Clinical Evaluation Report

For

DeVilbiss

5 Liter Oxygen Concentrator (model 525) with accessories

and

iGo Portable Oxygen Concentrator (model 306) with accessories

Version 1.0

28 August 2015

Signature Page

Report Title	5 Liter Oxygen Concentrator (model 525) with accessories and iGo Portable Oxygen Concentrator (model 306) with accessories
Customer Name	DeVilbiss
Report Version	V1

Signature	Beata Wilkinson
Print Name	Beata Wilkinson PhD
Date of Signature	**28 August 2015**
Project Role	Report Writer

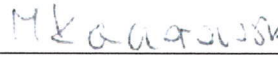
Approved by:

Signature	George Illar
Print Name	George Illar
Date of Signature	31 August 2015
Project Role	Quality Manager, DeVilbiss Healthcare

Signature	J. Chandra
Print Name	Chandra Jay
Date of Signature	31 August 2015
Project Role	Director of Quality & Regulatory Affairs, DeVilbiss Healthcare

Signature	
Print Name	Allan Jones
Date of Signature	August 31, 2015
Project Role	Director of Engineering, DeVilbiss Healthcare

I have read and evaluated this CER and conclude with its findings:

Signature	
Print Name	Malgorzata Kaczorowska MD PhD
Date of Signature	29 Aug. 2015
Project Role	Clinical Evaluator

The effective date is the date of the last signature.

Signature	
Print Name	Allan Jones
Date of Signature	
Project Role	Director of Engineering, DeVilbiss Healthcare

I have read and evaluated this CER and conclude with its findings:

Signature	MKaczorowska
Print Name	Malgorzata Kaczorowska MD PhD
Date of Signature	28 Aug. 2015
Project Role	Clinical Evaluator

The effective date is the date of the last signature.

TABLE OF CONTENTS

Executive statement

DeVilbiss is currently marketing two types of oxygen concentrators - the stationary 5 L Oxygen Concentrator (model 525) and the portable iGo Oxygen Concentrator (model 306) – to provide supplementary low flow oxygen therapy for patients suffering from chronic obstructive pulmonary disease (COPD), cardiovascular disease, and lung disorders. Both are class IIa devices in accordance with Annex II of 93/42/EEC, as amended by Directive 2007/47/EC.

The DeVilbiss Oxygen Concentrators models 525 and 306 have been in production since 2008 and 2009, respectively. These devices are produced to well-known designs. The clinical safety and performance of DeVilbiss oxygen concentrators were therefore evaluated based on: compliance with recognized standards; a literature review; and post-market surveillance data. Data on equivalent devices was included in the clinical evaluation.

This clinical evaluation has shown that both models 525 and 306 are acceptable for safety and performance if used according to their respective Instruction Guides. Both devices incorporate a full range of desirable safety features. The Instruction Guides for models 525 and 306 reflect current best use practices and inform clinicians and patients of potential problems and hazards associated with the improper use of these devices.

The articles retrieved in the literature search performed for this clinical evaluation suggest further improvements to the way assessments of portable pulse delivery devices (such as DeVilbiss iGo Oxygen Concentrator model 306) are made by clinicians.

Between 1 January 2010 and 19 June 2015 customer complaints were made to DeVilbiss at a rate of 3.4% and 9.3% for models 525 and 306, respectively. Significantly, no adverse events or other patient effects were noted in the complaints. Search of the FDA's MAUDE database over the same period of time for reports of incidents associated with equivalent devices (Respironics EverFlo and Respironics EverGo) identified reports of patient deaths and injuries for the EverFlo device only. Smoking while using the device was a factor in some deaths and injuries (a warning about this appears in the Instruction Guide for the DeVilbiss 5L Oxygen Concentrator), but for most incidents a causative link to the device could not be definitively established.

It is concluded that the clinical evidence appraised in this CER demonstrates conformity with the relevant Essential Requirements of the MDD. The performance and safety of the devices as claimed have been established. The devices are manufactured in such a way that when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the health and safety of the user. The risks associated with the use of these devices are acceptable when weighed against benefits to patients with chronic hypoxaemia requiring long term oxygen therapy.

No new hazards or complications related to DeVilbiss Oxygen Concentrators (models 525 and 306) were identified in this Clinical Evaluation Report. Therefore, DeVilbiss does not believe post-market clinical follow-up is required to support the safety and performance of these devices for their stated indications. The need for additional post-market clinical follow-up will continue to be evaluated as part of the clinical evaluation process during post-market surveillance activities in accordance with MEDDEV 2.12.2 Rev. 2.

Abbreviations

ABG	Arterial blood gas
BTS	British Thoracic Society
CBG	Capillary blood gas
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
FiO2	Fraction of inspired oxygen
LTOT	Long term oxygen therapy
PaO2	Arterial oxygen tension (partial pressure)
PO2	Oxygen tension (partial pressure) in blood or alveolus
SpO2	Arterial oxygen saturation measured by pulse oximetry
SaO2	Arterial oxygen saturation measured by blood analysis (blood gases)
6MWT	6 minute walk test

Partial pressure units of measurement and conversion between them:

- Partial pressures of oxygen and carbon dioxide are measured using kilopascals (kPa) and millimetres of mercury (mm Hg) where:
- 1 kPa=7.5 mm Hg, and 1 mm Hg=0.133 kPa. Details

1. General details

This clinical evaluation report (CER) pertains to two oxygen concentrators manufactured by DeVilbiss Healthcare (Somerset, PA, USA) – 5 Liter Oxygen Concentrator (model 525) and iGo Portable Oxygen Concentrator (model 306).

This CER is written in accordance with directives MEDDEV 2.7.1 Rev. 3 and MEDDEV 2.12.2 Rev. 2 to provide evidence of the medical safety and performance of DeVilbiss oxygen concentrators for their intended use.

DeVilbiss' oxygen concentrators are devices that produce an oxygen enriched gas mixture by drawing in ambient air and extracting nitrogen allowing oxygen to be delivered at a range of prescribed flows to patients with low blood oxygen saturation levels. The patient typically receives the oxygen through a nasal cannula. The oxygen concentrators are supplied with accessory devices.

DeVilbiss' oxygen concentrators (models 525 and 306) are class IIa devices in accordance with Annex II of 93/42/EEC, as amended by Directive 2007/47/EC.

The 5 Liter Oxygen Concentrator (model 525) was first released on the US market in February 2008. It was released in the EU market April of 2008. The iGo Oxygen Concentrator (model 306) was released on the US market and the EU market in January 2009.

2. Description of the Device and its Intended Application and Indications for Use

2.1 5 Liter Oxygen Concentrator (base model 525)

Description of device

The DeVilbiss 5 Liter Oxygen Concentrator (base model 525) is a 0.5 to 5.0 liter per minute (L/MIN) continuous flow pressure swing adsorption (PSA) type system that produces oxygen.

The 5 Liter Oxygen Concentrator consists of pneumatic and electrical components. The system has inlet filtration, air compressor, and synthetic zeolite molecular sieve beds with a pneumatic valve, outlet filtration, electronic flow measuring, manual thorpe tube flowmeter and audible/visual alarms.

Figure 1: 5 Liter Oxygen Concentrator with a humidifier attached

Operating principle

The DeVilbiss 5 Liter Oxygen Concentrator is based on molecular sieve technology. The technology employed to generate the oxygen is well established.

Room air is drawn into the concentrator via a piston style compressor. The air then passes through a series of filters that remove dust, bacteria, and other particulates. A pneumatic valve directs air into one of the two sieve beds. Nitrogen is adsorbed in the bed as the pressure increases while oxygen flows through, thereby producing an enriched oxygen product for the patient. Simultaneously in the other bed, nitrogen is desorbed as the pressure decreases and is exhausted into the atmosphere. A momentary intermediate pneumatic sequence ties the beds together with the exhaust blocked for an enhanced oxygen purge. The cycle continues, providing a continuous flow of oxygen at a purity of 93% +/-3% to the patient.

Components

The base model 525 Series includes the following parts:

Catalogue #	Item
525DS[1] / 525KS[2] / 525PS[2]	Oxygen Concentrator, AC power cord
525DZ-609	Gross particle filter
MC44D-605	Intake Filter
SE-525	Instruction guide

[1] NO CE MARK

[2] CE Marked

Specifications:

Dimension (H x W x D)	62.2 x 34.2 x 30.4 cm
Weight	16.3 kg
Flow rate	0.5 to 5 L/min
Oxygen concentration (at 0.5 – 5 L/min)	93% +/- 3%
Electrical requirements	115/230 VAC, 50/60Hz
Power consumption	approx. 290 Watt at 2 L/min; approx. 312 Watt at 5 L/min

Features

The simplified, two-piece cabinet design (compared to predicate device) allowed for 15% typical sound quality improvement and an improved cooling process. Paired with patented DeVilbiss Turn-Down Technology, these improvements minimize wear on internal components and increase the life expectancy of the unit.

Patient safety/comfort features:

- Units are equipped with an Oxygen Sensing Device (OSD®) with oxygen flow measurement capabilities.
- Visual and audible alarms for low oxygen levels, power failure, pressure drop and service required
- Oxygen outlet incorporating a fire protection adapter
- Front label with easy to read pictograms

Environmentally friendly:

- Intelligent power management system utilises Turn-Down technology providing less power consumption below flow rates of 2.5 L/min

Accessories

Many types of humidifiers, oxygen tubing and cannulas/masks can be used with the DeVilbiss 5 Liter Oxygen Concentrator, although certain humidifiers and accessories may impair the device's

performance. A mask or any nasal cannula can be used with continuous flow delivery and may be sized according to the patient's prescription.

Intended use/indications for use (as stated in the DeVilbiss 525 Series Instruction Guide)

The DeVilbiss 5 Liter Oxygen Concentrator intended use is to provide supplemental low flow oxygen therapy for patients suffering from COPD, cardiovascular disease, and lung disorders. The DeVilbiss Concentrator is intended for use in home type environments, homes, nursing homes, patient care facilities, etc.

The Instruction Guide recommends cleaning and disinfection of the device when there is a patient change.

2.2 iGo Portable Oxygen Concentrator (base model 306)

Description of device

The iGo Portable Oxygen Concentrator (base model 306) is an oxygen concentrator of the pressure vacuum swing adsorption (PVSA) type. The 306 Series is light weight and can operate on an external battery pack, features which allow the 306 Series to be readily transported by the patient. The iGo device also operates from AC and DC power.

The iGo Portable Oxygen Concentrator consists of pneumatic and electrical components. The system has inlet filtration, air compressor, heat exchanger, and synthetic zeolite molecular sieve beds with a pneumatic valve, outlet filtration, electronic flow control and audible/visual alarms.

Figure 2: **iGo Portable Oxygen Concentrator with battery and AC/DC power supplies**

Operating principle

Like the DeVilbiss 5 Liter Oxygen Concentrator, the 306 iGo device is based on molecular sieve technology.

However, the 306 iGo device has two operating modes: continuous product flow at up to 3 L/MIN and pulse dosage mode at settings of 1to 6. In pulse dosage mode, the concentrator delivers a bolus of oxygen when the start of inhalation is detected. This conserves the use of oxygen and also extends battery life. The oxygen is delivered at each inhalation in an amount equal to 14cc times the setting value. The integrated PulseDose® oxygen-conserving technology delivers brief and consistent bursts of oxygen even at higher breath rates. According to the product literature, for many patients, these short bursts are almost undetectable and more comfortable than continuous operation. PulseDose also helps reduce throat and nasal dryness.

The continuous flow mode is recommended for use during sleep.

Components

The base catalogue number for the unit is 306DS. The base model includes the following parts:

Catalogue #	**Item**
306DS	Transportable Oxygen Concentrator
306D-413	2 battery packs
306DS-651	AC/DC adapter
306DS-612	Exhaust Muffler
306DS-616	Bacteria filter - installed
306DS-611	Air filter - installed
A-306-1, A-306-2	Instruction Guide

Specifications

Dimensions (H x W x D)	38 x 28 x 20 cm
Weight	8.6 kg with battery; 7.0 kg without battery
Settings	1 to 6 in PulseDose mode; 1 to 3 L/MIN in Continuous Flow mode
Max. recommended continuous flow	3 L/MIN
Oxygen concentration	91% +/- 3% (all flow settings)
Operating temperature	5 - 40 deg C
Altitude	0-4,000 meters, tested @ approx. 933 hPa

Features

- As with the 5 Liter Oxygen Concentrator, built in OSD® (oxygen sensing device) ensures accurate oxygen delivery and reduced periodic maintenance schedule

- Increased Battery Capabilities – Can last as long as 5.4 hours when operating on setting 1 in PulseDose Mode
- Audible alerts for Power Failure, Low Battery, Low Oxygen Output, High Flow/Low Flow, No Breath Detected in PulseDose Mode, High Temperature, Unit Malfunction
- Can be used with 50 foot tubing/cannula in continuous flow mode and 35 foot tubing/cannula in PulseDose mode
- Sound Level (3.0 PulseDose Mode) 40 dBA
- OxyTrack Software provides an integrated solution for viewing performance and usage information on any DeVilbiss iGo Portable Oxygen System. With two software versions available, it's easy for technicians and clinicians to effectively monitor oxygen therapy. OxyTrack provides: real-time unit performance monitoring; error logs; email/print reports; patient usage history; compliance information

Accessories

Catalogue #	**Item**
306D-413	Spare Li ion battery pack
306DS-651	Stand-alone AC battery charger / adapter
306DS-652	DC adapter
306DS-625	iGo rolling carrying case
306DS-626	iGo detachable wheeled cart
306DS-635	Deluxe iGo carrying case
306DS-627	Remote humidifier stand labelled (DO NOT USE IN PULSE DOSE MODE)

Indications for Use (as stated in the DeVilbiss Model 306DS Instruction Guide)

The DeVilbiss Portable Oxygen Concentrator is intended to provide supplemental oxygen to persons requiring low flow oxygen therapy. It is used at a patient's home or for their portable needs outside the home and can also be used in institutions such as nursing homes or subacute care facilities.

The Instruction Guide recommends cleaning and disinfection of the device when there is a patient change.

3. Intended Therapeutic and/or Diagnostic Indications and Claims

3.1 Intended Therapeutic and/or Diagnostic Indications

3.1.1 Supplemental oxygen therapy

The following definitions of different forms of supplemental oxygen therapy are taken from the British Thoracic Society's guidelines for home oxygen use in adults (Hardinge et al., 2015).

Long-term oxygen therapy (LTOT) can be defined as oxygen used for at least 15 hours per day in chronically hypoxaemic patients. Chronic hypoxaemia is defined as a PaO2 ≤7.3 kPa or, in certain clinical situations, PaO2 ≤8.0 kPa. LTOT is delivered via an oxygen concentrator and should be differentiated from the use of oxygen as a palliative measure for symptomatic relief in breathless patients. A knowledgeable and experienced clinician should perform the initial assessment of the patient who is beginning to receive LTOT.

Nocturnal oxygen therapy (NOT) is oxygen administered overnight alone without additional oxygen therapy during awake or daytime hours. It is administered to patients who are either normoxic during the day, or have mild daytime hypoxaemia but do not fulfil LTOT criteria.

Ambulatory oxygen therapy (AOT) is defined as the use of supplemental oxygen during exercise and activities of daily living. In mobile patients who are not sufficiently hypoxaemic to qualify for LTOT but who desaturate on exercise, AOT has historically been used to optimise saturations and short-term exercise capacity. AOT is also often supplied to LTOT users, either to allow those who are mobile outdoors to optimise their exercise capacity, or to enable more immobile patients to leave the house in a wheelchair/scooter on occasion. AOT can be delivered from portable oxygen concentrators, cylinders with compressed air or liquid oxygen cylinders.

The term "palliative oxygen therapy" (POT) refers to the use of oxygen to relieve the sensation of refractory persistent breathlessness in advanced disease or life-limiting illness irrespective of underlying pathology where all reversible causes have been or are being treated optimally.

Oxygen can be delivered in three basic ways: via concentrator, compressed oxygen gas, and liquid oxygen. The least expensive and most efficient method to deliver oxygen therapy at home is via an oxygen concentrator. Portable systems are used for AOT and are critical for maintaining independence and quality of life for hypoxemic patients.

3.1.2 Patient groups requiring supplemental oxygen therapy

The main groups of patients requiring supplemental oxygen therapy are discussed in detail by Hardinge et al. (2015). A brief overview follows:

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease characterized by persistent airflow limitation. It typically worsens over time. Patients with COPD can develop nocturnal hypoxaemia due to ventilation–perfusion mismatch, decreased functional capacity and nocturnal hypoventilation particularly pronounced during REM sleep. This in turn can lead to poor sleep quality with sleep fragmentation. COPD is the only major cause of death whose incidence is on the increase and is expected to be the third leading cause of death worldwide by 2030 (www.copdcoalition.eu/about-copd/key-facts). Patients with advanced COPD often require LTOT.

Studies carried out in the 1980s showed that LTOT treatment in appropriately selected patients can improve survival rates by around 40%, irrespective of chronic hypercapnia and previous episodes of oedema or pulmonary hypertension. Subsequent studies have confirmed that patients with clinically stable COPD with chronic hypoxaemia have improved pulmonary haemodynamics and life expectancy when treated with LTOT for at least 15 hours per day. LTOT has also been shown to correct nocturnal SO2, decrease sleep latency and improve sleep quality for patients with COPD who develop hypoxaemia (Eaton et al., 2001).

Other diseases

Patients with respiratory diseases interstitial lung disease (ILD) and cystic fibrosis (CF) may develop chronic hypoxaemia, leading to development of complications. The use of LTOT in patients with ILD or CF may improve survival and tissue oxygenation, and prevent complications associated with hypoxaemia such as worsening pulmonary hypertension.

