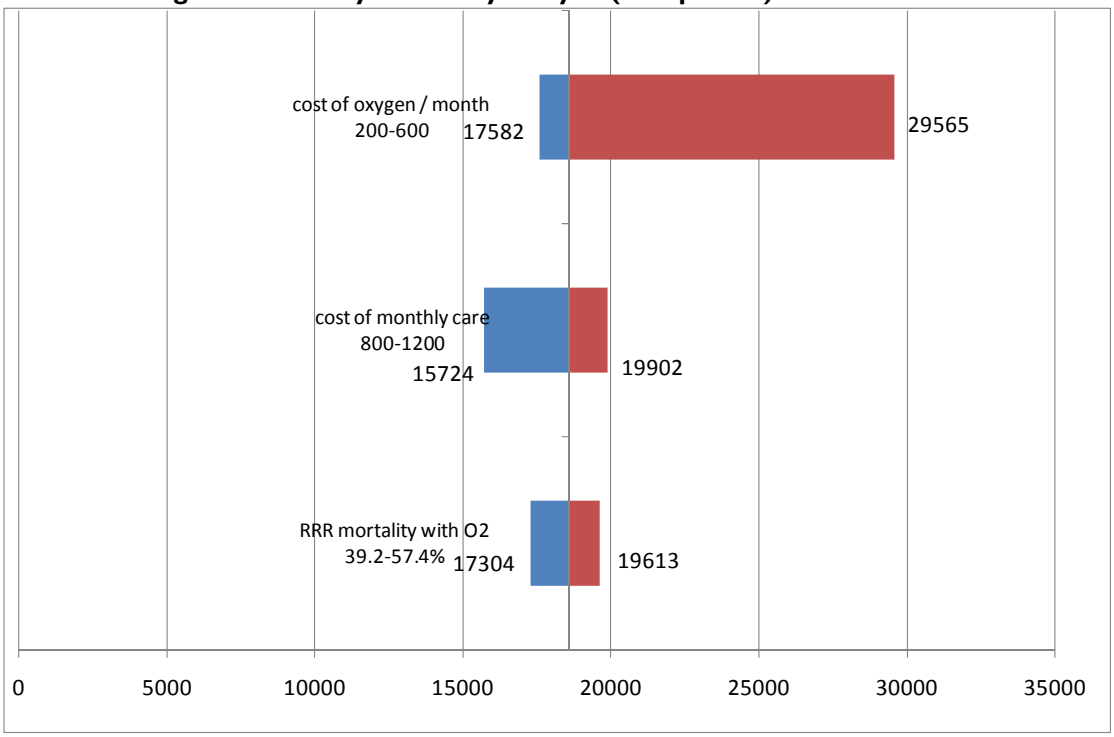
In the second scenario, when an impact on hospitalisation rates is assumed, the estimated ICER equals €18,239 per LY gained and €25,116 per QALY gained.

Table 7: secondary analysis incremental cost effectiveness analysis

	LYs	Incr. LYs	QALYs	Incr. QALYs	Costs (€)	Incr. costs (€)	ICER (€/LY)	ICER (€/QALY)
without O2	1.457		1.043		18647			
with O2	2.326	0.869	1.674	0.631	34504	15,857	18,239	25,116