Pulmonary hypertension may occur in a number of pulmonary vascular disorders. The use of LTOT in non-COPD patients with pulmonary hypertension is to improve tissue oxygenation and to prevent complications associated with hypoxaemia, such as worsening pulmonary hypertension, rather than to afford a specific survival benefit. There is no evidence of the effectiveness of LTOT in patients with pulmonary hypertension, with the exception of those patients who develop pulmonary hypertension as a complication of their COPD. However, the use of LTOT in patients with pulmonary hypertension may improve tissue oxygenation and prevent complications associated with hypoxaemia.

Patients with neuromuscular disorder or chest wall disease may develop nocturnal hypoventilation, which causes nocturnal hypoxaemia and leads to chronic respiratory failure. LTOT is not generally used in these patients, but may be used where there is co-existing airways disease or obesity causing hypoxaemia which non-invasive ventilation alone does not correct.

Some patients with advanced cardiac failure may have resting hypoxaemia although hypoxaemia is most consistently demonstrated during sleep in these patients. The use of LTOT in patients with advanced cardiac failure and resting hypoxaemia may improve survival, tissue oxygenation and prevent complications associated with hypoxaemia.

Nocturnal oxygen therapy (NOT) can be ordered for severe heart failure patients who do not fulfil indications for LTOT, and have evidence of SDB leading to daytime symptoms, after other causes of nocturnal desaturation have been excluded (e.g., obesity hypoventilation or obstructive sleep apnoea) and heart failure treatment has been optimised.

Palliative oxygen therapy (POT) may on occasion be considered by specialist teams for patients with intractable breathlessness unresponsive to all other modalities of treatment. It may relieve the sensation of refractory persistent breathlessness in advanced disease or life-limiting illness irrespective of underlying pathology where all reversible causes have been or are being treated optimally.

Short burst oxygen therapy delivering high flow oxygen (12 L/min via a nonrebreather mask) is an effective symptomatic treatment for acute cluster headache attacks. It should be noted that flows of 12 L/min cannot be achieved with DeVilbiss oxygen concentrators.

3.1.3 LTOT delivery from oxygen concentrators

A concentrator can either be fixed in a room in the house or is portable to go with the patient around the home, outside the home and in the workplace. An oxygen concentrator is an electrically driven device which takes room air and passes it through a filtering system, removing nitrogen, to supply an oxygen enriched gas mixture (usually 85–95% oxygen). Performance of oxygen concentrators can vary depending on the technology used.

Home concentrators are installed and regularly maintained by oxygen provider companies. All concentrators should have fire breaks inserted into the tubing—one at the patient end and one at the machine end—to reduce the risk of potentially catastrophic fires. Most oxygen concentrators deliver flow rates of up to 4 L/min, adjustable in 0.5 L/min increments.

Pulse-dose oxygen delivery devices (PDOD), demand oxygen delivery systems (DODS) and other types of oxygen-conserving devices may be used with oxygen concentrators and are normally incorporated to extend the functional time or duration of use of the oxygen system. PDOD/DODS devices are normally either electronic or mechanical (pneumatic) and may be time-cycled and/or operate on demand, responding to a pressure drop triggered by the user's inspiratory effort. PDOD/DODS have varying performance characteristics, which include bolus volume, trigger sensitivity and trigger response time.

Transportable/portable concentrators are similar to home concentrators but smaller in size, weighing up to 8.6 kg. They come with batteries as well as a mains attachment, allowing use outside as well as inside the home. Inside the home, a transportable concentrator can be used as a standard concentrator as well as fulfilling the patient's ambulatory needs. The battery for use outside the home does limit the time they can be used without recharging and will depend on the flow rate and whether the pulsed mode is used. They can be used and charged in cars. Most are now approved for use on commercial aircraft. Current models are available that deliver up to 3 L/min continuous oxygen and 6 L/min pulsed oxygen, and come with a power adapter to plug into an electrical source, or a battery back-up.

Some portable oxygen concentrators provide both continuous and pulse flow options, for use while the patient is sleeping or sedentary and to ambulate around the home and while traveling.

Portable oxygen concentrators weighing less than 4.5 kg (typically 3.3-4.5 kg) provide pulsed oxygen only. Therefore, they are not suitable for use when sleeping.

Methods of oxygen pulse delivery

When not in continuous flow (if this is an option), all portable oxygen concentrators use an electronic conserver that is built into the unit, thus all use a pulse delivery method. There are two methods of pulse delivery:

- Minute Volume – this method delivers a fixed amount of oxygen per minute. The amount of oxygen delivered with each breath depends on the breathing rate of the user. Slower breathing rate equals larger amount of oxygen per breath; faster breathing rate equals smaller amount of oxygen per breath.
- Uniform Pulse – this method delivers the same amount of oxygen with every breath, regardless of the breathing rate. Slower breathing rate equals less oxygen over the course of a minute; faster breathing rate equals more oxygen over the course of a minute.

3.1.4 Guidelines for home oxygen use in adults

The most recent guidelines for home oxygen use in adults have been issued by the British Thoracic Society (BTS) in 2015 (Hardinge et al., 2015).

The BTS Home Oxygen Guideline provides evidence statements and recommendations for the use of home oxygen for adult patients out of hospital. Although the majority of evidence comes from the use of oxygen in patients with chronic obstructive pulmonary disease (COPD), the scope of the guidance includes patients with a variety of long-term respiratory illnesses and other groups in whom oxygen is currently ordered.

Grades of recommendations

Grade	Type of evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+
√	Important practical points for which there is no research evidence, nor is there likely to be any research evidence. The guideline committee wishes to emphasise these as Good Practice Points.

Grade	Evidence
1++	*High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias*
1+	*Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias*
1−	*Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	*High quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal*
2+	*Well conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal*
2−	*Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal*
3	*Non-analytic studies, for example case reports, case series*
4	*Expert opinion*
RCT: randomised control trial	

Selected evidence statements (full list can be found in the BTS Home Oxygen Guideline)

Evidence statement	Evidence level
Patients whose clinical condition is stable with a resting PaO ≤7.3 kPa have improved life expectancy when treated with LTOT for at least 15 h/day.	1+
Patients with stable COPD and a resting PaO2 ≤8.0 kPa with evidence of cor pulmonale, polycythaemia and/or pulmonary hypertension have improved outcomes with LTOT.	1+
Use of continuous oxygen therapy (24 h) offers additional survival benefit compared to shorter durations (12–15 h) but can contribute to higher PaCO2 levels.	1−
Use of LTOT in hypercapnic respiratory patients with COPD does not lead to increased morbidity, mortality or healthcare utilisation.	1+

Selected Recommendations (full list can be found in the BTS Home Oxygen Guideline)

Recommendation	Grade
Patients with stable COPD and a resting PaO2 ≤7.3 kPa should be assessed for LTOT, which offers survival benefit and improves pulmonary haemodynamics.	A
LTOT should be ordered for patients with stable COPD with a resting PaO2 ≤8 kPa with evidence of peripheral oedema, polycythaemia (haematocrit ≥55%) or pulmonary hypertension.	A
LTOT should be ordered for patients with resting hypercapnia if they fulfil all other criteria for LTOT.	B
Patients with a resting stable oxygen saturation (SpO2) of ≤92% should be referred for a blood gas assessment in order to assess eligibility for LTOT.	C
Patients should undergo formal assessment for LTOT after a period of stability of at least 8 weeks from their last exacerbation	B

LTOT should be ordered for a minimum of 15 h per day, and up to 24 h per day may be of additional benefit.	C
Patients eligible for LTOT should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until SpO2 >90%. An ABG should then be performed to confirm that a target PaO2 ≥8 kPa (60 mm Hg) at rest has been achieved.	B
Patients initiated on LTOT who are active outdoors should receive an ambulatory oxygen assessment to assess whether their flow rate needs increasing during exercise.	B
Oxygen concentrators should be used to deliver LTOT at flow rates of 4 L/min or less.	B
Portable oxygen should be delivered by whatever mode is best suited to the individual needs of the patient to increase the daily amount of oxygen used and activity levels in mobile patients.	C
The type of portable device selected should balance patient factors with cost effectiveness, resources and safety.	√
Patients initiated on LTOT should be provided with formal education by a specialist home oxygen assessment team to ensure compliance with therapy.	D

3.1.5 Paediatric use of oxygen concentrators

The paediatric use of DeVilbiss oxygen concentrators is determined by the physician and the medical providers. Paediatric use requires low flows. DeVilbiss markets a flow meter that can be used with its oxygen concentrators to provide low flows (1/8th litre increments) and the providers can use that flow meter when the physician prescribes use of an oxygen concentrator for paediatric use.

The British Thoracic Society issued separate guidelines for home oxygen use in children in 2009 which remain unchanged (Balfour-Lynn et al., 2009).

The range of conditions seen in children is quite distinct from adults. There is a tendency for children's diseases to improve with time, whereas with adults they tend to deteriorate. Exceptions in children include cystic fibrosis and neuromuscular disease.

Oxygen concentrators should be provided for LTOT, unless it is likely that the child will only require low flow oxygen for a short while. There is no evidence available to support whether an oxygen concentrator or cylinder is best for use in children. Oxygen concentrators are usually the preferred devices with large back-up cylinders for breakdown or power cuts. Low flow meters are preferable, but very low flow meters are not recommended. Low flow meters (0.1–1 L/min) must be available for infants and very young children.

3.2 Safety and/or Performance Claims

Safety and performance claims for the DeVilbiss oxygen concentrator devices (models 525 and 306) are in line with the Indications for Use presented in Section 2.1 and 2.2.

No additional specific safety or performance claims are made for the device in the Instruction Guides.

4. Context of the Evaluation and Choice of Clinical Data Types

4.1 Developmental Context

History of the technology

DeVilbiss 5L Oxygen Concentrator model 525 is produced to a well-known design. The current 525 model was introduced into the market in February 2008, but substantially equivalent predecessor devices have been on the market for over 15 years. Due to continuing improvements the current compact 525 model incorporates an expanded range of safety features. There are many similar competitor stationary oxygen concentrator devices on the market, including Respironics EverFlo, Invacare Perfecto2 V, AirSep VisionAire and Caire Companion 5.

The iGo (model 306) oxygen concentrator was introduced into the market in January 2009. These devices are produced to well-known designs. Comparable devices on the market deliver both continuous and pulse flow. They include Respironics SimplyGo, InvaCare SOLO2, SeQual Eclipse 5, and OxLife Independence. These devices are similar to stationary oxygen concentrators but smaller in size, weighing up to 8.6 kg. There are also smaller portable devices, weighing less than 4.5 kg, that only deliver pulse flow oxygen.

Essential Requirements

Please refer to the Essential Requirements Checklist included in the Technical File.

4.2 Justification of Clinical Data Type

According to MEDDEV 2.7.1 Rev.3 (2009) guidelines (section 5.1) clinical evaluation of medical devices that are based on existing, well established technologies and intended for an established use of the technology is most likely to rely on compliance with recognized standards and/or literature review and/or clinical experience with the device or equivalent devices.

DeVilbiss oxygen concentrators (models 525 and 306) have been on the market since 2008/2009. There is also long-term commercial experience with similar devices on the market. The clinical safety and performance of DeVilbiss oxygen concentrators are therefore evaluated based on: compliance with recognized standards; a literature review, and post-market surveillance data:

- The recognized standards to which compliance is claimed are listed in the Declaration of Conformity documents issued on 23 September 2014.
- Data generated through literature search that relates directly to the devices in question or to equivalent devices (MEDDEV 2.7.1, Rev,3, Section 6.1); and
- Post-market surveillance data: clinical experience with the DeVilbiss oxygen concentrators and equivalent devices on the market (section 6.2 MEDDEV 2.7.1 Rev 3, Section 6.2). This includes customer complaints made directly to DeVilbiss for both oxygen concentrators (models 525 and 306) and reports of suspected device-associated adverse events and malfunctions for the equivalent devices recorded in FDA's MAUDE database.

The Literature Review Report (Appendix A) contains details specific to the Literature Search Methodology and the Results of the Methodology. In addition, the Search of Key Words can be found in Appendix B.

The internal complaint summary and the output of the search of the MAUDE database for equivalent devices are provided in Appendix G.

4.3 Justification of Equivalent Devices

The tables below detail the similarities and differences among the oxygen concentrator devices that feature in the articles evaluated in section 6 (“Data Analysis”) of this CER. The analysis of equivalence is bbased on MEDDEV 2.7.1. Rev.3 Guidelines on Medical Devices (section 3.2.3).

Table 1 Stationary oxygen concentrators

Device characteristics	**Device manufacturer/name**			**GAP**
	DeVilbiss/ 5L Oxygen Concentrator (model 525)	Respironics/ EverFlo	Puritan Bennett/ Companion 492a	
CLINICAL				
Used for the same clinical condition or purpose	used to provide supplemental low flow oxygen therapy	used to provide supplemental low flow oxygen therapy	used to provide supplemental low flow oxygen therapy	No
Used at the same site in the body	pulmonary delivery via a nasal cannula	pulmonary delivery via a nasal cannula	pulmonary delivery via a nasal cannula	No
Used in a similar population (including age, anatomy, physiology)	patients with low blood oxygen saturation levels	patients with low blood oxygen saturation levels	patients with low blood oxygen saturation levels	No
Have similar relevant critical performance according to expected clinical effect for specific intended use	expected to improve symptoms associated with hypoxaemia	expected to improve symptoms associated with hypoxaemia	expected to improve symptoms associated with hypoxaemia	No
TECHNICAL/Functional				
Used under similar conditions of use	stationary device for home type environments	stationary device for home type environments	stationary device for home type environments	No
Have similar specifications and properties:				
Oxygen flow	0.5-5 L/min	0.5-5 L/min	0-4 L/min	Yes
Oxygen purity	93%+/-3%	93%+/-3%	95%+/-3% (at 1-3 L/min) 92%+/-3% (at 4 L/min)	Yes
Weight (kg)	16.3	14.0	25.6	Yes

Dimensions WxHxD (cm)	34x62x30	38x58x24	32x65x42	No (similar)
Materials used (raw material and final)	Contains synthetic zeolite	Contains synthetic zeolite	Contains synthetic zeolite	No
Source and composition of materials used	N/A - the unit is not in contact with the patient	N/A - the unit is not in contacts with the patient	N/A - the unit is not in contacts with the patient	No
Of similar design	Compact cabinet consists of pneumatic and electrical components	Compact cabinet consists of pneumatic and electrical components	Compact cabinet consists of pneumatic and electrical components	No
Use similar deployment methods (if relevant)	Used with a plastic cannula	Used with a plastic cannula	Used with a plastic cannula	No
Have similar principles of operation	Based on molecular sieve technology	Based on molecular sieve technology	Based on molecular sieve technology	No
BIOLOGICAL				
Use same biocompatible materials in contact with the same human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	No
Animal-origin materials present	*No*	No	No	No
Presence of human blood derivatives	*No*	No	No	No

Information used to populate the table above has been sourced from the devices' Instructions for Use, 510k summaries, marketing brochures and published studies (Appendix D).

Comments on the significance of the findings: The key performance descriptor for the oxygen concentrator devices is the oxygen purity performance at .5-5 L/M of oxygen output.

There are slight differences between the three stationary, compact devices but any GAPs are not substantial. EverFlo is an equivalent device. There are only small differences between the DeVilbiss 525 device and Companion 492a. The latter device is the subject of a study described in section 6.1.2. employing flows of 2 L/min. The Companion 492a device will be considered "equivalent" to the DeVilbiss 525 device for the purposes of this evaluation.

Table 2 Portable oxygen concentrators

Device characteristics	Device manufacturer/name			GAP
	DeVilbiss/ iGo Oxygen Concentrator (model 306)	SeQual/ Eclipse 3	Respironics/ EverGo	
CLINICAL				
Used for the same clinical condition or purpose	used to provide supplemental low flow oxygen therapy	used to provide supplemental low flow oxygen therapy	used to provide supplemental low flow oxygen therapy	No
Used at the same site in the body	pulmonary delivery via a nasal cannula	pulmonary delivery via a nasal cannula	pulmonary delivery via a nasal cannula	No
Used in a similar population (including age, anatomy, physiology)	patients with low blood oxygen saturation levels	patients with low blood oxygen saturation levels	patients with low blood oxygen saturation levels	No
Have similar relevant critical performance according to expected clinical effect for specific intended use	expected to improve symptoms associated with hypoxaemia	expected to improve symptoms associated with hypoxaemia	expected to improve symptoms associated with hypoxaemia	No
TECHNICAL/Functional				
Used under similar conditions of use	for the patient's portable needs outside the home as well as home use	for the patient's portable needs outside the home as well as home use	for the patient's portable needs outside the home as well as home use	No
Have similar specifications and properties:				
Oxygen delivery method	Continuous up to 3 L/min; Pulse-dose settings 1-6	Continuous up to 3 L/min; Pulse-dose settings 1-6	N/A Pulse-dose settings 1-6	Yes (EverGo)
Oxygen pulse-dose bolus volume, ml	14-84	16-192	12-70	Yes (Eclipse 3)

Oxygen purity	91%+/-3% (all flow settings)	90%+/-3%	89%+/-3%	No
Trigger sensitivity,cm H_2O	-0.05 to -0.12	-0.15 to 0.45	-0.2	Yes
Weight (kg)	8.6 with one battery	8.4 with one battery	4.5 with two batteries	Yes (EverGo)
Dimensions WxHxD (cm)	28x38x20	31x49x18	15x22x31	Yes (EverGo)
Materials used (raw material and final)	Contains synthetic zeolite	Contains synthetic zeolite	Contains synthetic zeolite	No
Source and composition of materials used	N/A - the unit is not in contact with the patient	N/A - the unit is not in contacts with the patient	N/A - the unit is not in contacts with the patient	No
Of similar design	Compact cabinet consists of pneumatic and electrical components	Compact cabinet consists of pneumatic and electrical components	Compact cabinet consists of pneumatic and electrical components	No
Use similar deployment methods (if relevant)	Used with a plastic cannula	Used with a plastic cannula	Used with a plastic cannula	No
Have similar principles of operation:				
Oxygen purification	based on molecular sieve technology	based on molecular sieve technology	based on molecular sieve technology	No
Operating modes	both continuous and pulse flow	both continuous and pulse flow	pulse flow only	Yes (EverGo)
Pulse flow method	Uniform Pulse (fixed volume of oxygen per pulse)	Uniform Pulse (fixed volume of oxygen per pulse)	Uniform Pulse (fixed volume of oxygen per pulse)	No
BIOLOGICAL				
Use same biocompatible materials in contact with the same human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	No

Animal-origin materials present	*No*	No	No	No
Presence of human blood derivatives	*No*	No	No	No

Information used to populate the table above has been sourced from the devices' Instructions for Use (IFU), 510k summaries, marketing brochures and published studies (Appendix D).

Comments on the significance of the findings: All three devices can deliver pulse flow oxygen and all deliver uniform pulse. The main differences between the devices are highlighted. When operating in the pulse mode, the main difference is the maximum volume of the oxygen pulse that can be delivered. With the exception of the differences highlighted, the three devices are considered equivalent for pulse dose oxygen delivery with respect to their other characteristics.

Table 3 Portable oxygen concentrators (contd.)

Device characteristics	Device manufacturer/name			GAP
	DeVilbiss/ iGo Oxygen Concentrator (model 306)	Inogen/ Inogen One G2	CAIRE/ AirSep LifeStyle (superseded by AirSep FreeStyle)	
CLINICAL				
Used for the same clinical condition or purpose	used to provide supplemental low flow oxygen therapy	used to provide supplemental low flow oxygen therapy	used to provide supplemental low flow oxygen therapy	No
Used at the same site in the body	pulmonary delivery via a nasal cannula	pulmonary delivery via a nasal cannula	pulmonary delivery via a nasal cannula	No
Used in a similar population (including age, anatomy, physiology)	patients with low blood oxygen saturation levels	patients with low blood oxygen saturation levels	patients with low blood oxygen saturation levels	No
Have similar relevant critical performance according to expected clinical effect for specific intended use	expected to improve symptoms associated with hypoxaemia	expected to improve symptoms associated with hypoxaemia	expected to improve symptoms associated with hypoxaemia	No
TECHNICAL/Functional				
Used under similar conditions of use	for the patient's portable needs outside the home as well as home use	for the patient's portable needs outside the home as well as home use	for the patient's portable needs outside the home as well as home use	No
Have similar specifications and properties:				
Oxygen delivery method	Continuous up to 3 L/min; Pulse-dose settings 1-6	Continuous: N/A Pulse-dose settings 1-5	Continuous: N/A Pulse-dose settings 1-5	Yes
Oxygen pulse-dose bolus volume, ml	14-84	N/A	No data for settings	Yes

Oxygen purity	91%+/-3% (all flow settings)	90%-3% / +6% (all flow settings)	90%+/-3% (all flow settings)	No
Trigger sensitivity (cm H_2O)	-0.05 to -0.12	-0.12	no data	Yes
Weight (kg)	8.6 with one battery	3.2 with one battery	4.4	Yes
Dimensions WxHxD (cm)	28x38x20	10x24x27	18x14x41	Yes
Materials used (raw material and final)	Contains synthetic zeolite	Contains synthetic zeolite	Contains synthetic zeolite	No
Source and composition of materials used	N/A - the unit is not in contact with the patient	N/A - the unit is not in contacts with the patient	N/A - the unit is not in contacts with the patient	No
Of similar design	Compact cabinet consists of pneumatic and electrical components	Compact cabinet consists of pneumatic and electrical components	Compact cabinet consists of pneumatic and electrical components	No
Use similar deployment methods (if relevant)	Used with a plastic cannula	Used with a plastic cannula	Used with a plastic cannula	No
Have similar principles of operation:				
Oxygen purification	based on molecular sieve technology	based on molecular sieve technology	based on molecular sieve technology	No
Operating modes	both continuous and pulse flow	pulse flow only	pulse flow only	Yes
Pulse flow method	Uniform Pulse (fixed volume of oxygen per pulse)	Fixed Minute Volume (fixed amount of oxygen per minute)	Uniform Pulse (fixed volume of oxygen per pulse)	Yes
BIOLOGICAL				

Use same biocompatible materials in contact with the same human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	The basic unit is not in contact with human tissues or body fluids	No
Animal-origin materials present	*No*	No	No	No
Presence of human blood derivatives	*No*	No	No	No

Information used to populate the table above has been sourced from the devices' Instructions for Use (IFU), 510k summaries, marketing brochures and published studies (Appendix D).

Comments on the significance of the findings: Only iGo delivers both continuous and pulse flow oxygen. There are a few other differences between the devices. The main difference is that Image One delivers fixed amounts of oxygen per minute, while iGo and AirSep LifeStyle both deliver fixed volume of oxygen per pulse.

5. Summary of the Clinical Data and Appraisal

The following clinical data sets have been used in the clinical evaluation of DeVilbiss oxygen concentrators (models 525 and 306):

Safety Data	**Performance Data**
2 Publications	4 Publications
Customer Complaints: • Oxygen Concentrator model 525 • Oxygen Concentrator model 306	
Reports of adverse events in FDA's MAUDE: • DeVilbiss concentrators (models 525 and 306) – no reports • 2 equivalent devices	

Details of the table above, along with data appraisal methods used in the evaluation, including any weighting criteria, and a summary of the key results can be found in the following appendixes:

- Data generated through literature search (Appendixes A, B, C, D and E)
- Post market surveillance report (Appendix G)
- Risk management reports (Appendix I)

6. Data Analysis

6.1 Description of analysed data used to assess the device safety

6.1.1 Literature review

6.1.1.1 Devices of concern

DeVilbiss' oxygen concentrators are intended for long term use by patients, and therefore the features they possess must ensure their safe operation. An early study evaluated the features of six stationary oxygen concentrators, including DeVO2, a predecessor to the current 525 model, in the laboratory (Johns et al., 1985).

The study concluded that the main disadvantage of concentrators compared with cylinders is the possibility of machine failure or power failure. However, this risk can be minimized if a stock of spare parts and a standby machine centrally located are readily available.

The study also highlighted significant differences between the models tested as regards safety features. It should be noted that many of these devices are now outdated and technology has superseded them. The investigators concluded that, in addition to safety features relating to electric shock hazard and fire hazard, other safety features may be considered desirable, including:

- Purity of the gas: (i) Outlet filter to exclude the possibility of sieve material reaching the patient; (2) Inlet filter(s) for both dust and bacteria.
- Dosage (and maintenance scheduling) Time elapsed meter
- Correct function (i) Visual and audible alarms to include indication of (a) power failure and (b) inlet filter blockage/system pressure failure. (ii) Alarm test facility whereby the integrity of the battery powering the alarm can be checked. (iii) Power on-off switch that illuminates when in the on position.

The DeVO2 was one of DeVilbiss original models that was manufactured from 1979 to 1981. It had most of the desirable safety features, but lacked visual alarms. Current models have visual and audible alarms that are tested and those tests are documented in the Device History Records as the units are assembled. They also incorporate an oxygen sensing device and low oxygen alarm.

6.1.1.2 Equivalent devices

Risk of uncorrected hypoxaemia with the use of stationary oxygen concentrators

In hypoxaemic patients with chronic respiratory disease formal assessment of long term oxygen therapy (LTOT) is required which is usually conducted in the hospital and performed on wall (piped) oxygen to ensure correction of the hypoxaemia. However, an oxygen concentrator is the standard oxygen source for the patient at home who requires LTOT. The oxygen concentration delivered is lower from a concentrator than piped oxygen.

Bolton et al. (2006) carried out a study of ten hypoxaemic patients using both delivery sources in a cross-over design. Patients were randomly commenced on either wall oxygen (five of 10 patients) or an oxygen concentrator (Puritan Bennett Companion 492a). The concentration of oxygen delivered by the concentrator was measured on two occasions, 12 months apart, during the study period. The patients received oxygen for 30 minutes at a flow rate of 2L/min, via nasal cannulae following which a blood gas sample was taken and analysed immediately. The method of oxygen delivery was then reversed and further blood gas samples were taken after 30 minutes. Finally the patient was given the original source for 30 minutes and the last blood gas samples taken. The flow rate was always maintained at 2L/min via the nasal cannulae. The PaO_2 of the patients on both the concentrator and wall oxygen were compared. The mean difference of 6.4 mmHg (=0.84 kPa) between the sources was significant at P = 0.02, regardless of which source was used first.

Although this was a small study, it demonstrated significantly lower PaO_2 measured in the patients who were receiving oxygen via a concentrator compared to wall oxygen. This suggests that clinicians should consider formally assessing patients on an oxygen concentrator in order to ensure that the hypoxaemia will be corrected when they are prescribed a concentrator for home use. Continuing to conduct the assessments on wall oxygen, whilst prescribing a concentrator for home use could lead to uncorrected hypoxaemia with potential survival implications if a PaO_2 greater than 60mmHg is not achieved. As different types of concentrators deliver slightly different concentrations of oxygen, the ideal assessment would be performed on the same make and model as the patient would have at home.

Use of portable pulsed-dose oxygen concentrators during sleep

Despite the widespread use of pulsed-dose oxygen concentrators in awake and ambulating patients, few studies report their use during sleep. A common concern regarding their use during sleep is the effect of slower respiratory rate and smaller tidal volume (hypoventilation) on oxygenation. In a study conducted by Chatburn et al. (2006), Inogen One was able to maintain adequate oxygen saturation (SpO_2) during sleep comparable to continuous-flow oxygen in 9 of 10 patients. The authors attribute this finding to the fact that Inogen One operates on the “fixed minute volume” principle; the device has a microprocessor that monitors the respiratory rate and adjusts the bolus volume to maintain a consistent minute volume of oxygen. Lobato et al. (2011) caution against the use of Inogen One connected to a non-invasive ventilator (NIV) at night. The authors speculate that NIV may hinder triggering of portable oxygen concentrators.

The finding of safe use of Inogen One during sleep cannot be extrapolated to oxygen concentrators that operate on the “uniform pulse volume” principle (such as iGo).

6.1.2 Post-market surveillance data (DeVilbiss)

Complaints, CAPAs and recalls (DeVilbiss L Liter Oxygen Concentrator model 525)

The overall complaints rate for the 5 Liter Oxygen Concentrator over the period 1 January 2012 – 19 June 2015 was 3.4% per unit sold (Appendix G). No patient effect was noted in the complaints. The most frequently reported issues for the 5 Liter Oxygen Concentrator were sieve bed issues (23.0%) and compressor issues (15.8%).

There were no CAPAs or recalls on the 5 Liter Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

There were no records identified in the MAUDE database involving the 5 Liter Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

Complaints, CAPAs and recalls (iGo Portable Oxygen Concentrator model 306)

The overall complaints rate for the iGo Portable Oxygen Concentrator (model 306) over the period 1 January 2012 – 19 June 2015 was 9.3% per unit sold (Appendix G). No patient effect was noted in the complaints. The most frequently reported issues for the iGo Portable Oxygen Concentrator were key pad issues (32.6%), valve issues (17.4 %), and sieve bed issues (14.2%).

There were no CAPAs or recalls on the iGo Portable Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

There were no records identified in the MAUDE database involving the iGo Portable Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

6.1.3 Post-market surveillance data (equivalent devices)

Searches were carried out for equivalent devices in the FDA’s MAUDE database over the period 1 January 2012 to 19 June 2015.

Respironics EverFlo

Respironics EverFlo is a device equivalent to DeVilbiss 5L Oxygen Concentrator model 525 (see section 4.3, Table 1). Seventy reports of individual events were identified for EverFlo that occurred within the specified timeframe. Of these 70 reports, 11 described patient deaths, 39 described patient injuries and 20 described device malfunctions.

Smoking was found to be a contributing factor in two of the incidents resulting in patient death. Product labeling instructs not to smoke while using the device. There was one case in which a power outage caused the EverFlo device to stop functioning and the patient was unable to utilize their backup oxygen. In the remaining eight cases it was not possible to determine definitive device involvement in the patient deaths.

There were 39 reports of injuries for Respironics EverFlo device. The most frequently reported injury involved smoking while using the device (nine reports). There were eight reports that the device may have caused or exacerbated a medical condition, but no definitive evidence was provided linking the device to the medical condition. There were eight reports of injuries resulting from issues with oxygen delivery; two of these were confirmed as due to device malfunctions. There were six reports of fire events involving the device, but the device was not returned for evaluation in four of the reported events; the device was found not to have caused or contributed to the fire in the other two cases. There were three reports of injuries resulting from a solenoid valve issue. The remaining five injuries were due to miscellaneous issues.

Full details of all of the MAUDE findings can be found in Appendix G.

Respironics EverGo

Respironics EverGo is a device equivalent to DeVilbiss iGo portable Oxygen Concentrator model 306 (see section 4.3, Table 2). Eight records were identified for EverGo. All described device malfunctions. Of these eight records, two described device malfunctions that did not result in patient injury and six described device malfunctions that did result in patient injury.

Full details of all of the MAUDE findings can be found in Appendix G.

6.2 Description of analysed data used to assess the device performance

6.2.1 Literature review

6.2.1.1 Devices of concern

Meeting oxygen needs during exercise (iGo)

Patients with chronic lung disease using long term oxygen therapy benefit from an active lifestyle, and portable oxygen systems are of particular interest to this patient population. Leblanc et al. (2013) compared the ability of 3 portable oxygen concentrators (POCs) to maintain SpO_2 > 90% during exercise in patients with chronic lung disease. Twenty-one subjects with chronic lung disease (18 with COPD, 3 with pulmonary fibrosis) and documented room air exertional SpO2 < 85% performed four 6-min walk tests: a control walk using the subject's current oxygen system and prescribed exertional flow rate, and one walk with each of the 3 POCs (iGo, Eclipse 3, and EverGo) at their maximum pulse-dose setting. The order in which POCs were used was randomly assigned for each subject. Each 6-min walk test was separated by a minimum 20-min rest period. Subjects were placed on the assigned POC 10 minutes prior to the next walk. SpO_2 was measured continuously during the walk. The therapist terminated a walk if the subject's SpO_2 reached <85% for any length of time. SpO_2 was significantly higher pre-walk and post-walk with the Eclipse 3, compared to the other POCs (all P < 0.01). The subjects also walked farther and maintained a mean SpO_2 > 90% with the Eclipse 3 (both P <0.01). The authors suggested that the larger oxygen pulse bolus volume of the Eclipse 3 was an important contributing factor enabling it to better meet the subjects' oxygen needs during exercise.

The authors concluded that users of portable oxygen concentrators should be appropriately tested during all activities of daily living, to ensure adequate oxygenation. The healthcare provider should

provide information and help to direct the subject toward the most clinically appropriate oxygen system, while being mindful of the patient's preferences and lifestyle.

6.2.1.2 Equivalent devices

Meeting oxygen needs during exercise (portable oxygen concentrators)

Nasilowski et al. (2008) conducted a randomised, single-blind clinical trial involving 13 COPD patients with respiratory failure. The aim of the study was to determine if a portable oxygen concentrator delivering a uniform pulse of oxygen (AirSep LifeStyle) is as effective as liquid oxygen in reducing exercise-induced hypoxaemia in severe COPD patients on long term oxygen therapy.

All patients underwent a series of 6-min walk tests carried out in random order among one of the three devices: AirSep LifeStyle portable oxygen concentrator, liquid oxygen cylinder (LOC) and cylinder with compressed air (CA). Oxygen supplementation was 3 L/min for LO and an equivalent to 3 L/min in AirSep LifeStyle (at this setting the bolus according to manufacturer is 26.25 cm^3; it should be noted that the total amount of inhaled oxygen per minute depends on bolus amount and number of breaths).

The mean SpO_2 was equally improved at rest: 92.9%+/-2.8% with LifeStyle and 91.7%+/-2.0% with LO compared 87.8%+/-2.7% with CA (LifeStyle and LO vs. CA $p<0.05$). LifeStyle and LO significantly improved oxygenation during 6-min walk test (mean SpO_2 was 84.3%+/-5% and 83.8%+/-4.2%, respectively) compared to breathing CA 77.6%+/-7.4%, $p<0.05$. These results suggest that the effects of oxygen supplementation with LifeStyle device did not differ from the LO portable units during the 6-min walk test in walking distance and SpO_2. It appears that the LifeStyle device may be safely used for ambulatory oxygen treatment.

The mean oxygen flow prescribed for patients in this study in resting condition was 1.7+/-0.7 L/min. The study showed that continuous flow or equivalent to 3 L/min of oxygen, which corresponded approximately to doubling resting dose, did not prevent hypoxaemia during strenuous exercise. However, it may be sufficient during less vigorous activities of daily life. The authors suggested that in order to prevent hypoxaemia during strenuous exercise three-fold increase of oxygen flow should be prescribed.

6.3 Product Literature and Instructions for Use

All residual risks identified through the risk activities performed by the manufacturer during product development to evaluate the two oxygen concentrators (model 525 and model 306) have been addressed during the development of DeVilbiss oxygen concentrators (models 525 and 306) (525 Oxygen Concentrator Risk Management Report Rev 1, issued 1/3/2008; and 306D Oxygen Concentrator, issued 10/10/2008). The DeVilbiss 5 Liter Oxygen Concentrator Instruction Guide and the DeVilbiss iGo Model 306 Instruction Guide carry comprehensive safety information about hazards (in particular, fire) that may arise due to improper use of the equipment and that could result in serious injury or death. Both Instruction Guides describe a wide range of safety features incorporated into the design of these devices.