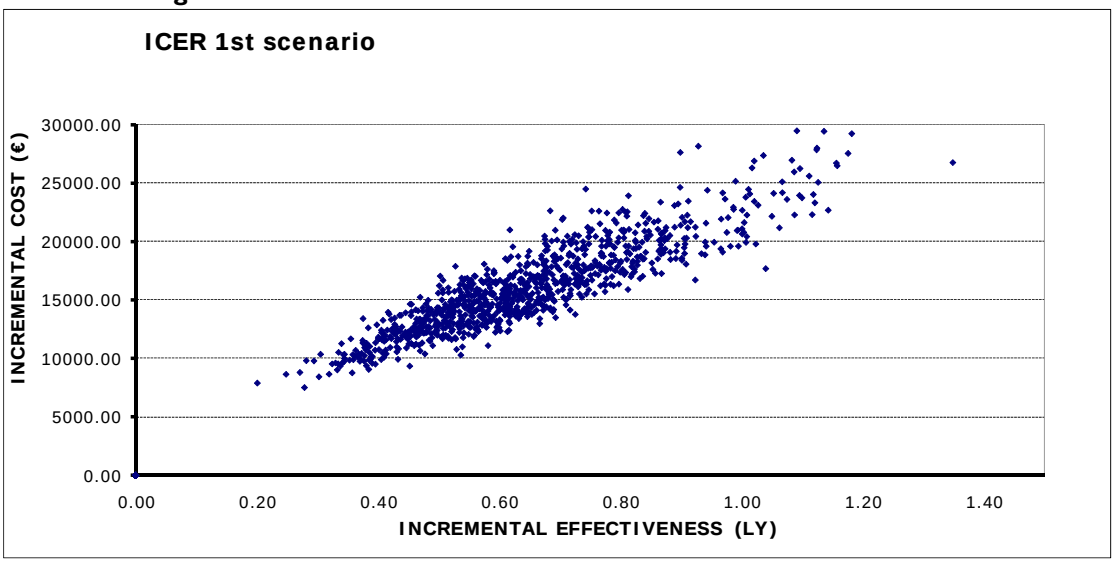
The impact on hospitalisation rates has very small effects on the results. The one-way sensitivity analysis shows that these results are quite robust (figure 2), except for the cost of oxygen.

Figure 2: one way sensitivity analysis (cost per LY)



Results from the Monte Carlo analysis (1000 runs of the model) are illustrated on a cost-effectiveness plane (fig 3), showing that the basecase result is subject to some uncertainty.

Figure 3: Monte Carlo simulation basecase scenario



4 DISCUSSION AND CONCLUSION

Our results show that at its current cost, LTOT in COPD patients is associated with additional costs from a health care payers' perspective and with additional QALYs leading to a ratio of +/- €18,000 per LY and +/- €25,000 per QALY gained. Its impact on hospitalisations does not strongly affect these results, which is explained by the high background costs and the small benefit in QALYs when avoiding a hospital stay.

The results are most sensitive to the cost of oxygen itself. At an average cost of €222 per month, as estimated by the EPS database, the cost-effectiveness is about 18,000€ per LY gained, whereas in case of costs up to 600 € per month the ICER increases to more than 29,500 €/LY gained.

In order to prevent costs of LTOT from increasing to levels that would be considered unacceptably high from a societal point of view, attention should be given to the adequate application of liquid oxygen.

It should also be noted that we applied a mix of different LTOT modalities to arrive at the average cost. This mix is based on the 2008 EPS database and may not be entirely representative for today's COPD population.

Nevertheless the results are quite robust and are mainly explained by the applied effect on mortality.

Thereby it is noteworthy that our analysis assumed that LTOT in Belgium would have the same impact on mortality as was shown in the meta-analyses. Note however that the data from the meta-analyses are based on RCTs where the use of oxygen was as much as possible standardized. This implies that in order to be effective and cost-effective LTOT should be used adequately and according to clinical practice guidelines in terms of patient eligibility, conditions of use (e.g. at least 15 hours a day) and conditions of continuation.

More importantly, in the old trials the included population is not anymore comparable to the today's population on LTOT. The current population is older and has more co-morbidities than the population included in the meta-analyses. This is also expressed in mortality rates in our study that are quite different from the ones in the meta-analysis. Yet, assuming that the RRR as obtained from the meta-analysis is still applicable, the current use of LTOT still shows an acceptable cost-effectiveness ratio. Also, changing this RRR by 10% less or more did not affect this conclusion.

Our model must finally be interpreted with caution because the cost data were obtained from the EPS database and several simplifications and assumptions needed to be made in order to arrive at a reasonable estimate of the cost per month. Yet, a variation of the cost inputs did not influence the results to a large extent.

Chapter 5
International Comparison

1 INTRODUCTION

Between countries, several differences in the organisation and financing of LTOT exists. The aim of this chapter is to establish an outline of the situation in France, The Netherlands, Germany and the United Kingdom. The comparison can help to capture potentially positive factors for the improvement of LTOT in Belgium.

2 METHODOLOGY

Prof. Kampelmacher was interviewed by Prof. Buyse (face to face Interview without using a structured questionnaire) on the organisation of LTOT in The Netherlands, the CBO guideline 'Zuurstofbehandeling thuis' [118], and " Hulpmiddelen Kompas-Zuurstofapparatuur ," College voor Zorgverzekeringen (CVZ) 2004 were also used for this international comparison.