Both guides stress that the oxygen concentrators must be used according to the prescription determined by the patient's physician and the patient is cautioned not to increase or decrease the flow of oxygen.

Both guides follow established guidelines in instructions/warnings/cautions/notes for the users of the devices. The iGo Model 306 Instruction Guide also follows guidelines in its instructions to the physician's/respiratory therapists. These instructions are as follows:

1. Use only continuous flow mode of operation with patients who breathe below 6 Breaths Per Minute (BPM); refer to specifications for maximum breath rate.

2. Use only continuous flow mode of operation with patients who consistently fail to trigger equipment (i.e. mouth breathing with closed soft palates).

3. PulseDose settings should be determined for each patient individually. Settings from continuous flow applications may not be applicable to PulseDose mode.

4. Verify patient is getting adequate Pa02 or Sa02 levels in PulseDose delivery mode.

5. Use only standard nasal cannula with PulseDose delivery. Do not use pediatric (low-flow) nasal cannula with PulseDose delivery. Any nasal cannula can be used with continuous flow delivery.

6. PulseDose settings should be determined for each patient individually. Settings from Continuous Flow applications may not be applicable to PulseDose Mode.

7. Do not use with other equipment (i.e. humidifier, nebulizer, etc.) when in PulseDose delivery mode.

Further in the 306 Instruction Guide “Operating your iGo” the instructions 5-7 above are repeated for the patients’ benefit. The following warnings are highlighted:

WARNING: As with conserving devices, the iGo may not be able to detect some respiratory efforts in PulseDose mode.

WARNING: Under certain circumstances, oxygen therapy can be hazardous. Seeking medical advice before using an oxygen concentrator is advisable. It is very important to follow your oxygen prescription. Do not increase or decrease the flow of oxygen - consult your physician.

Suggested improvements to assessments of portable devices

The articles retrieved in the literature search and analysed in section 6.1 and 6.2 suggest improvements to the way assessments of portable pulse delivery devices are made by the clinicians. These suggestions have not yet been incorporated into official guidelines. The prescribing clinicians are to urged to consider formally assessing patient on an oxygen concentrator that is being prescribed rather than wall oxygen to ensure that hypoaemia will be corrected (Leblanc et al. (2013) and testing individual patients’ needs during typical exercise activities to ensure adequate oxygenation (Leblanc et al. (2013).

Use of the iGo (model 306) oxygen concentrator during sleep

A common concern regarding the use of portable oxygen concentrators in the pulse dose mode during sleep (the effect of slower respiratory rate and smaller tidal volume on oxygenation). The literature review provides support for the use of devices operating on the constant minute volume principle only (Chatburn et al., 2006). The iGo Model 306 Instruction Guide does not contain any information about use of the portable device during sleep, but the website www.igopoc.com recommends the continuous flow mode for use during sleep. The iGo Model 306 Instruction Guide does carry the following information for the patient: “When operating in PulseDose mode, an alert will beep after 30 seconds if a breath is not detected. If another 60 seconds elapses and no breath is detected, the unit will switch to Continuous Flow at the last Continuous Flow setting used”.

7. Post Market Surveillance and Clinical Follow-Up

Post Market Clinical Follow-up (PMCF), in accordance with MEDDEV 2.12.2 is considered for devices where identification of possible emerging risks and the evaluation of long term safety and performance are critical. In identifying such emerging risk, the following checklist has been completed for the DeVilbiss Oxygen Concentrators (models 525 and 306).

It should be noted that PMCF studies may not be required when the medium/long-term safety and clinical performance are already known from historical use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the risks.

(When answering the following questions, new is defined as the product having a new indication for use which is not cleared/approved for any other device in the market.)

Risk Criteria that may justify a PMCF study:	**Yes**	**No**	**NA**
• **innovation, e.g., where the design of the device, the materials, substances, the principles of operation, the technology or the medical indications are novel**		No	
• **significant changes to the products or to its intended use for which premarket clinical evaluation and re-certification has been completed**		No	
• **high product related risk e.g. based on design, materials, components, invasiveness, clinical procedures**		No	
• **high risk anatomical locations**		No	
• **high risk target populations e.g. paediatrics, elderly**	Yes		
• **severity of disease/treatment challenges**	Yes		
• **questions of ability to generalize clinical investigation results**		No	
• **unanswered questions of long-term safety and performance**		No	
• **results from any previous clinical investigation, including adverse events or from post-market surveillance activities**		No	
• **identification of previously unstudied subpopulations which may show different benefit/risk-ratio e.g. hip implants in different ethnic populations**		No	
• **continued validation in cases of discrepancy between reasonable premarket follow-up time scales and the expected life of the product**		No	
• **risks identified from the literature or other data sources for similar marketed devices**		No	
• **interaction with other medical products or treatments**		No	
• **verification of safety and performance of device when exposed to a larger and more varied population of clinical users**		No	
• **emergence of new information on safety or performance**		No	
• **where CE marking was based on equivalence***		No	

It has been determined that the long-term clinical data demonstrate acceptable safety and performance for the DeVilbiss oxygen concentrator's (models 525 and 306) intended use. No additional hazards or complications related to these devices were identified in this Clinical Evaluation Report that have not been considered in the risk documentation or Instruction Guides.

Therefore, DeVilbiss does not believe post-market clinical follow-up is required to support the safety and performance of the oxygen concentrators (models 525 and 306) for their stated indications. The need for additional post-market clinical follow-up will continue to be evaluated as part of the clinical evaluation process during post-market surveillance activities in accordance with MEDDEV 2.12.2 Rev. 2.

8. Conclusions

The DeVilbiss Oxygen Concentrators models 525 and 306 have been in production since 2008 and 2009, respectively. This clinical evaluation has shown that both are acceptable for safety and performance if used according to their respective Instruction Guides. The devices incorporate a full range of desirable safety features. The Instruction Guides reflect current best use practices and inform clinicians and patients of potential problems and hazards associated with the improper use of these devices.

The articles retrieved in the literature search performed for this clinical evaluation and analysed in section 6 suggest further improvements to the way assessments of portable pulse delivery devices (such as DeVilbiss iGo Oxygen Concentrator model 306) are made by clinicians.

The iGo Oxygen Concentrator model 306 Instruction Guide does not contain a recommendation about use of this device during sleep, but the website www.igopoc.com recommends the continuous flow mode for use during sleep. This information would be conveyed to the patient by the prescribing physician. Devices delivering constant pulse volume have not been tested in the sleep clinic. Therefore DeVilbiss will add a statement to future editions of the Instruction Guide recommending against the use of the device in pulse mode during sleep. It should be noted that the iGo unit will automatically switch to continuous flow mode after 90 seconds if a breath is not detected.

The DeVilbiss Oxygen Concentrators (models 525 and 306) have been in production since 2008/2009. The overall complaints rate (complains per unit sold) over the period 1 January 2011 – 19 June 2015 was 3.4% for model 525 and 9.3% for model 306. Significantly, no adverse events or other patient effects were noted in the complaints. Search of the FDA's MAUDE database over the period 1 January 2011 to 1 March 2015 for reports of incidents associated with Respironics EverFlo (a device equivalent to the DeVilbiss 5L Oxygen Concentrator) identified reports of patient deaths and injuries in addition to device malfunctions. Smoking while using the device was a factor in some deaths and injuries (a warning about this appears in the Instruction Guide for the DeVilbiss 5L Oxygen Concentrator), but for most incidents a causative link to the device could not be definitively established. Only eight malfunctions were reported for Respironics EverGo (a device equivalent to the DeVilbiss iGo portable oxygen concentrator) over the same period of time.

It can be concluded that the clinical evidence appraised in this CER demonstrates conformity with the relevant Essential Requirements of the MDD. The performance and safety of the devices as claimed have been established. The devices are manufactured in such a way that when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the health and safety of the user. The risks associated with the use of the devices are acceptable when weighed against benefits to patients with chronic hypoxaemia requiring long term oxygen therapy.

No new hazards or complications related to DeVilbiss Oxygen Concentrators (models 525 and 306) were identified in this Clinical Evaluation Report. Therefore, DeVilbiss does not believe post-market clinical follow-up is required to support the safety and performance of these devices for their stated indications. The need for additional post-market clinical follow-up will continue to be evaluated as part of the clinical evaluation process during post-market surveillance activities in accordance with MEDDEV 2.12.2 Rev. 2.

As part of post market surveillance review safety, performance, and the clinical benefit risk assessment of the device will be performed and appropriate updates will be made to the clinical evaluation.

Appendix A: Literature Review Report

1. Device name/model: DeVilbiss 5 Liter Oxygen Concentrator (model 525) and iGo Portable Oxygen System (model 306)

2. Scope of the literature search: A comprehensive search aimed at identifying all publications relating to the safety and performance of DeVilbiss oxygen concentrators and equivalent devices

3. Methods

(i) Date of search: 30 July 2015 and 4 August 2015

(ii) Search performed by: Beata Wilkinson

(iii) Period of search: 2005 - current

(iv) Literature sources used to identify data: Search performed on PubMed.

PubMed is a service of the US National Library of Medicine® that:

- Provides free access to MEDLINE®, the NLM® database of indexed citations and abstracts to medical, nursing, dental, veterinary, health care, and preclinical sciences journal articles
- Includes additional selected life sciences journals not in MEDLINE
- Adds new citations daily
- Was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM)

(v) Database search - details in Appendix B

(vi) Selection criteria used to choose articles:

Selection criteria used to choose articles were established prior to abstract review.

Articles were selected for inclusion if they met all of the following criteria:

- Included devices of interest or equivalent devices
- Article provided enough information to evaluate the safety and performance of the applicable product
- Human research
- English language
- Clinical Trial, Comparative Study, Case Reports

4. Outputs

(i) Copy of literature citations retrieved from each database search - listed in Appendix C

(ii) Data selection process - All citations were assessed for suitability for inclusion in the clinical evaluation - details in Appendix D.

Appendix B: Search of keywords

Advanced searches performed in PubMed:

Search #1

Search: (((oxygen) AND (concentrator OR "concentration system" OR "concentrating system" OR generator OR "generation system" OR "generating system")) AND patient) NOT monoxide Filters: Clinical Trial, Case Reports, Comparative Study, From 1995/01/01 to 2015/07/31, Humans, English

Results: 48

Search #2

Search: "iGo" Filters: Case Reports, Clinical Trial, Comparative Study, 5 years, Humans

Results: 9

Appendix C: 1st level of selection: excluded articles

Exclusion Code	Exclusion Criteria
E1	Not featuring oxygen concentrator(s)
E2	Unspecified oxygen concentrator(s)
E3	Not addressing safety or performance of oxygen concentrator(s)
E4	Oxygen concentrator(s) for different target population or use than the device under evaluation

Search #1 Results: 48

Author(s)	Date	Title	Journal	Exclusion reason
Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE 2nd, Marcello J, Young IH, Bull J, Wilcock A, Booth S, Wheeler JL, Tulsky JA, Crockett AJ, Currow DC.	2010	Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial.	Lancet. 2010 Sep 4;376(9743):784-93.	E2
Akerø A, Edvardsen A, Christensen CC, Owe JO, Ryg M, Skjønsberg OH.	2011	COPD and air travel: oxygen equipment and preflight titration of	Chest. 2011 Jul;140(1):84-90.	E2

		supplemental oxygen.		
Andersson A, Ström K, Brodin H, Alton M, Boman G, Jakobsson P, Lindberg A, Uddenfeldt M, Walter H, Levin LA.	1998	Domiciliary liquid oxygen versus concentrator treatment in chronic hypoxaemia: a cost-utility analysis.	Eur Respir J. 1998 Dec;12(6):1284-9.	E3
Biedunkiewicz B, Tylicki L, Rachon D, Hak L, Nieweglowski T, Chamienia A, Debska-Slizien A, Mysliwska J, Rutkowski B.	2004	Natural killer cell activity unaffected by ozonated autohemotherapy in patients with end-stage renal disease on maintenance renal replacement therapy.	Int J Artif Organs. 2004 Sep;27(9):766-71.	E1
Bolton CE, Annandale JA, Ebden P.	2006	Comparison of an oxygen concentrator and wall oxygen in the assessment of patients undergoing long term oxygen therapy assessment.	Chron Respir Dis. 2006;3(1):49-51.	Include
Borggrefe MM, Lawo T, Butter C, Schmidinger H, Lunati M, Pieske B, Misier AR, Curnis A, Böcker D, Remppis A, Kautzner J, Stühlinger M, Leclerq C, Táborsky M, Frigerio M, Parides M, Burkhoff D, Hindricks G.	2008	Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure.	Eur Heart J. 2008 Apr;29(8):1019-28. doi: 10.1093/eurheartj/ehn020. Epub 2008 Feb 12.	E1
Burioka N, Takano K, Suyama H, Chikumi H, Hoshino E, Sasaki T.	1997	Efficacy of newly developed pressure swing adsorption type oxygen concentrator with	Intern Med. 1997 Dec;36(12):861-4.	E1

		membrane humidifier: comparison with conventional oxygen concentrator with bubble water humidifier.		
Butter C, Wellnhofer E, Schlegl M, Winbeck G, Fleck E, Sabbah HN.	2007	Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption.	J Card Fail. 2007 Mar;13(2):137-42.	E1
Campbell AJ, Ferrier K, Neill AM.	2012	Effect of oxygen versus adaptive pressure support servo-ventilation in patients with central sleep apnoea-Cheyne Stokes respiration and congestive heart failure.	Intern Med J. 2012 Oct;42(10):1130-6.	E2
Chatburn RL, Lewarski JS, McCoy RW.	2006	Nocturnal oxygenation using a pulsed-dose oxygen-conserving device compared to continuous flow.	Respir Care. 2006 Mar;51(3):252-6.	Include
Cullen DL, Koss JA.	2005	Oxygen tubing lengths and output flows: implications for patient care.	Chron Respir Dis. 2005;2(4):193-7.	E1
Das SK, Das S.	1995	Study of clinical anaesthesia with pedius A anaesthesia system using	J Indian Med Assoc. 1995 Oct;93(10):377-9.	E1

		ketamine or halothane with muscle relaxant.		
De Ridder D, Vanneste S, Van Laere K, Menovsky T.	2013	Chasing map plasticity in neuropathic pain.	World Neurosurg. 2013 Dec;80(6):901.	E1
Dogra G, Ward N, Croft KD, Mori TA, Barrett PH, Herrmann SE, Irish AB, Watts GF.	2001	Oxidant stress in nephrotic syndrome: comparison of F(2)-isoprostanes and plasma antioxidant potential.	Nephrol Dial Transplant. 2001 Aug;16(8):1626-30.	E1
Fauroux B, Boulé M, Lofaso F, Zérah F, Clément A, Harf A, Isabey D.	1999	Chest physiotherapy in cystic fibrosis: improved tolerance with nasal pressure support ventilation.	Pediatrics. 1999 Mar;103(3):E32.	E1
Gierula J, Cubbon RM, Jamil HA, Byrom R, Baxter PD, Pavitt S, Gilthorpe MS, Hewison J, Kearney MT, Witte KK.	2013	Cardiac resynchronization therapy in pacemaker-dependent patients with left ventricular dysfunction.	Europace. 2013 Nov;15(11):1609-14. doi: 10.1093/europace/eut148. Epub 2013 Jun 4.	E1
Grianti F, Montecchia F, Di Bari L, Baldassarri M.	1996	A versatile mechanical ventilator (DIGIT) with high flow stability and a programmable inspiratory phase flow pattern.	IEEE Trans Biomed Eng. 1996 Nov;43(11):1062-72.	E1
Grossebner M, Arifi A, Bourov Y, Taylor G, Gray S, Ritchie A.	1999	No change in O2 saturation but measurable difference in thenar flexor power after radial artery harvest.	Eur J Cardiothorac Surg. 1999 Aug;16(2):160	E1

Herrero P, Hartman JJ, Green MA, Anderson CJ, Welch MJ, Markham J, Bergmann SR.	1996	Regional myocardial perfusion assessed with generator-produced copper-62-PTSM and PET.	J Nucl Med. 1996 Aug;37(8):1294-300.	E1
Jackson M, Shneerson J.	1998	An evaluation of the use of concentrators for domiciliary oxygen supply for less than 8 h day-1.	Respir Med. 1998 Feb;92(2):250-5.	E3
Jansson S, Lie-Karlsen K, Stenqvist O, Körner U, Lundholm K, Tisell LE.	2001	Oxygen consumption in patients with hyperthyroidism before and after treatment with beta-blockade versus thyrostatic treatment: a prospective randomized study.	Ann Surg. 2001 Jan;233(1):60-4.	E1
Katsenos S, Charisis A, Daskalopoulos G, Constantopoulos SH, Vassiliou MP.	2006	Long-term oxygen therapy in chronic obstructive pulmonary disease: the use of concentrators and liquid oxygen systems in north-western Greece.	Respiration. 2006;73(6):777-82. Epub 2006 Jun 30.	E2
Khaing TT, Yu S, Brock-Utne JG.	1997	Inspired oxygen concentrations with or without an oxygen economizer during ether draw-over anaesthesia.	Anaesth Intensive Care. 1997 Aug;25(4):417-9.	E4
Khairy P, Landzberg MJ, Gatzoulis MA, Mercier LA, Fernandes SM, Côté JM,	2006	Transvenous pacing leads and systemic thromboemboli in patients	Circulation. 2006 May 23;113(20):2391-7.	E1

Lavoie JP, Fournier A, Guerra PG, Frogoudaki A, Walsh EP, Dore A; Epicardial Versus ENdocardial pacing and Thromboembolic events Investigators.		with intracardiac shunts: a multicenter study.	Epub 2006 May 15.	
Ko D, Heck C, Grafton S, Apuzzo ML, Couldwell WT, Chen T, Day JD, Zelman V, Smith T, DeGiorgio CM.	1996	Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging.	Neurosurgery. 1996 Aug;39(2):426-30; discussion 430-1.	E1
Kuroda M, Kawamoto M, Yuge O.	2005	Undisrupted pulse wave on pulse oximeter display monitor at cardiac arrest in a surgical patient.	J Anesth. 2005;19(2):164-6.	E1
Lacasse Y, Lecours R, Pelletier C, Bégin R, Maltais F.	2005	Randomised trial of ambulatory oxygen in oxygen-dependent COPD.	Eur Respir J. 2005 Jun;25(6):1032-8.	E2
Lobato SD, Rodríguez EP, Alises SM.	2011	Portable pulse-dose oxygen concentrators should not be used with noninvasive ventilation.	Respir Care. 2011 Dec;56(12):1950-2.	Include
MacLeod JB, Gravelin S, Jones T, Gololov A, Thomas M, Omondi B, Bukusi E.	2009	Assessment of acute trauma care training in Kenya.	Am Surg. 2009 Nov;75(11):1118-23.	E3
Milési C, Matecki S, Jaber S, Mura T, Jacquot A, Pidoux O, Chautemps N, Novais AR, Combes C, Picaud JC,	2013	6 cmH2O continuous positive airway pressure versus conventional oxygen therapy in	Pediatr Pulmonol. 2013 Jan;48(1):45-51. doi: 10.1002/ppul.22533. Epub 2012 Mar 19.	E1

Cambonie G.		severe viral bronchiolitis: a randomized trial.		
Moll JR, Vieira JE, Gozzani JL, Mathias LA.	2014	Oxygen concentrators performance with nitrous oxide at 50:50 volume.	Braz J Anesthesiol. 2014 May-Jun;64(3):164-8. doi: 10.1016/j.bjane.2013.06.011. Epub 2013 Oct 11.	E4
Mwenge GB, Rombaux P, Dury M, Lengelé B, Rodenstein D.	2013	Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study.	Eur Respir J. 2013 Feb;41(2):360-7. doi: 10.1183/09031936.00042412. Epub 2012 May 17.	E1
Nasilowski J, Przybylowski T, Zielinski J, Chazan R.	2008	Comparing supplementary oxygen benefits from a portable oxygen concentrator and a liquid oxygen portable device during a walk test in COPD patients on long-term oxygen therapy.	Respir Med. 2008 Jul;102(7):1021-5. doi: 10.1016/j.rmed.2008.02.005. Epub 2008 Mar 21.	Include
Nonoyama ML, Brooks D, Guyatt GH, Goldstein RS.	2008	Ambulatory gas usage in patients with chronic obstructive pulmonary disease and exertional hypoxemia.	J Cardiopulm Rehabil Prev. 2008 Sep-Oct;28(5):323-9. doi: 10.1097/01.HCR.0000336144.79192.5e.	E2
Page E, Defaye P, Bonnet JL, Durand C, Amblard A.	2003	Comparison of the cardiopulmonary response to exercise in recipients of dual sensor DDDR pacemakers Versus a Healthy control group.	Pacing Clin Electrophysiol. 2003 Jan;26(1 Pt 2):239-43.	E1
Petrakis E, Sciacca V.	2000	Prospective study of	Int Angiol. 2000 Mar;19(1):18-25.	E1

		transcutaneous oxygen tension (TcPO2) measurement in the testing period of spinal cord stimulation in diabetic patients with critical lower limb ischaemia.		
Pittau F, Levan P, Moeller F, Gholipour T, Haegelen C, Zelmann R, Dubeau F, Gotman J.	2011	Changes preceding interictal epileptic EEG abnormalities: comparison between EEG/fMRI and intracerebral EEG.	Epilepsia. 2011 Jun;52(6):1120-9. doi: 10.1111/j.1528-1167.2011.03072.x. Epub 2011 Apr 19.	E1
Prior JO, Allenbach G, Valenta I, Kosinski M, Burger C, Verdun FR, Bischof Delaloye A, Kaufmann PA.	2012	Quantification of myocardial blood flow with 82Rb positron emission tomography: clinical validation with 15O-water.	Eur J Nucl Med Mol Imaging. 2012 Jun;39(6):1037-47. doi: 10.1007/s00259-012-2082-3. Epub 2012 Mar 8.	E1
Ragab A, Shreef E, Behiry E, Zalat S, Noaman M.	2009	Randomised, double-blinded, placebo-controlled, clinical trial of ozone therapy as treatment of sudden sensorineural hearing loss.	J Laryngol Otol. 2009 Jan;123(1):54-60.	E1
Reisfield GM, Wilson GR.	2004	The cost of breathing: an economic analysis of the patient cost of home oxygen therapy.	Am J Hosp Palliat Care. 2004 Sep-Oct;21(5):348-52.	E3
Ringbaek T, Martinez G, Lange P.	2013	The long-term effect of ambulatory oxygen in normoxaemic COPD	Chron Respir Dis. 2013 May;10(2):77-84.	E4

		patients: a randomised study.		
Rodriquez D Jr, Blakeman TC, Dorlac W, Johannigman JA, Branson RD.	2010	Maximizing oxygen delivery during mechanical ventilation with a portable oxygen concentrator.	J Trauma. 2010 Jul;69 Suppl 1:S87-93. doi: 10.1097/TA.0b013e3181e44b27.	E4
Sofic E, Sapcanin A, Tahirovic I, Gavrankapetanovic I, Jellinger K, Reynolds GP, Tatschner T, Riederer P.	2006	Antioxidant capacity in postmortem brain tissues of Parkinson's and Alzheimer's diseases.	J Neural Transm Suppl. 2006;(71):39-43.	E1
Su CL, Lee CN, Chen HC, Feng LP, Lin HW, Chiang LL.	2014	Comparison of domiciliary oxygen using liquid oxygen and concentrator in northern Taiwan.	J Formos Med Assoc. 2014 Jan;113(1):23-32. doi: 10.1016/j.jfma.2012.03.013. Epub 2012 Jun 21.	E2
Sutton PJ, Perkins CL, Giles SP, McAuley DF, Gao F.	2005	Randomised controlled cross-over comparison of continuous positive airway pressure through the Hamilton Galileo ventilator with a Dräger CF 800 device.	Anaesthesia. 2005 Jan;60(1):72-6.	E1
Trivedi NS, Ghouri AF, Shah NK, Lai E, Barker SJ.	1997	Effects of motion, ambient light, and hypoperfusion on pulse oximeter function.	J Clin Anesth. 1997 May;9(3):179-83.	E1
Yamauchi R, Morita A, Yasuda Y, Grether-Beck S, Klotz LO, Tsuji T, Krutmann J.	2004	Different susceptibility of malignant versus nonmalignant human T cells toward ultraviolet A-1 radiation-induced apoptosis.	J Invest Dermatol. 2004 Feb;122(2):477-83.	E1

Zygun DA, Nortje J, Hutchinson PJ, Timofeev I, Menon DK, Gupta AK.	2009	The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury.	Crit Care Med. 2009 Mar;37(3):1074-8. doi: 10.1097/CCM.0b013e318194ad22.	E1

Search #2

Engelman CD, Meyers KJ, Iyengar SK, Liu Z, Karki CK, Igo RP Jr, Truitt B, Robinson J, Sarto GE, Wallace R, Blodi BA, Klein ML, Tinker L, LeBlanc ES, Jackson RD, Song Y, Manson JE, Mares JA, Millen AE.	2013	Vitamin D intake and season modify the effects of the GC and CYP2R1 genes on 25-hydroxyvitamin D concentrations.	J Nutr. 2013 Jan;143(1):17-26. doi: 10.3945/jn.112.169482.	E1
Krim SR, Vivo RP, Patel A, Xu J, Igo SR, Zoghbi WA, Little SH.	2012	Direct assessment of normal mechanical mitral valve orifice area by real-time 3D echocardiography.	JACC Cardiovasc Imaging. 2012 May;5(5):478-83. doi: 10.1016/j.jcmg.2011.06.024	E1
Leblanc CJ, Lavallée LG, King JA, Taylor-Sussex RE, Woolnough A, McKim DA.	2013	A comparative study of 3 portable oxygen concentrators during a 6-minute walk test in patients with chronic lung disease.	Respir Care. 2013 Oct;58(10):1598-605. doi: 10.4187/respcare.02275	Include
Louttit MD, Kopplin LJ, Igo RP Jr, Fondran JR, Tagliaferri A, Bardenstein D, Aldave AJ, Croasdale CR, Price MO, Rosenwasser GO, Lass JH, Iyengar SK; FECD Genetics Multi-	2012	A multicenter study to map genes for Fuchs endothelial corneal dystrophy: baseline characteristics and heritability.	Cornea. 2012 Jan;31(1):26-35. doi: 10.1097/ICO.0b013e31821c9b8f.	E1

Center Study Group.				
Meyers KJ, Mares JA, Igo RP Jr, Truitt B, Liu Z, Millen AE, Klein M, Johnson EJ, Engelman CD, Karki CK, Blodi B, Gehrs K, Tinker L, Wallace R, Robinson J, LeBlanc ES, Sarto G, Bernstein PS, SanGiovanni JP, Iyengar SK.	2014	Genetic evidence for role of carotenoids in age-related macular degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS).	Invest Ophthalmol Vis Sci. 2014 Jan 29;55(1):587-99. doi: 10.1167/iovs.13-13216.	E1
Sun Y, Wei Z, Li N, Zhao Y.	2013	A comparative overview of immunoglobulin genes and the generation of their diversity in tetrapods.	Dev Comp Immunol. 2013 Jan-Feb;39(1-2):103-9. doi: 10.1016/j.dci.2012.02.008.	E1
Thavendiranathan P, Liu S, Datta S, Rajagopalan S, Ryan T, Igo SR, Jackson MS, Little SH, De Michelis N, Vannan MA.	2013	Quantification of chronic functional mitral regurgitation by automated 3-dimensional peak and integrated proximal isovelocity surface area and stroke volume techniques using real-time 3-dimensional volume color Doppler echocardiography: in vitro and clinical validation.	Circ Cardiovasc Imaging. 2013 Jan 1;6(1):125-33. doi: 10.1161/CIRCIMAGING.112.980383.	E1
Verhoeven VJ, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, Höhn R, MacGregor S, Hewitt AW, Nag A, Cheng CY, Yonova-Doing E, Zhou X, Ikram MK, Buitendijk GH, McMahon G, Kemp JP, Pourcain BS, Simpson CL, Mäkelä KM, Lehtimäki T, Kähönen M, Paterson AD,	2013	Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia.	Nat Genet. 2013 Mar;45(3):314-8. doi: 10.1038/ng.2554. Epub 2013 Feb 10.	E1

Hosseini SM, Wong HS, Xu L, Jonas JB, Pärssinen O, Wedenoja J, Yip SP, Ho DW, Pang CP, Chen LJ, Burdon KP, Craig JE, Klein BE, Klein R, Haller T, Metspalu A, Khor CC, Tai ES, Aung T, Vithana E, Tay WT, Barathi VA; Consortium for Refractive Error and Myopia (CREAM), Chen P, Li R, Liao J, Zheng Y, Ong RT, Döring A; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, Evans DM, Timpson NJ, Verkerk AJ, Meitinger T, Raitakari O, Hawthorne F, Spector TD, Karssen LC, Pirastu M, Murgia F, Ang W; Wellcome Trust Case Control Consortium 2 (WTCCC2), Mishra A, Montgomery GW, Pennell CE, Cumberland PM, Cotlarciuc I, Mitchell P, Wang JJ, Schache M, Janmahasatian S, Igo RP Jr, Lass JH, Chew E, Iyengar SK; Fuchs' Genetics Multi-Center Study Group, Gorgels TG, Rudan I, Hayward C, Wright AF, Polasek O, Vatavuk Z, Wilson JF, Fleck B, Zeller T, Mirshahi A, Müller C, Uitterlinden AG, Rivadeneira F, Vingerling JR, Hofman A, Oostra BA, Amin N, Bergen AA, Teo YY, Rahi JS, Vitart V, Williams C, Baird PN, Wong TY, Oexle K, Pfeiffer N, Mackey DA,				

Young TL, van Duijn CM, Saw SM, Bailey-Wilson JE, Stambolian D, Klaver CC, Hammond CJ.				
Zhang X, Igo RP Jr, Fondran J, Mootha VV, Oliva M, Hammersmith K, Sugar A, Lass JH, Iyengar SK; Fuchs' Genetics Multi-Center Study Group.	2013	Association of smoking and other risk factors with Fuchs' endothelial corneal dystrophy severity and corneal thickness.	Invest Ophthalmol Vis Sci. 2013 Aug 27;54(8):5829-35.	E1

In addition, an article provided by DeVilbiss, (Johns et al., 1985) was included in 2nd level of selection.

Appendix D: 2nd level of selection: included and excluded articles

Author/ Date / Ref	*Clinical results: Safety, performance and equivalence*	*Criteria for suitability (mandatory)*				*Oxford level of evidence (optional)*	*Comments*	*Included: Yes/No*
CE Bolton, JA Annandale and P Ebden (2006) Comparison Of An Oxygen Concentrator And Wall Oxygen In The Assessment Of Patients Undergoing Long Term Oxygen Therapy Assessment. Chronic Respiratory Disease 3: (pp 49-51)	• *Description of the study:* Cross-over design study using both piped wall oxygen and an oxygen concentrator. • *Number of patients* : *1*0 (adult) • *Follow-up* : NA • *Procedure* : After 30 minutes of rest, the patient was started on either piped wall oxygen or an oxygen concentrator for 30 minutes at 2L/minute via nasal speculae. After 30 minutes, an arterial blood gas (ABG) was taken and analysed immediately. The oxygen delivery method was then switched. Another ABG was taken. The patient was returned to the original oxygen source for 30 minutes. The final ABG was taken. • *Device Name* :	**D2**	**A1**	**P1**	**R1**	Level 2		Yes

	Piped wall oxygen or Puritan Bennett Companion 492a							
	• **Safety:** description and relevance NA • **Performance:** description and relevance PaO2 was significantly lower in patients who received oxygen via an oxygen concentrator than those who received oxygen via piped wall oxygen. The oxygen concentration delivered by the study concentrator was 93% on both occasions it was tested.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Author/ Date / Ref	***Clinical results: Safety, performance and equivalence***	***Criteria for suitability (mandatory)***				***Oxford level of evidence (optional)***	***Comments***	***Included: Yes/No***
Robert L Chatburn RRT-NPS FAARC, Joseph S Lewarski RRT FAARC, and Robert W McCoy RRT FAARC (2006) Nocturnal Oxygenation Using a Pulsed-Dose Oxygen-	• *Description of the study:* This study compared the heart rate and oxygen saturation of sleeping patients receiving oxygen via a pulsed dose oxygen conserving device (PDOCD) or continuous flow oxygen. Each patient acted as their own control. • *Number of patients* : 10 (adults) • *Follow-up* :NA • *Procedure* :	**D3**	**A1**	**P1**	**R1**	Level 2	The Inogen One provided the same clinical benefit as a continuous-flow nasal cannula in 90% of a small sample of patients during sleep. The authors attributed this to the “fixed minute volume” mode of operation. The result cannot be extrapolated to devices utilizing “uniform pulse” (such as iGo)	Yes (significance of the different modes of oxygen pulse delivery)

Conserving Device Compared to Continuous Flow Respiratory Care 51(3) 252-256	Each patient was switched from continuous flow oxygen to pulsed dose oxygen. The pulsed dose oxygen was adjusted to produce an SpO2 equal to the SpO2 on continuous flow. The mean PDOCD setting was 3 (range1-5) • *Device Name* : Inogen One, (Inogen, Goleta, California)							
	• **Safety:** description and relevance One patient in the default (lower) sensitivity group experienced a clinically important lowerSpO2 with the PDOCD than with continuous-flow (86% vs 97%), and the oxygen concentrator data log suggested that he frequently failed to trigger the PDOCD throughout the sleep period. Note: No device adjustments were performed during the single-night sleep study. In actual clinical practice this situation could be remedied by increasing the oxygen sensitivity and setting during sleep. • **Performance:** description and relevance Patients slept an average of 1 hour more when using the PDOCD than continuous flow. There was a statistically significant but clinically unimportant difference in SpO2 between continuous flow and PDOCD							

	(95.7% vs 93.2%, p = 0.043). For the subset of patients whose PDOCD was set on sensitive, there was a statistically significant but clinically unimportant difference in SpO2 (continuous-flow 95.6% vs PDOCD 93.2%, p=0.044). No difference in heart rate was detected.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Author/ Date / Ref	***Clinical results:*** ***Safety, performance and equivalence***	***Criteria for suitability (mandatory)***	***Oxford level of evidence (optional)***	***Comments***	***Included: Yes/No***

C.LeBlanc, L.Lavallee, J.King, et al (2013) A Comparative Study of 3 Portable Oxygen Concentrators During a 6-Minute Walk Test in Patients With Chronic Lung Disease Respiratory Care 58(10) pp 1598-1605	• *Description of the study:* Comparison of the ability of 3 portable oxygen concentrators to maintain SpO2 ≥ 90% during exercise • *Number of patients* : 21 (adult) • *Follow-up* : NA • *Procedure* : Four 6-minute walking tests were performed. First test used the current oxygen system and prescribed exertional flow rate. The remaining tests used each of the portable oxygen concentrators at their maximum pulse-dose setting. • *Device Name* : EverGo (Respironics, Murrysville, Pennsylvania), iGo (DeVilbiss Healthcare, Summerset, Pennsylvania), Eclipse 3 (Caire Medical, Ball Ground, Georgia).	**D1**	**A1**	**P1**	**R1**	Level 2	Bolus size can be an important factor in determining the effectiveness of a POC. Lifestyle factors should be taken in consideration in choosing a POC system.	Yes