For France, Prof. Muir from ANTADIR was contacted and data were gathered from the paper 'L' oxygénothérapie de longue durée à domicile' by Pombourcq & Cuvelier from Service de Pneumologie et Soins Intensifs Respiratoires, CHU de Rouen, from the home oxygen order form and from a syllabus from a stakeholder (Vitalair France).

The answers of Prof. Welte from Germany (provided by E-mail) together with the 'Guidelines for Long-Term Oxygen Therapy' of the German Society for Pneumology and Respiratory Medicine formed the basis for the outline of the German situation of LTOT.

For the United Kingdom, the report of the Royal College of Physicians, 'Clinical guidelines and advice for prescribers for Domiciliary oxygen therapy services', was used together with the paper of Wedzicha & Calverley [119] on the changes to the guidelines.

No systematic literature search was conducted.

The above mentioned experts provided an answer to the following questions:

1. What are the conditions for prescription (home alone, home + ambulatory, gaseous versus liquid O2);
2. Channel(s) of provision of home oxygen and reimbursement system(s) (Any Physician or only pneumologist, pharmacist, home care company, NHS…) .Are there official contracts with one or more home care company(/ies) for the deliverance at home? Are there standardized application forms?
3. Do you make a difference between LTOT and short term therapy and palliative care?
4. Who is responsible for education, installation, motivation?
5. Is smoking cessation mandatory?
6. When there is a problem at home who has to help to solve the problem (GP, pneumologist, home care company?)
7. Is there any charge for the patient?
8. Is the reimbursement period limited (1 year?) with possible renewal?

3 RESULTS

Organisational data of LTOT in the different countries, gathered from the above mentioned sources, are collected in a grid (Table 1) with the countries in the columns and the organisational aspects in the rows, to make comparison possible.

3.1 REGULATION OF PRESCRIPTION

The conditions for prescription of LTOT are comparable in the four countries. In all countries arterial blood gas tensions must be measured. Arterial PaO2 should be below 7.3kPa (55mmHg) in France, Germany or Great-Britain or below 8 kPa (60mmHg) in The Netherlands. A patient with an arterial PaO2 between 55mmHg and 60mmHg can also obtain prescription for LTOT in France, Germany and Great-Britain, when the chronic hypoxaemia is associated with pulmonary heart disease or nocturnal hypoxaemia. In Germany 3 measurements are necessary, in the other countries at least 2. These measurements are executed in rest during daytime on room air with an interval of 3 weeks in The Netherlands, France and Great-Britain, and 4 weeks in Germany. In the guidelines, prior to assessment, optimal medical management of the conditions and clinical stability is advised. Smoking cessation is not mandatory, but is recommended for the patient's safety. Prescription of LTOT is in all countries seen as not appropriate in patients who won't stop smoking.

In most countries LTOT is prescribed by the pulmonologist because arterial PaO2 values are necessary for assessment. Only in Great-Britain and France, a standardized home oxygen order form exists for starting LTOT.

The threshold PaO2 or SaO2 that optimally improves survival and quality of life is not known. A PaO2 of 60 to 65 mmHg(≥8kPa) or an SaO2 of 90 to 92 percent is generally considered to be acceptable. This threshold is adopted by all countries included in this overview.

Medical follow-up is executed in all four the countries, but in different ways. In every country the arterial blood gas tensions are measured at least 1 time per year with the supplemental oxygen. In France, Germany and Great-Britain, during the first year, after 3 months the patient has already a medical surveillance. In Great-Britain, 4 weeks after initiation of LTOT, a home visit is planned and from then on at 6-monthly intervals.

3.2 CHANNELS OF PROVISION AND HOME SUPERVISION

In The Netherlands and Germany, insurance companies have contracts with home care companies for oxygen supply, while in Great-Britain only 1 single contractor exists in a given region for oxygen supply. In France, distribution of oxygen is possible via 3 ways, always under the responsibility of a pharmacist: via community pharmacists, via private companies or via non-profit organisations.

In all four the countries, the deliverer of oxygen is available for technical problems, but there are no clear rules on who is responsible for education, installation and motivation of LTOT. It is however recommended that the health care companies are responsible for installation, safety instructions, provision, maintenance, surveillance and correct use of LTOT. The prescribing physician is then responsible for a good motivation and education of the patient.