	• **Safety:** description and relevance N/A • **Performance:** description and relevance The SpO2 was significantly higher pre-walk and post-walk with the Eclipse 3, compared to the other POCs (all P < .01). The subjects also walked farther and maintained a mean SpO2 > 90% with the Eclipse 3 (both P < .01), which delivers the largest oxygen bolus. The subjects indicated that they preferred the EverGo's physical characteristics, but that the Eclipse 3 responded best to their breathing. The iGo was rated less favorably than Eclipse 3 or EverGo during preference testing.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Author/ Date / Ref	***Clinical results: Safety, performance and equivalence***	***Criteria for suitability (mandatory)***				***Oxford level of evidence (optional)***	***Comments***	***Included: Yes/No***
Salvador Díaz Lobato PhD, Esteban Pe´rez Rodríguez PhD, and Sagrario Mayoralas Alises PhD (2011) Portable Pulse-Dose Oxygen Concentrators Should Not Be Used With Noninvasive Ventilation. Respiratory Care 56(12):1950-1952	• *Description of the study:* This is a case study report of one patient who without a medical recommendation, was using a portable oxygen concentrator during nocturnal non-invasive ventilation (NIV). • *Number of patients* : 1 (adult) • *Follow-up* : *N/A* • *Procedure* : Laboratory testing with the patient using the concentrator and ventilator was conducted. • *Device Name* :	**D3**	**A1**	**P1**	**R3**	Level 4	Pulse-dose oxygen technology generally works by detecting the patient's inspiratory effort and triggering the delivery of a bolus of oxygen in the first 100 ms of the inspiration. The oxygen flow then turns off until the next inspiration is detected. Like other portable oxygen concentrators, the Inogen One uses pressure sensing to identify the onset of inspiration. The Inogen One also monitors the respiratory rate and adjusts the bolus volume to maintain a consistent minute volume of oxygen. The NIV inspiratory and expiratory pressures in the ventilator circuit prevented the Inogen One from identifying the onset of inspiration, so the	Yes (in association with Chatburn et al., 2006)

	Inogen One, (Inogen, Goleta, California)						concentrator simply did not work as it is supposed to.	
	• **Safety:** description and relevance N/A • **Performance:** description and relevance The concentrator did not detect the patient's inspiratory effort or deliver the preset oxygen flow at any of the tested settings.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Author/ Date / Ref	***Clinical results: Safety, performance and equivalence***	***Criteria for suitability (mandatory)***				***Oxford level of evidence (optional)***	***Comments***	***Included: Yes/No***
JR Moll, JE Vieira, JL Gozzani et al (2013) Oxygen Concentrators Performance With Nitrous Oxide At 50:50 Volume Brazilian Society of Anesthesiology 64(3):164-168	• *Description of the study:* *Comparison study of surgical patients receiving either oxygen from concentrators or oxygen from concentrators plus nitrous oxide.* • *Number of patients* : 60 (adults) • *Follow-up* : N/A • *Procedure* : Adult patients were randomly allocated into two groups, receiving a fresh gas flow of oxygen from concentrators (O293) or of oxygen from concentrators and nitrous oxide (O293N2O). The fraction of inspired oxygen and the percentage of oxygen from fresh gas flow were measured every 10 min. The ratio of FiO2/oxygen concentration delivered was compared at various time intervals and between the groups • *Device Name* : 0293	**D2 or D3**	**A3**	**P3**	**R1**	Level 2	Concentrators connected to medical gas pipeline systems can be considered a stable source of oxygen for use during short anesthetic procedures, either pure or in association with nitrous oxide at 50:50 volume.	No (not a listed indication for DeVilbiss 5L oxygen concentrator)

	• **Safety:** description and relevance N/A • **Performance:** description and relevance There was no difference in oxygen from concentrators over time for both groups, but there was a significant improvement in the FiO2 ($p < 0.001$) for O293 group while a significant decline ($p < 0.001$) for O293N2O. The FiO2/oxygen ratio varied in both groups, reaching a plateau in the O293 group. Pulse oximetry did not fall below 98.5% in either group.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Author/ Date / Ref	***Clinical results: Safety, performance and equivalence***	***Criteria for suitability (mandatory)***				***Oxford level of evidence (optional)***	***Comments***	***Included: Yes/No***
J Nasilowski, T Przybylowski, J Zielinski et al (2008) Comparing Supplementary Oxygen Benefits From A Portable Oxygen Concentrator And A Liquid Oxygen Portable Device During A Walk Test In COPD Patients On Long-Term Oxygen Therapy Respiratory Medicine102: (pp 1021-1025)	• *Description of the study:* Randomized, single-blind clinical trial to determine if oxygen from a portable oxygen concentrator (POC) is as effective as piped wall oxygen (LO) in reducing exercise-induced hypoxaemia in severe COPD patients on LTOT. • *Number of patients* : 13 (adult) • *Follow-up* : N/A • *Procedure* : Subjects underwent a series of five-6-minute walk tests (6 MWT). First 2 tests were considered training sessions. Last 3 tests were performed with one of three tested devices • • *Device Name* : LifeStyle AirSep, (Buffalo, NY, USA), LO cylinder (Taema, France) Cylinder with compressed air (CA) .	**D2**	**A1**	**P1**	**R1**	Level 2	POCs may be safely used for ambulatory oxygen treatment.	Yes

	• **Safety:** description and relevance N/A • **Performance:** description and relevance No statistically significant differences in oxygenation between POC and portable LO. However, in order in order to prevent hypoxaemia during strenuous exercise the authors suggest that three-fold increase of oxygen flow should be prescribed.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Author/ Date / Ref	***Clinical results:*** ***Safety, performance and equivalence***	***Criteria for suitability (mandatory)***	***Oxford level of evidence (optional)***	***Comments***	***Included: Yes/No***

DP Johns, PD Rochford and JA Streeton (1985) Evaluation Of Six Oxygen Concentrators Thorax 40: (pp 806-810)	• *Description of the study:* Laboratory study comparing the performance, safety and operation of six oxygen concentrators. • *Number of patients* : None – Laboratory Study • *Follow-up* : N/A • *Procedure* : *Six litres of gas was collected from each concentrator in a rebreathing bag for analysis*. • • *Device Name* $DeVO_2$ (Devilbiss Co, USA) Dom 10 (RImer-Alco, UK) $Econo_2$ (Mountain Medical Equipment, USA) Hudson 6200 (Ventronics, USA) Permox (Dragerwerk, Germany) Roomate (Cryogenic Associates, USA)	**D3**	**A1**	**P3**	**R1**	N/A	The main disadvantage of concentrators compared with cylinders is the possibility of machine failure or power failure. However, this risk can be minimized if a stock of spare parts and a standby machine centrally located are readily available.	Yes (highlights desirable safety feature added in the development of DeVilbiss 5L Oxygen Concentrator)

	• **Safety:** description and relevance Spectral analysis was conducted on the gas produced by the Hudson concentrator (only) and showed oxygen, argon (3.6%) and nitrogen to be the major components with oxygen and argon approximately equal. Carbon dioxide was detected in trace concentrations only. • **Performance:** description and relevance The oxygen concentration produced varied in a cyclical manner in all models, especially at the higher flow settings. No significant changes in delivered flow of $\%O_2$ were found when short (2m) and long (7-15 m) delivery tubes were used.							

D) Device: D1 (actual device), D2 (equivalent device), D3 (other device)

I) Application/ Intended use: A1 (same use), A2 (minor deviation), A3 (deviation)

P) Patient group: P1 (applicable), P2 (limited), P3 (different population)

R) Report/data collation: R1 (high quality), R2 (minor deficiencies), R3 (insufficient information)

Criteria for data contribution: Oxford level of evidence (March 2011), report to appendix F

NA: not applicable

Appendix E: Criteria of suitability and Oxford level of evidence

Criteria of Suitability (According to MEDDEV2.7.1 Rev 3 (2009))

Suitability Criteria	Description		Grading System
Appropriate device	Were the data generated from the device in question?	D1 D2 D3	Actual device Equivalent device Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1 A2 A3	Same use Minor deviation Major deviation
Appropriate patient group	Where the data generated from a patient group that is representative of the intended treatment population e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P1 P2 P3	Applicable Limited Different population
Acceptable report/ data collection	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1 R2 R3	High quality Minor deficiencies Insufficient information

Criteria of Contribution: Oxford level of Evidence (March 2011)

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

Appendix F: Search of clinical trial register (ie. Clinicaltrials.gov, WHO…)

N/A

This is specific to completed trials that have results posted on a registry where the data has not been available via publication.

Appendix G: Complaint/ Incidence Report

Complaints to DeVilbiss

5 Liter Oxygen Concentrator (base model 525)

A total of 823 customer complaints were registered over the period 1 January 2012 – 19 June 2015. The total number of unit sales was 23,996. The overall complaints rate for the 5 Liter Oxygen Concentrator was therefore 3.43%. No patient effect was noted in the complaints.

The most frequently reported issues for the 5 Liter Oxygen Concentrator were sieve bed issues (23.0%), compressor issues (15.8%), non-specific issues (13.0%), tubing issues (7.3%) and exhaust muffler or silencer issue (5.6%). The remaining 21 complaint categories were reported at a rate of <5.0% per category..

Summary of complaints registered for the 5 Liter Oxygen Concentrator over the period 1 January 2012 – 19 June 2015:

Complaint category	Brief Description	# of Complaints	(%)
SB01, SB02, SB04, SB05	Sieve bed issue	189	23.0%
MT01, MT02, MT05, MT09, MT13, MT15, MT18, MT26, MT31, MT32, MT49, MT50, MT59, MT62, MT63	Compressor issue	130	15.8%
MS05. MS14, MS17	Non-specific issue	107	13.0%
BD06, BD012, BD015, BD016, BD17, BD20	Board (main, mother or motor) issue	87	10.6%
TB03, TB04, TB05	Tubing issue	60	7.3%
ES01, ES02	Exhaust muffler or silencer issue	46	5.6%
VA06, VA07, VA16, VA19, VA24, VA25, VA34	Valve issue	31	3.8%
IC01, IC02, IC03	Intake canister issue	26	3.2%
WH03, WH06, WH08	Wiring Issue	24	2.9%
CP02, CP03, CP04, CP05, CP23, CP28, CP58	Capacitor issue	18	2.2%
FA02, FA03	Fan issue	14	1.7%
FG11, FG12, FG13	Outlet port issue	14	1.7%
FM01, FM04	Flow meter issue	13	1.6%
FT03, FT04, FT05, FT07	Filter issue	12	1.5%
OR01	O_2 port issue	11	1.3%
CK01	Check valve issue	7	0.9%
FG03, FG08	Fitting issue	6	0.7%
PK	Packaging Material	6	0.7%
CA06, CA07	Bib issue	4	0.5%
FS02, FS06, FS11, FS12	Clamp issue	4	0.5%
LC10, LC12	Line cord issue	3	0.4%
WE01, WE02	Wheel issue	3	0.4%
MM01, MM05	Motor issue	2	0.2%
CP58	Piezo defective	2	0.2%
RG01, RG11	Regulator issue	2	0.2%

Complaint category	Brief Description	# of Complaints	(%)
CP34	Switch issue	1	0.1%
RB01	Component for refurb	1	0.1%

CAPAs and recalls

There were no CAPAs or recalls on the 5 Liter Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

Analysis of the search of the MAUDE database

There were no records identified involving the 5 Liter Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

iGo Portable Oxygen Concentrator (base model 306)

A total of 190 customer complaints were registered over the period 1 January 2012 – 19 June 2015. The total number of unit sales was 2,034. The overall complaints rate for the iGo Portable Oxygen Concentrator was therefore 9.34%. No patient effect was noted in the complaints.

The most frequently reported issues for the iGo Portable Oxygen Concentrator were key pad issues (32.6%), valve issues (17.4 %), sieve bed issues (14.2%), motor issues (8.9%), and non-specific issue (7.9%). The remaining 10 complaint categories were reported at a rate of <5.0% per category.

Summary of complaints registered for the iGo Portable Oxygen Concentrator over the period 1 January 2012 – 19 June 2015:

Complaint category	Brief Description	# of Complaints	(%)
KP01, KP03	Keypad defective or not connected	62	32.6%
VA01, VA02, VA03, VA05, VA06, VA07, VA16	Valve issue	33	17.4%
SB01, SB02	Sieve bed issue	27	14.2%
MT03, MT04, MT05, MT08, MT26, MT50	Motor issue	17	8.9%
MS05	Non-specific issue	15	7.9%
WH04, WH06, WH09, WH11	Wiring issue	9	4.7%
BD05, BD06, BD07, BD08, BD15	Board (main, mother or motor) issue	8	4.2%
AD08,AD11, AD13	Car adaptor issue	4	2.1%
BA06, BA11	Battery issue	3	1.6%
FA03, FA04	Fan issue	3	1.6%
FG12	Outlet port issue	3	1.6%
MS10	Unit vibration issue	2	1.1%
TB03, TB01	Tubing issue	2	1.1%
CP34	Switch issue	1	0.5%
RG03	Regulator leaking	1	0.5%

CAPAs and recalls

There were no CAPAs or recalls on the iGo Portable Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

Analysis of the search of the MAUDE database

There were no records identified involving the iGo Portable Oxygen Concentrator during the period 1 January 2012 – 19 June 2015.

Search of the FDA's MAUDE database 1 Jan 2012– 19 Jun 2015

The database was searched by manufacturer and brand name. Terms searched:

- "Respironics" and "EverFlo" and "EverGo"
- "DeVilbiss" and "iGo" and "5L Concentrator"

No records were identified for either of the DeVilbiss' devices. Seventy three records were identified for EverFlo and eight records were identified for EverGo. The search results are presented in tabular format in Table 1.

Table 4 MAUDE Search results

Manufacturer/ Brand Name	Respironics/ EverFlo	Respironics/ EverGo	DeVilbiss/ iGo	DeVilbiss/ 5L Concentrator
# of Records Returned	73	8	0	0

Of the seventy three records identified for EverFlo, 3 records described the same event and 1 record described an event that occurred outside of the specified timeframe. These records were removed from consideration leaving a total of 70 records for analysis. A breakdown of the reported events for each device, according to the categories of 'Deaths', 'Injury' or 'Malfunction' is presented in Table 2.

Table 5 Event Breakdown

Manufacturer/Brand Name	Deaths	Injury	Malfunction	Total Records Analyzed
Respironics/EverFlo	11	39	20	70
Respironics/ EverGo	0	6	2	8

Of the eight records identified for EverGo, two records described device malfunctions that did not result in patient injury and six records described events that did result in patient injury. A detailed analysis of EverGo events is presented in Table 3.

Table 6 EVERGO MAUDE Events

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERGO	10/22/2014	Patient complaint of low oxygen output. Patient was hospitalized but has since been released. Health care provider noted patient has other health issues which may have contributed to the	Injury	Leaking compressor

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			hospitalization. Complaint confirmed by the manufacturer. Device evaluation revealed a leaking compressor.		
RESPIRONICS, INC	EVERGO	12/16/2013	Patient complained of an odor from the concentrator which caused the patient to suffer smoke inhalation and a subsequent infection which required the patient to be treated with antibiotics. A third party service center evaluated the device and was not able to confirm the odor. Furthermore, the device was found to operate according to design specifications.	Injury	Odor
RESPIRONICS, INC	EVERGO	02/18/2014	Patient suffered a heart attack and brain damage while using the device. The device was not returned to the manufacturer for evaluation.	Injury	Not Specified (NS)
RESPIRONICS, INC	EVERGO	11/28/2012	Healthcare professional reported a patient using the device during air travel had low blood oxygen levels and was taken to the hospital. The patient was released the same day. The manufacturer evaluated the device and found that the batteries were depleted. The batteries were charged and the device passed all functional testing.	Injury	Low Batteries

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERGO	10/15/2012	Patient received a burn when removing the dc adaptor from the car's dc outlet. The burn became infected and the patient required antibiotics. The device was not returned to the manufacturer for evaluation.	Injury	DC adapter
RESPIRONICS, INC	EVERGO	05/31/2012	A patient using the device had a low blood oxygen saturator and was admitted to the hospital for treatment. The device was not returned to the manufacturer for evaluation.	Injury	Not Specified (NS)
RESPIRONICS, INC	EVERGO	08/01/2014	Patient rented a POC for use during air travel and away from home. The patient experienced multiple technical problems. Patient returned the first POC for another (same make and model) and continued to experience multiple technical problems. Patient experienced panic but no physical injuries.	Malfunction	Multiple technical issues
RESPIRONICS, INC	EVERGO	04/09/2013	A thermal event associated with the device's power cord occurred. No report of patient injury or harm. The device was not returned to the manufacturer for evaluation.	Malfunction	Power cord issue

Considerably more records were returned for Respironics' EverFlo device than for their EverGo device. A detailed analyses of these events is present in Tables 4,5 and 6.

Although there were 11 deaths reported in conjunction with the use of the EverFlo device, no definitive device involvement was determined. Smoking while using the device was found to be a contributing factor in 2 of the deaths. Product labeling instructs the user not to smoke while using the device. A detailed analysis of the reported deaths for the EverFlo device is presented in Table 4.