3.3 REIMBURSEMENT SYSTEM

In Germany both private & public health services are in charge of the costs for LTOT. There is no patient charge and the reimbursement period is not limited.

In The Netherlands, the pulmonologist is indirectly reimbursed from a 'Care Project', while ambulatory pharmacists don't get a fee. We were able to get some information about the reimbursement policy in The Netherlands. The insurance company establishes the requirements to be fulfilled by the home care companies. A tender is then launched and the best cost/effective proposal is selected. In the Netherlands, tendering is made possible by clearly differentiating and defining the subprocesses leading to an effective LTOT. A clear distinction is made between indicating LTOT, specifying the minimum requirements for both patients and devices, the selection of oxygen sources, the home delivery of and education about these devices, as well as the periodic evaluation of the previous processes for every patient. A good description of these subprocesses can be found in "Hulpmiddelen Kompas- Zuurstofapparatuur," College voor Zorgverzekeringen (CVZ), 2004. A marked difference with the Belgian situation is that the selection of the oxygen source is left to the free market that emerged between healthcare insurers and oxygen delivery companies, while quality remains assured by the specified minimum requirements for each patient. By contrast, in Belgium the patient and device specification as well as the source selection are primarily established by the reimbursement rules. Following this tendering methodology, the cost of oxygen therapy in the Netherlands has been dramatically reduced over the past 15 years to such an extent that in 2009 the average price per patient was almost 4 times less than in Belgium. However, no information is available on electricity costs in the Netherlands. The absence of any tender system in Belgium is appalling and can be interpreted as infracting with the following legislation:

- Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts
- The Belgian Law of 24 december 1993 on public procurement and certain contracts for works, supplies and services.

In France the patients can receive 2 non-cumulative weekly forfaits for provision, electricity, surveillance and replacement or reparation, depending on their level of oxygen use. Both in The Netherlands and in France, renewal of the reimbursement period is possible when the patient is medically followed-up and can present similar application forms with new arterial PaO2 values. The patient's values must always be in the conditions required for the prescription of LTOT.

Great-Britain shows a more streamlined oxygen funding system since 2006. Before, no formal ambulatory oxygen service has been available, only concentrators were funded by the government for LTOT. When a patient required oxygen for daily activities, provided by small cylinders, this wasn't funded by the government, but by charitable, hospital or private sources. Since 2006, ambulatory oxygen therapy can also be reimbursed. Before prescription, the level of outside activity of the patient is determined and assigned to 1 of the 3 categories for prescription of ambulatory oxygen. The 3 categories are: LTOT low activity, LTOT active group and non-LTOT patients who are exercise desaturators. The Primary Care Trusts have unified budgets for reimbursement of LTOT in primary & secondary care. There is no patient charge.

Table 1: International comparison LTOT

	The Netherlands	France	Germany	Great-Britain
Conditions for prescription	Arterial PO_2 (PaO_2) ≥2x <8.0kPa or 60mmHg in rest during daytime on room air, with an interval of ≥3 weeks; No exacerbation in last 3 months (temporary oxygen) Smoking cessation, optimal treatment PaO_2 with extra O_2: 8.0kPa or 60mmHg AND $PaCO_2$ & pH acceptable Medical surveillance: pulmonologist/GP: PaO_2 measurement with extra O_2 >1x/year	Arterial PaO_2 2x <55mmHg in rest during daytime on room air, with an interval of 3 weeks; 55mmHg – 60mmHg: polyglobulie, signes de coeur pulmonaire chronique, hypertension artérielle pulmonaire, désaturation artérielle nocturne non apnéique PaO_2 with extra O_2: ≥60mmHg AND O_2 saturation (Sa O_2)>92% Prescription by pulmonologist or by GP Medical surveillance: **1st year**: after 2 months, then after 3 to 6 months; **after 1st year**: 1 or 2 times per year: arterial blood gas + yearly respiratory functioning & ECG	Arterial PaO_2 3x ≤55mmHg (7.3kPa) in rest on room air, during 4 weeks; 50-60mmHg in pulmonary heart disease or polyglobuly; in exercise ≤55mmHg or hypoxemic in sleep Stable disease, optimal therapy Objective: ≥60mmHg or increase by 10mmHg; or improvement in burden (for problems in exercise) No contraindications Medical surveillance: every 3 months by pulmonologist	Arterial PaO_2 2x ≤55mmHg (7.3kPa) in rest on room air, with interval of 3 weeks; 7.3 – 8kPa when together with nocturnal hypoxaemia, peripheral oedema or pulmonary hypertension Ambulatory O_2 therapy available on prescription: determination of level of outside activity necessary (3 categories) Response to O_2 therapy: aim at PaO_2 ≥8kPa Medical follow-up: *3months after initiation with arterial blood gases on air & with supplemental O_2 at prescribed flow rate; yearly check arterial blood gases *4weeks after initiation home visit + at 6 monthly intervals
Channels of provision of home oxygen	Each insurance company: contract with O_2 home care company for installation. Since very	3 ways of distribution, under responsibility of a pharmacist & with respect to the BPDOUM (Bonne pratiques de dispensation à	Some health care assurances (not all): contracts with home care companies/different distributors.	1 single contractor in a given region for supply of different modalities (4 contractors for 11 regions in