Table 7 EVERFLO – MAUDE Events - Deaths

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	2/12/2014	Patient died while using the device. Device to be returned for evaluation.	Death	Not Specified (NS)
RESPIRONICS, INC	EVERFLO	12/3/2014	Power outage caused the device to stop functioning. Patient was unable to utilize their back up oxygen supply. Patient died. Device not returned to manufacturer for evaluation.	Death	Power outage
RESPIRONICS, INC	EVERFLO	12/7/2013	Device malfunctioned. Patient suffered a brain injury due to lack of oxygen and died a few months later. Device not returned to manufacturer for evaluation.	Death	NS
RESPIRONICS, INC	EVERFLO	05/14/2014	Device malfunction and patient died. Device not returned for evaluation.	Death	NS
RESPIRONICS, INC	EVERFLO	02/13/2014	Patient expired while using the device. Pt was smoking. No report of a device malfunction. Patient had been educated not to smoke when using the device. Device has yet to be returned.	Death	Smoking while using the device
RESPIRONICS, INC	EVERFLO	06/14/2013	Device involved in a fire. patient died the day after. Device not yet returned for	Death	Fire

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			manufacturer evaluation.		
RESPIRONICS, INC	EVERFLO	04/18/2013	Patient expired while using the device. Manufacturer evaluation revealed no malfunctions or deficiencies. The device was found to operate to design specs.	Death	NS
RESPIRONICS, INC	EVERFLO	04/04/2013	Patient expired while using the device. Device not yet returned for manufacturer evaluation.	Death	NS
RESPIRONICS, INC	EVERFLO	08/21/2012	Nasal cannula caught on fire while connected to the device and while the patient was smoking. The patient died. Manufacture evaluation confirmed product labeling provides adequate warning against using the device while smoking.	Death	Smoking while using the device
RESPIRONICS, INC	EVERFLO	02/17/2012	Patient expired while concentrator was in use with a ventilator. A yellow light was illuminated. The manufacturer could not duplicate the malfunction and found the device to operate to design specs. (Note: Device returned to manufacturer for evaluation 03/06/2012).	Death	NS
RESPIRONICS, INC	EVERFLO	02/17/2012	Oxygen concentrator not working while the patient was not breathing. Family member states device was working prior to, and following the event.	Death	NS

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			Reason for use – chronic respiratory failure and neuromuscular weakness. (Note: Device returned to manufacturer for evaluation 02/24/2012).		

There were 23 reports of device malfunctions for Respironic's EverFlo device. Upon further review of the records, 3 reports involved patient injuries and were moved to the injury category leaving 20 device malfunctions for analysis. The most frequently reported malfunction involved power cord issues (12). The remaining malfunctions were fire (4), smoking while using the device (3) and circuit board issue (1). Of the 4 events involving 'fire', the device was returned to the manufacturer for evaluation for 2 of the events. The manufacturer found that the device operated to design specifications. The device was not returned for the other 2 events. Product labeling was evaluated for the events that involved smoking while using the device and found to be sufficient as product labeling does instructs the user not to smoke while using the device. A detailed analysis of the reported malfunctions for the EverFlo device is presented in Table 5.

Table 8 EVERFLO – MAUDE Events – Malfunctions

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	03/22/2015	Nasal cannula caught on fire from a lit cigarette. No reports of patient harm or injury. Manufacturer evaluation found thermal damage caused by an external source. Product labeling warns against using near open flames.	Malfunction	Smoking while using the device
RESPIRONICS, INC	EVERFLO	10/01/2013	Nasal cannula showed evidence of thermal damage. No reports of patient harm or injury. The durable medical equipment supplier suggested the patient's smoking could have been the source of the fire. Product labeling warns against smoking when using the concentrator.	Malfunction	Smoking while using the device

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERGO	01/25/2015	Device caught on fire while in use. No reports of patient injury or harm. Manufacturer Follow-Up: Fire Marshall report stated the fire was ignited by the patient smoking. Manufacturer concludes device did not cause the fire. Product labeling warns against smoking while using the device.	Malfunction	Smoking while using the device
RESPIRONICS, INC	EVERFLO	06/15/2012	Oxygen tubing caught on fire while in use. No reports of patient harm or injury. Device not yet returned to manufacturer for evaluation.	Malfunction	Fire
RESPIRONICS, INC	EVERFLO	06/07/2015	Complaint that device caused a house fire. No reports of patient harm or injury. Device evaluation by the manufacturer revealed device operated to design specifications. Power cord was replaced for cosmetic reasons.	Malfunction	Fire
RESPIRONICS, INC	EVERFLO	12/16/2014	Report that the device caught on fire while in use. No report of patient injury or harm. Manufacture evaluation found no evidence of internal thermal damage or any manufacturing defect or internal problem.	Malfunction	Fire
RESPIRONICS, INC	EVERFLO	08/19/2012	Device caught on fire while in use. No reports of patient harm or injury. Device has not yet been returned for evaluation.	Malfunction	Fire

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	03/09/2015	Thermal damage to the power cord. No report of patient injury.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	02/03/2015 (3 records describe the same event)	Thermal damage to power cord. No report of patient injury or harm. Device has yet to be returned for evaluation. Device evaluated by a third party lab. Complaint confirmed. Product labeling states to inspect power cord for signs of wear or damage.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	0/26/2015	Device had exposed wires to the power cord. No reports of patient harm or injury. Device to be returned for evaluation.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	12/23/2014	Report that device emitted a burning odor and noise. No report of patient injury or harm. Manufacturer evaluation found no evidence of thermal damage but did observe damage to the power cord which is consistent to loose contacts in an ac outlet.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	10/21/2014	Device plugged into an ac outlet. Flames were seen coming from the outlet. Thermal damage to the plug. No report of patient injury or harm. Third party evaluation found power cord had evidence of being chewed. Power cord replaced.	Malfunction	Power cord issue

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	8/29/2014	Device plugged into a power strip and then plugged into the wall ac outlet. Flames observed on the power strip. No report of patient injury or harm. Device not returned for evaluation.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	7/11/2014	Power cord shorted. No report of patient injury or harm.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	06/18/2014	Damage to the power cord. No report of patient injury or harm. Device not yet returned to manufacturer.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	10/10/2013	Device had evidence of damage to the power cord. No report of patient injury or harm. Power cord replaced by third party service center.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	10/03/2013	Device had evidence of damage to the power cord. No report of patient injury or harm. Device not yet returned for manufacturer evaluation.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	07/17/2013	Device had evidence of damage to the power cord. No report of patient injury or harm. Device not yet returned for manufacturer evaluation.	Malfunction	Power cord issue
RESPIRONICS, INC	EVERFLO	08/15/2013	Device had evidence of damage to the power cord. No report of patient injury or harm. Device not yet returned for manufacturer evaluation.	Malfunction	Power cord issue

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	12/16/2013	Flames observed from the device. No report of patient injury or harm. Device evaluation revealed thermal damage caused by the printed circuit board.	Malfunction	Circuit Board issue

There were 39 reports of injuries for Respironic's EverFlo device.

The most frequently reported injury involved receiving burns from smoking while using the device (9). The remaining reported injuries were 'may have caused or exacerbated a medical condition' (8), low blood oxygen resulting from 'oxygen delivery issues' (8), smoke inhalation or burns resulting from 'fire' (6), low blood oxygen resulting from 'solenoid valve issues' (3). Additional injury reports were burns from either the nasal cannula (1) or a spark from a nebulizer (1), electrical shock from an electrical issue (1) and low oxygen from a locked compressor (1). There was one injury whose cause was not specified.

Product labeling was evaluated for the events that involved smoking while using the device and found to be sufficient as product labeling does instructs the user not to smoke while using the device.

No definitive evidence was found linking the device to having caused or exacerbated a medical condition.

The device was returned for evaluation in 7 of the 8 situations involving low blood oxygen as a result of oxygen delivery issues. The evaluator (s) found the device was operating to design specifications in 4 of the events, in 1 event the sieve canister was leaking and the filters were dirty and in 1 event the microdisk tubing was disconnected causing a no flow event. The evaluation is pending for 1 event and the device was not returned for evaluation in 1 event.

The device was not returned for evaluation in 4 of the 6 reported cases of fire. The device was found not to have caused or contributed to the fire in the other 2 cases.

A detailed analysis of the reported injuries for the EverFlo device is presented in Table 6.

Table 9 EVERFLO – MAUDE Events – Injuries

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	04/14/2015	Complaint that the nasal cannula caught	Injury	Smoking while using the device

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			on fire from a lit cigarette and burned the patient on the nose. Patient did not seek medical treatment. Third party service center evaluated the product and found no malfunction. Product labeling warns against using near open flames. Manufacturer concluded user error caused the event.		
RESPIRONICS, INC	EVERFLO	12/07/2014	Report that patient received burns to the face while using the device while smoking. The patient was admitted to the hospital.	Injury	Smoking while using the device
RESPIRONICS, INC	EVERFLO	09/17/2014	Patient lit a cigarette while using the device. Patient received burns and respiratory complications. Admitted to the hospital for treatment.	Injury	Smoking while using the device

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	04/20/2014	Patient smoking while using the device. House fire reported. Patient hospitalized. Device not returned for evaluation (destroyed in fire).	Injury	Smoking while using the device
RESPIRONICS, INC	EVERFLO	03/18/2014	Patient smoking a cigarette while using the device. Received burns and was hospitalized for treatment. Device not returned for evaluation due to extensive damage received during the fire. Product labeling states do not smoke when the concentrator is in use.	Injury	Smoking while using the device
RESPIRONICS, INC	EVERFLO	12/13/2013	Patient was smoking while using the device. Received burns and was admitted to the hospital for treatment. Device evaluation	Injury	Smoking while using the device

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			determined fire originated external to the device. Product labeling states do not smoke when concentrator is in use.		
RESPIRONICS, INC	EVERFLO	06/17/2013	Patient smoking while using device and ignited a fire. Received severe burns and admitted to the hospital for treatment. The device was destroyed in the fire.	Injury	Smoking while using the device
RESPIRONICS, INC	EVERFLO	01/15/2013	Patient burned while using the device and smoking. Manufacturer evaluation confirmed thermal damage originated external to the device. The device operated according to specification.	Injury	Smoking while using the device
RESPIRONICS, INC	EVERFLO	05/14/2012	Patient smoking while using the device and received burns. Unknown if medical attention was	Injury	Smoking while using the device

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			required. Device not returned for evaluation.		
RESPIRONICS, INC	EVERFLO	04/28/2015	Complaint that the device caused ventricular tachycardia requiring a visit to the hospital. Device evaluation pending.	Injury	Caused or exacerbated a medical condition
RESPIRONICS, INC	EVERFLO	01/10/2015	Patient claims odor emitted by device damaged his lungs. Doctor visit but no medical treatment required. Device evaluation by the manufacturer revealed device operated to design specifications.	Injury	Caused or exacerbated a medical condition
RESPIRONICS, INC	EVERFLO	12/11/2014	Report that device contributed to a lung infection. No report of medical intervention being required.	Injury	Caused or exacerbated a medical condition
RESPIRONICS, INC	EVERFLO	09/03/2014	Device may have caused	Injury	Caused or exacerbated a

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			pneumonia. Patient sought medical treatment. Manufacturer investigation states patient did not seek medical attention. Device not returned for evaluation.		medical condition
RESPIRONICS, INC	EVERFLO	05/05/2014	Patient has suffered a respiratory and sinus infection while using the device. Patient admitted to hospital for treatment. Follow Up to Follow.	Injury	Caused or exacerbated a medical condition
RESPIRONICS, INC	EVERFLO	01/09/2014	Patient complained of and odor. Patient contracted a mold infection after using the device. Physician prescribed antibiotics. A third party evaluator did not confirm the odor. Device to be returned to manufacturer for evaluation.	Injury	Caused or exacerbated a medical condition

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
RESPIRONICS, INC	EVERFLO	09/26/2013	Device caused patient to have asthma. According to the patient, the device contains phthalates which can cause asthma. Device not yet returned for manufacturer evaluation.	Injury	Caused or exacerbated a medical condition
RESPIRONICS, INC	EVERFLO	04/30/2013	Device emitted a white powder substance which was inhaled by the patient. The patient became congested. She was prescribed medications by her doctor. Device not yet returned for manufacturer evaluation.	Injury	Caused or exacerbated a medical condition
RESPIRONICS, INC	EVERFLO	2/10/2015	Patient claims device did not deliver oxygen and did not alarm. Patient admitted to the hospital one week for low blood oxygen levels. Device evaluation by the manufacturer revealed device operated to	Injury	Oxygen delivery

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			design specifications		
RESPIRONICS, INC	EVERFLO	1/14/2015	Patient claims concentrator did not provide enough oxygen resulting in low blood oxygen levels and a hospital stay of 10 days. Device evaluation by the manufacturer revealed device operated to design specifications and did not cause or contribute to the injury.	Injury	Oxygen delivery
RESPIRONICS, INC	EVERFLO	01/07/2015	Patient's blood oxygen level was low while using the device. Patient switched to back up oxygen. No medical intervention required. Third party service center determined sieve canister leaking and filters dirty.	Injury	Oxygen delivery
RESPIRONICS, INC	EVERFLO	05/12/2014	Device not producing oxygen. Patient's blood	Injury	Oxygen delivery

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			oxygen saturation decreased. Patient placed on supplemental oxygen. Device returned for evaluation. Follow Up to follow.		
RESPIRONICS, INC	EVERFLO	02/05/2013	Patient's blood oxygen was low when using the device. Patient admitted to hospital for respiratory distress. Third party supplier reported device was used with 49 ft oxygen tubing and that the nasal cannula was not manufactured by Respironics. The device was tested by the supplier and found to operate properly.	Injury	Oxygen delivery
RESPIRONICS, INC	EVERFLO	11/19/2012	Patient hospitalized for low blood oxygen saturation while using the device. Manufacturer	Injury	Oxygen delivery

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			evaluation revealed the device was operating to design specifications.		
RESPIRONICS, INC	EVERFLO	06/29/2012	Device would not go above 3L per min. Patient did seek medical attention. Device not yet returned to manufacturer for evaluation.	Injury	Oxygen delivery
RESPIRONICS, INC	EVERFLO	5/29/2012	Concentrator had no flow when used with a ventilator. Patient's blood oxygen level decreased and the patient was hospitalized. The device was evaluated by the manufacture and the internal microdisk tubing was disconnected causing a no flow event.	Injury	Oxygen delivery
RESPIRONICS, INC	EVERFLO	11/25/2013	Device caught fire while in use. Patient taken to the hospital – treated and released for	Injury	Fire

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			smoke inhalation. Device not yet returned for manufacturer evaluation.		
RESPIRONICS, INC	EVERFLO	11/25/2013	Device caught fire while in use. Open flame present. Patient received minor burns and was treated by a doctor in her home. Device not yet returned for manufacturer evaluation.	Injury	Fire
RESPIRONICS, INC	EVERFLO	09/25/2013	Device involved in a house fire. Patient hospitalized. Family member treated for smoke inhalation. Device not returned for manufacturer evaluation. Fire scene investigated and device located in a different area from origin of fire. Device did not cause or contribute to fire.	Injury	Fire
RESPIRONICS,	EVERFLO	08/20/2015	Device caught	Injury	Fire

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
INC			on fire while in use. Patient received burns and was hospitalized. Device not yet returned for manufacturer evaluation.		
RESPIRONICS, INC	EVERFLO	05/29/2013	Device caught on fire. Patient taken to hospital and released. Manufacturer evaluation found thermal damage externally which was caused by an external source.	Injury	Fire
RESPIRONICS, INC	EVERFLO	02/05/2013	Device involved in a fire. Patient received burns and was hospitalized. Device is not being returned to manufacturer.	Injury	Fire
RESPIRONICS, INC	EVERFLO	12/13/2013	Complaint of low oxygen concentration causing the patient's disease (emphysema) to worsen. Device evaluation revealed faulty solenoid and	Injury	Solenoid Valve Issue

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			loose flow meter screw and leaking sieve.		
RESPIRONICS, INC	EVERFLO	11/08/2013	Device did not work properly. Patient admitted to hospital. Patient has returned to baseline. Third party service center found solenoid valve not shifting properly.	Injury	Solenoid Valve Issue
RESPIRONICS, INC	EVERFLO	10/24/2013	Device alarming and not providing oxygen. Patient hospitalized. Manufacturer evaluation revealed solenoid pilot valve sticking.	Injury	Solenoid Valve Issue
RESPIRONICS, INC	EVERFLO	11/29/2012	Patient received burns when a spark from the nebulizer (unknown manufacturer) ignited the nasal cannula connected to the device. Patient was hospitalized. Manufacturer evaluation revealed no	Injury	Spark from a nebulizer

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			evidence of thermal damage to the device and that it was operating according to design specifications.		
RESPIRONICS, INC	EVERFLO	10/0/02012	Device not producing oxygen. Patient admitted for low blood oxygen. Discharged after one day. Manufacturer evaluation revealed compressor was locked and not producing oxygen.	Injury	Compressor Locked
RESPIRONICS, INC	EVERFLO	12/12/2013	Shock received while concentrator being serviced. No medical invention needed. Device not yet returned to manufacturer for evaluation.	Injury	Electrical issue
RESPIRONICS, INC	EVERFLO	10/16/2012	Nasal cannula caught on fire while the device was in use. Patient received burns and was treated at the hospital. Device	Injury	Nasal cannula

Manufacturer	Product	Event Date	Description	Event Type	Failure Mode
			evaluation revealed no evidence of thermal damage. Nasal cannula was not returned. Failure mode consistent with patient smoking.		
RESPIRONICS, INC	EVERFLO	02/03/2014	Device malfunctioned and patient hospitalized.	Injury	NS

Appendix H: IFU document number or IFU

DeVilbiss 5 Liter Oxygen Concentrator Instruction Guide

SE-252K Rev G

EN **DeVilbiss® 5 Liter Oxygen Concentrator Instruction Guide**

WARNING–*Read instruction guide before operating this equipment.*
CAUTION– *Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.*
MADE IN THE USA of U.S. and Imported Parts

DANGER–NO SMOKING

ES **Guía de instrucciones del concentrador de oxígeno de 5 litros de DeVilbiss®**

ADVERTENCIA–*Lea la guía de instrucciones antes de poner a funcionar este equipo.*
PRECAUCION– *La ley federal (EE.UU.) establece que este aparato sólo lo puede vender un médico o por prescripción del mismo.*
FABRICADO EN EE. UU. de partes nacionales e importadas

PELIGRO–NO FUMAR

FR **Guide d'instructions du concentrateur d'oxygène 5 litres DeVilbiss®**

AVERTISSEMENT–*Lire le mode d'emploi avant d'utiliser ce dispositif.*
ATTENTION–*En vertu de la Loi fédérale américaine, la vente de cet appareil n'est autorisée que par un médecin ou sur ordonnance de ce dernier.*
FABRIQUÉ AUX ÉTATS-UNIS avec des pièces des États-Unis et des pièces importées

DANGER–NE PAS FUMER

DE **DeVilbiss® 5 Liter-Sauerstoffkonzentrator Bedienungsanleitung**

WARNUNG–*Vor Inbetriebnahme des Gerätes Bedienungshinweise lesen.*
ACHTUNG– *Dieses Gerät darf US-Bundesgesetzen zufolge nur von Ärzten oder auf deren Anweisung hin verkauft werden.*
Gefertigt in den USA unter Verwendung amerikanischer und importierter Teile.