	recently, community pharmacists effectively responsible for oxygen delivery	domicile de l'O_2 à usage médical), with respect to same tariffs of the LPPR (La Liste des Produits et Prestations Remboursables): Community pharmacists: direct to patient or via a contract with distributor agent Private companies (Vitalaire, Orkyn, Air Products, ...) (30% in France) Non-profit organisations, grouped under ANTADIR or independent (ADEP, ALLP) (70% in France)		England & Wales; no role for community pharmacists)
Application form	Different application forms from the health care insurances: Diagnosis, arterial blood gases (not specified when...), O_2source, type O_2therapy, timing, dosing,	Diagnosis, arterial blood gases without extra O_2 at different timings, spirometry, O_2source, type O_2therapy, timing, dosing, smoking, advise from medical control, decision	There application forms, but everyone can applicate (majority by specialists because of O_2 blood gas analysis needed). Content (not standardized): diagnosis, degree of hypoxemie, objective, patient mobility, O_2 system, smoking behaviour, duration of therapy (≥16h/d), possibility of re-evaluation in 3 to 6 months	Special dedicated prescription/home O_2 order form: for use in both primary & secondary care
Reimbursement systems	Ambulatory pharmacists: now incorporated in the delivery circuit . Indirectly reimbursement to the pulmonologist (zorgtraject, not from insurance company).	2 forfaits, weekly, not cumulative (provision, electricity, surveillance, replacement/reparation): Fixed charge (patients with<1h active) **€ 48.87** Intensive charge (very active/debit>5l/min) **€ 112.19**	Both public and private health services are in charge of the costs for LTOT.	More streamlined: Prescribing in primary & secondary care: Primary Care Trusts unified budgets
Difference	Prescriber: For	Short term:	Short term &	LTOT mostly

between LTOT & short term therapy & palliative care	LTOT arterial blood gas analysis is necessary, so pulmonologists prescribe chronic oxygen. For cluster headache or palliative care, respectively neurologists or general practitioners can prescribe oxygen	less than 3 months: 1 month prescription & 2 times renewal possible no titration of O_2 debit necessary & surveillance after prescription instable phases of long & heart diseases, or cancer no provision of liquid O_2 forfait: weekly €46.51	palliative care: only reimbursed when above mentioned criteria for hypoxemia are fulfilled.	prescribed from secondary care, for palliative use primary care is also able to prescribe. Follow-up: only 1/year seen by GP/hospital specialist
Who is responsible for education, installation, motivation?	No uniform policy! *(CBO-guideline, 2000) Prescribing physician: medical information, motivation, smoking cessation. O_2 home care company: technical information & safety instructions, installation, provision, maintenance, surveillance on correct use & stop smoking, regular check up.*	Treating physician: **motivation & surveillance** of understanding safety rules, motivate not to smoke near the O_2 sources. **Education**: both pulmonologist & GP. Distributors: technical & logistic **information**	No clear rules: normally health care companies; when patients start O_2 in hospital, education is done there.	**Installation**: 1 of the 4 contractors: installation + 3 monthly visit to read O_2 meters **Education & motivation**: recommendation: 4weeks after initiation: home visit by respiratory nurse specialist, physiotherapist or technician for education & support + oximetry on air & on prescribed O_2 flow rate
Smoking cessation	Yes (not on application form)	Not mandatory (but it is asked in application form)	Not mandatory	Not mandatory
Problem at home: who solves it?	Acute technical problems: deliverer of O_2 24h telephonically available.	Distributors of O_2 for technical & logistic aspects.	Health care company, if not possible: patients contact clinic or pulmonologist.	Contractor
Patient charge	No	No	No	No
Reimbursement period limited? Possible renewal?	Renewal: patient is medically followed-up & present similar application forms with new blood gases etc.	Renewal: patient is medically followed-up & present similar application forms with new blood gases etc.	Not limited	Concentrators used to be prescribed for 5 years

4 DISCUSSION & CONCLUSION

Despite several methodological limitations, the available data show that The Netherlands, France, Germany and Great-Britain share a lot of similar aspects related to the indications for the prescription of LTOT.

Although the reimbursement systems strongly differ between countries, the Dutch system seems to be the most cost/effective.

Ideally, a European uniform and standardized prescription form should be used to be in accordance with the prescription rules/recommendations.

The responsibilities of the general practitioners, pulmonologists, home care companies and pharmacists should be more clearly defined and standardized.

Chapter 6
Final Conclusions and limitations

This final chapter includes a summary of the main findings and limitations of the current health technology assessment report.

Given that the original search strategy used for both the clinical and economic reviews dated from 2010, these searches were duplicated in Pubmed in April 2011 to check whether any relevant articles had been published ever since. Results from this exercise did not show any additional relevant literature worth adding to our economic review and only one relevant clinical article was found [31], whose results were considered in our analysis

The remaining of this section lists further limitations of this HTA review and provides an answer to each of the four main research questions.

1 CLINICAL EFFICACY

The search question is "Which patients are most likely to benefit from home oxygen therapy?"

The population looked at included patients suffering from chronic obstructive pulmonary disease (COPD); hypoxaemic disease necessitating palliative care; chronic heart failure; cystic fibrosis (any age); or interstitial lung disease.

1.1.1 COPD

Mortality/ morbidity	COPD with severe hypoxaemia (paO2 ≤55mm Hg or PaO2 < 60 mmHg with disturbances of pulmonary hemodynamic, right heart failure or erythrocytosis • LTOT versus no oxygen: improves mortality at 5 years (Peto odds ratio 0.42, 95%CI 0.18 to 0.98) • LTOT continuous (14 à 19u/day) versus nocturnal improves mortality at 2 years (Peto odds ratio 0.45, 95%CI 0.25 to 0.81) • Studies limitations o Only 2 trials (published round 1981) o Including relatively young patients, o No blind o No consideration of a bias due to smoking cessation • External validity o Patients currently older o Clinical status not similar o Other co-treatments • Low probability of further studies (ethical reasons)
	COPD with mild or moderate hypoxaemia, or who only desaturate at night • Currently no evidence of efficacy • Ongoing studies
Quality of life (validated scales)	• Quality of life : no difference • Dyspnea: no difference
Exercise	• Improves exercise time : 2,71 minutes (95%CI 1.96 à 3.46) • Improves 6 minutes exercise distance : 20,43 m (95% CI 14;84 à 26.02) • These differences might not be clinically relevant
Others	• Physiological parameters such as SaO2, or VE (minute ventilation), or

	exercise intensity, may be positively affected • Clinical relevance to be clarified
Patients preference	• No formal conclusion (due to the search strategy)
Productivity	• Our search does not yield published data

1.1.2 Patients necessitating palliative care (PC)

Mortality/ morbidity	• Our search does not yield published data
Quality of life (validated scales)	• Quality of life : no difference • Dyspnea: no difference • Fatigue : no difference
Exercise	• Exercise distance : no difference
Others	• Daily activity: no difference
Patients preference	• conflicting results between studies s
Productivity	• Our search does not yield published data

1.1.3 Heart failure (HF)

Mortality/ morbidity	• Mortality during 52 weeks: no difference
Quality of life (validated scales)	• Quality of life : no difference
Exercise	• Dyspnea at 3 minutes : no difference • Peak exercise testing : no difference • Dyspnea at 6 minutes : small difference of -0,84 (95%CI -1.26 to -0.22), on a VAS/Borg scale going from 0 to 10
Others	• Physiological parameters: changes in arousal index, apnoea-hypopnoea index (AHI), central apnoea index (CAI), sleep stage 1, sleep stage 2, and REM (rapid eye movement) sleep in favour of oxygen therapy, but no differences in total sleep time. • Clinical relevance to be clarified
Patients preference	• Our search does not yield published data
Productivity	• Our search does not yield published data

1.1.4 Cystic fibrosis (CF)

Mortality/ morbidity	• Survival at 36 months : no difference
Quality of life (validated scales)	• Our search does not yield published data
Exercise	• longer duration: 1,03 minute (95% CI 0.11 à 1.95) during maximal exercise.
Others	• Modification of physiological parameters • Clinical relevance to be clarified
Patients preference	• Our search does not yield published data

Productivity	• Improvement in regular attendance at school or work at 6 and 12 months

1.1.5 Interstitial lung disease (ILD)

Mortality/ morbidity	• Survival at 12, 24 and 36 months : no difference
Quality of life (validated scales)	• Our search does not yield published data
Exercise	• Our search does not yield published data
Others	• Modification of physiological parameters • Clinical relevance to be clarified
Patients preference	• Our search does not yield published data
Productivity	• Our search does not yield published data

2 COMPARISON OF AVAILABLE PRODUCTS

The search question is "How do the available products for home oxygen therapy compare with each other in terms of efficacy, safety, and convenience?"

It should be reminded that the answer to this question was mostly based on a narrative review. We only used a systematic review to find clinical studies comparing different oxygen supply systems.

There have been few comparative studies of different oxygen supply systems.

An AETMIS HTA report from Canada in 2004 about portable oxygen therapy in COPD concluded that there is very limited evidence about the clinical efficacy or cost effectiveness of portable oxygen therapy. To date, only one controlled trial has been conducted with these issues in mind. According to that study, portable oxygen equipment apparently offers no benefits in terms of quality of life, compliance with treatment or exercise tolerance. It should be pointed out, however, that the sample size in this trial was too small to generalize the results to all patients.

Another AETMIS HTA report on liquid oxygen therapy at home, published in 2005 reports there is very limited information about the effectiveness of liquid oxygen therapy in comparison to compressed gas delivery systems in terms of enhanced patient compliance, mobility or quality of life.

Existing systematic reviews did not select the studies according to the type of devices. Several devices are combined in systematic reviews about LTOT or about portable oxygen.

In terms of number of reported adverse events, data from France indicate that proportionally more serious adverse events occur with gaseous oxygen compared to the other systems (concentrators and liquid oxygen).

3 COST IN BELGIUM

The search question considers the cost comparison addressing the total cost in Belgium for home oxygen therapy between the different modalities and in different patient types.

Based on our own health economic evaluation it can be confirmed that LTOT in eligible COPD patients leads to an acceptable ratio between costs and effects. This conclusion is drawn based on cost data from the Belgian EPS data and health effects (reduction in mortality) obtained from meta-analyses. The cost of LTOT (222 Euro per month) was derived from a weighted average of all modalities as observed in the EPS database. The cost of the different modalities varied quite importantly with liquid oxygen being +/- 3 times more expensive than the average cost. It is thereby important to emphasize that the results are quite sensitive to the cost of oxygen and hence that the proportional use of the different modalities must be monitored very closely.

4 ORGANISATION MODELS

The search question considers the comparison of the Belgian model with models existing in France, the Netherlands, United Kingdom and Germany. The "a priori' idea was to capture any positive factors for improvement of LTOT in Belgium.

This review suffers from several methodological limitations including the use unstructured interviews, the absence of a systematic literature search, and lack of data about the real costs in each country. Nevertheless, we were able to get some information about the reimbursement policy in The Netherlands. The insurance company establishes the requirements to be fulfilling by the home care companies. A tender is then launched and the best cost/effective proposal is selected. Following this methodology, the average costs of oxygen therapy per patient have been reduced dramatically in the last 15 years. The cost of oxygen therapy (including devices and accessories) was 25.745.000 euros in 2009 for 29.500 users for a global population of 16.500.000 inhabitants (http://www.gipdatabank.nl).

Ideally, a European uniform and standardized prescription form should be used to be in accordance with the prescription rules/recommendations.

The responsibilities of the general practioners, pulmonologists, home care companies and pharmacists should be more clearly defined and standardized.

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Wettelijk depot : D/2011/10.273/23

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
7. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
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27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
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29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.
32. Feedback : onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport : deel II. D/2006/10.273/19.
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34. Trastuzumab bij vroegtijdige stadia van borstkanker. D/2006/10.273/23.
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