GEFAHR–RAUCHEN VERBOTEN

IT **Concentratore di ossigeno da 5 litri DeVilbiss® Istruzioni per l'uso**

AVVERTENZA–*Leggere il manuale di istruzioni prima di usare l'apparecchio*
ATTENZIONE–*La legislazione federale degli Stati Uniti limita la vendita di questo prodotto al personale medico o alle persone munite di prescrizione medica.*
ASSEMBLATO NEGLI USA con componenti prodotti negli Stati Uniti e importati.

PERICOLO - NON FUMARE

NL **Instructiehandleiding DeVilbiss® 5 liter zuurstofconcentrator**

WAARSCHUWING–*Lees dit instructiehandboekje zorgvuldig door voordat u het apparaat gaat gebruiken.*
ATTENTIE–*De federale wetgeving in de Verenigde Staten schrijft voor dat dit apparaat uitsluitend mag worden verkocht of voorgeschreven door een arts.*
GEPRODUCEERD IN DE VERENIGDE STATEN met Amerikaanse en geïmporteerde onderdelen

GEVAAR– VERBODEN TE ROKEN

TR **DeVilbiss® 5 Litre Oksijen Konsantratörü Kullanım Kılavuzu**

UYARI–*Cihazı kullanmaya başlamadan önce bu kılavuzu okuyunuz.*
DİKKAT– *A.B.D. Federal yasalarına göre bu cihaz yalnızca bir doktor tarafından veya doktorun siparişi ile satılmalıdır.*
ABD içi ve İthal Parçalar ABD'de ÜRETİLMİŞTİR

TEHLİKE–SİGARA İÇİLMEZ

PT **Manual de instruções do Concentrador de oxigênio DeVilbiss® de 5 litros**

ADVERTÊNCIA– *Leia o manual de instruções antes de operar este equipamento.*
CUIDADO– *A lei federal (EUA) restringe a venda deste aparelho a médicos ou à sua ordem.*
FABRICADO NOS EUA com peças dos EUA e importadas

PERIGO – PROIBIDO FUMAR

PL **Instrukcja obsługi 5-litrowego koncentratora tlenu DeVilbiss®**

OSTRZEŻENIE – *Przeczytaj instrukcję obsługi przed rozpoczęciem korzystania z tego urządzenia.*
UWAGA – *Zgodnie z obowiązującymi przepisami federalnymi Stanów Zjednoczonych niniejsze urządzenie może być sprzedawane przez lub na zlecenie lekarza.*
WYPRODUKOWANO W USA z części amerykańskich i zagranicznych.

NIEBEZPIECZEŃSTWO–NIE PALIC

Model 306DS Instruction Guide

A-306-1 Rev F

MODEL 306DS INSTRUCTION GUIDE

CE 0044

EN DeVilbiss iGo® Portable Oxygen System

WARNING– *Read instruction guide before operating this equipment.*

CAUTION– *Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.*

DANGER–NO SMOKING

ES Sistema de oxígeno portátil DeVilbiss iGo®

ADVERTENCIA–*Lea la guía de instrucciones antes de poner a funcionar este equipo.*

PRECAUCIÓN–*La ley federal de EE. UU. limita la venta de este dispositivo a médicos o a personas que dispongan de la correspondiente orden médica.*

PELIGRO–NO FUMAR

FR Système d'approvisionnement portable en oxygène DeVilbiss iGo®

AVERTISSEMENT–*Lisez ce guide d'instructions avant d'utiliser l'équipement.*

ATTENTION–*En vertu de la loi fédérale américaine, cet appareil ne peut être vendu que par un médecin ou sur ordonnance de celui-ci.*

DANGER–NE PAS FUMER

DE Tragbares DeVilbiss iGo® Sauerstoffsystem

WARNUNG–*Vor Inbetriebnahme des Gerätes Bedienungshinweise lesen.*

ACHTUNG–*Nach US-Bundesgesetzen darf dieses Gerät nur von einem Arzt bzw. auf Anordnung eines Arztes verkauft werden.*

GEFAHR–RAUCHEN VERBOTEN

IT Sistema portatile DeVilbiss iGo® per ossigenoterapia™

AVVERTENZA–*Non mettere in funzione l'apparecchiatura senza aver prima letto le istruzioni riportate in questo manuale.*

ATTENZIONE–*La legge federale statunitense limita la vendita di questo dispositivo ai medici o su loro prescrizione.*

PERICOLO – VIETATO FUMARE

NL DeVilbiss iGo® draagbaar zuurstofsysteem

WAARSCHUWING–*Lees dit instructiehandboekje zorgvuldig door voordat u het apparaat gaat gebruiken.*

ATTENTIE–*De federale wetgeving in de Verenigde Staten schrijft voor dat dit apparaat uitsluitend mag worden verkocht of voorgeschreven door een arts.*

GEVAAR– VERBODEN TE ROKEN

Appendix I: Risk Analysis Report number or Risk Files

Risk Management Report 525 ISO14971

306D Risk Management report per ISO14971-200 Rev 1

Appendix J: Justification of the choice of the evaluator(s) (ie. curriculum vitae / biographical sketch of medical writer and clinical reviewer)

Dr Wilkinson was selected as author of this CER for the following reasons:

- Dr Wilkinson is employed by a leading contract research organisation.
- Dr Wilkinson has extensive experience authoring CERs.
- Dr Wilkinson is an independent unbiased author.

Curriculum vitae

GENERAL INFORMATION			
Name and Surname	Beata Wilkinson		
Surname prior to 2012	Langlands		
Place of birth	Warsaw, Poland		
Nationality	British		
Mother tongue Language	Bilingual – English and Polish		
Present Job Position	Head of Regulatory Services Unit / Regulatory and Scientific Writing Manager		
EDUCATION			
Education	PhD; Doctoral Thesis in Biomedical Science		
Institution – City (Country)	The University of Glasgow, UK		
Date	1981		
Education	BSc (Hons) in Molecular Biology		
Institution – City (Country)	The University of Glasgow, UK		
LANGUAGE SKILLS			
Language	English	Level	4
Language	Polish	Level	4
Language		Level	
Level 1: Beginner understands read and spoken language, not able to clearly formulate his thoughts in the given language, makes grammar mistakes and uses very basic vocabulary when speaking or writing. Level 2: Speaking skills are better but the vocabulary used and sentence structures are still basic; makes pronunciation mistakes, lacks fluency. Level 3: Comfortable speaker and writer, can build more complex structures and formulate thoughts in a clear manner, makes some grammar mistakes. Level 4: Experienced and fluent user, pronunciation & accent are correct, speaking rhythm is regular, writing skills are developed, language used is rich.			
PROFESSIONAL EXPERIENCE/CAREER HISTORY			
Company	CROMSOURCE		

Job Position	Head of Regulatory Services Unit / Regulatory and Scientific Writing Manager
Date (from-to)	13/Oct/2014 – ongoing
Main tasks and Responsibilities:	Responsible for the growth objectives, revenue and value added of the Regulatory Services Unit. My remit is to ensure timely delivery of regulatory services with high quality standards to CROMSOURCE Clients. Responsible for delivery of writing services to CROMSOUCE Clients. This includes preparing and writing CERs and other regulatory and scientifically-sound documents. Wrote two white papers for publication on CROMSOURCE website: • Clinical Evaluation Reports: Meeting the demands of a more stringent regulatory environment • Clinical Data for Medical Device: Preparing for increased requirements in the EU
Company	ConvaTec International UK Ltd
Job Position	Clinical Evaluation Program Specialist, Clinical & Regulatory Affairs Department
Date (from-to)	June 2013 – October 2014
Main tasks and Responsibilities, if relevant for your present position:	Responsible for the preparation of the company's Clinical Evaluation Reports (CERs) in accordance with the Medical Device Directive (MEDDEV 2.7.1) including coordination and scheduling of resources. Preparation of CERs involved evaluation of preclinical data, risk assessments, scientific literature, clinical investigations, complaints and other relevant data sets. Responsible for preparation of CERs for audits by Notified Bodies. Responsible for training and supervision of other in-house medical writers and liaison with external medical writing agencies Participation in cross-functional product development teams Achievements: Raised general awareness of the key role of CERs in the company's product design validation process Developed a new and improved internal Standard Operating Procedure focused on Clinical Evaluation Developed a new CER template to reduce the average time of CER preparation
Company	Biophoenix Biomedical Consultancy Ltd
Job Position	Research Director/Medical Writer
Date (from-to)	July 1998 – June 2013
Main tasks and Responsibilities, if relevant for your present position:	I co-founded Biophoenix Ltd in 1998 with the late Dr Sreten Bogdanovic to provide timely regulatory, scientific and market information to pharmaceutical and medical device companies. Researched and wrote over 50 off-the-shelf biomedical business reports. Wrote marketing copy and instructed sales teams which resulted in our reports being sold to many of the world's leading organisations, including: pharmaceutical multinationals (for example Roche, Pfizer, and Novartis); management consulting firms (for example Boston Consulting Group); and universities (for example John Hopkins School of Medicine). Liaised closely with major publishing companies and secured significant repeat business. Established a comprehensive, proprietary database of pharmaceutical companies and their

	products. Audited biotechnology-based enterprises with regard to the risk of intellectual property litigation on behalf of Lloyds of London insurers. During the period December 2010 – June 2013 I worked on commissioned projects for publishers of healthcare market intelligence reports aimed at customers in the pharmaceutical and medical device industries. Generated ideas for new studies and submitted proposals, in addition to accepting work assignments. My main client was Datamonitor (part of Informa plc). Duties included: data collection and collation; data processing and analysis; telephone interviews with healthcare industry executives; preparation of written reports; presentation of study findings; and production of marketing collateral to support the sales of reports. A report written by me for Datamonitor (Point-of-Care Testing) was used as a model for other authors to emulate.
Company	Coventry University, UK
Job Position	Senior Lecturer in the Department of Biological Sciences
Date (from-to)	October 1989 – June 1998
Main tasks and Responsibilities, if relevant for your present position:	I taught a wide variety of undergraduate courses in biological sciences at degree and postgraduate level and supervised students carrying out research projects. Appointed Course Tutor for the European MSc in Biotechnology which enabled me to secure industrial placements for students in prominent healthcare companies. Developed and taught a final-year undergraduate BSc course module entitled “Biochemical diagnosis of disease”, which led to the establishment of a new degree in Biomedical Science.
Company	Orbec Ltd
Job Position	Project Leader
Date (from-to)	1984-1985
Main tasks and Responsibilities, if relevant for your present position:	Responsible for the development of applications for a novel automated microbiological urine screening analyser. The initial work included assessment and development of the unit itself in order to provide reliable and reproducible operation. Further work was concerned with carrying out clinical trials.

Company	Public Health Laboratory, Coventry and Birmingham Heartlands Hospital, Birmingham
Job Position	Hospital Scientist
Date (from-to)	1980-1984
Main tasks and Responsibilities, if relevant for your present position:	Routine and research work in clinical diagnostic testing and disease surveillance. Responsibilities included performing specialist assays for the investigation of complement function in disease. Duties involved the development of new tests and improvement of existing techniques.

CLINICAL RESEARCH EXPERIENCE

Therapeutic area (pathology)	Countries Managed	Phase	Main responsibilities	
Wound care	EU	CE mark	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☒ Regulatory submissions ☐ Medical Monitoring	☒ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Critical care	EU	CE mark	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☒ Regulatory submissions ☐ Medical Monitoring	☒ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Ostomy and continence		CE mark	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☒ Regulatory submissions ☐ Medical Monitoring	☒ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics

PUBLICATIONS

Advances in Gene Therapy for Human Diseases (Datamonitor, 2013)
Advances in the Use of Biomarkers in Biochip and Microarray Testing (Business Insights, 2009)
Angiogenesis Modulators: Strategies for Drug Discovery (D&MD, 2005)
Angiogenesis Players (Financial Times Pharmaceuticals, 1999)
Angiogenesis: A Therapeutic and Market Outlook (PJB Publications, 2002)
Antibody-Drug Conjugates in Cancer Therapy (Datamonitor, 2013)
Apoptosis 2009: Opportunities in Cancer and Other Diseases (Biophoenix, 2009)
Biomedical Patents in the Postgenomic Era: Proprietary Drug Targets and Therapies (D&MD, 2005)
Biosimilars and Biobetters: Positioning for a New Market (Biophoenix, 2009)
Biosimilars, Biogenerics, and Follow-On Biologics (Scrip/Informa, 2007)
Cancer Therapeutics (Financial Times Pharmaceuticals, 1998)
Convergence of Biomarkers and Diagnostics (Business Insights, 2008)
Dyslipidemia: Opportunities in Cardiovascular Risk Reduction (Biophoenix, 2008)
Gene Therapy Players, 2nd edition (Financial Times Pharmaceuticals, 1999)
Immunodiagnostics and Nucleic Acid Testing Kits for the Veterinary Industry (PJB Publications, 2003)
Immunomodulators (Business Insights, 2007)
Innovations in Bioinformatics (Business Insights, 2008)
Innovations in Molecular Diagnostics for Infectious Diseases (Business Insights, 2011)
Innovations in Protein Kinase Therapies: Company pipelines, therapeutic applications, and market forecasts (Business Insights, 2009)

Kinases: Advanced Strategies and Multiple Targets for Drug Discovery (D&MD, 2006)
Lifestyle Drugs: New Opportunities in Obesity (Nicholas Hall & Company, 2001)
Lifestyle Drugs: New Opportunities in Rejuvenation Pharmaceuticals (Nicholas Hall & Company, 2001)
Lifestyle Drugs: New Opportunities in Sexual Dysfunction (Nicholas Hall & Company, 2001)
Livestock Performance Products and Markets (Animal Pharm/Informa, 2007)
Metabolic Syndrome: New Opportunities in Diagnostics and Therapeutics (D&MD, 2004)
Micro and Nano Technologies for Point-of-Care Testing (Datamonitor, 2012)
Molecular Diagnostics: Effective Tools for Disease Management, 3rd edition (D&MD, 2006)
Molecular Diagnostics: Transforming the Pharmaceutical Market, 2nd edition (D&MD, 2004)
Molecular Diagnostics: Transforming the Pharmaceutical Market (D&MD, 2002)
Next-Generation Protein and Peptide Therapeutics (Business Insights, 2011)
Next Generation Protein Engineering and Drug Design (Business Insights, 2007)
Oligonucleotide Players (Financial Times Pharmaceuticals, 1999)
Pharmacogenomics Players (Financial Times Pharmaceuticals, 1999)
Point-of-Care Testing (Business Insights, 2010)
Proteases as Drug Targets: Technologies and Opportunities for Drug Discovery (D&MD, 2004)
Protein Kinases: Technologies and Opportunities for Drug Discovery (D&MD, 2003)
Smarter Ways to Diagnose Cardiovascular and Heart Disease (PJB Publications, 2003)
Stem Cells: Identifying Commercial Opportunities (Reuters, 2006)
Systems Biology: The future of integrated drug discovery (PJB Publications, 2004)
The Emerging Drug Targets Outlook: An Analysis of Novel Molecular Targets (Reuters, 2005)
The Future of In Vitro and In Vivo Diagnostic Integration (Business Insights, 2011)
The Future of RNAi Therapeutics: Drug Pipelines and Prospects (Business Insights, 2008)
The Outlook for the Biotech Sector in the Post-Genomic Era (Reuters, 2002)
Theranostics: Commercial Opportunities for Diagnostic and Pharmaceutical Companies (D&MD, 2001)
Transmembrane Transporters: High Sales, High Potential (D&MD, 2006)
Veterinary Immunodiagnostics - A Global Survey (PJB Publications, 2000)

OTHER CERTIFICATIONS RELEVANT FOR YOUR POSITION/ ORGANIZATIONS MEMBERSHIP

In October 2013 I completed a Clinical Evaluation for Medical Devices Training Course delivered by BSI (British Standards Institution). As a Notified Body under the Medical Devices Directives, BSI has one of the broadest scopes of any Notified Body.

TRAININGS AND COURSES: Professional Development Log – available on request as attachment to this CV

COMPUTER/TECHNICAL SPECIFIC COMPETENCES

Systems:	N/A
Program Languages:	N/A
Software: (in addition to Microsoft Package)	N/A

I, the undersigned, in relation to all the projects and activities conducted within CROMSOURCE, to all the information and connected material and, furthermore, to the intellectual property rights,

Declare:

- to keep strictly confidential all information, data and strategies which will be communicated by CROMSOURCE;

- to maintain all the documentation and the materials strictly confidential and not to disclose their content, wholly or in part, to any third party;

- to strictly limit this documentation only to those collaborators who necessarily require access to it for the purpose of their job, who have been informed of its confidential nature and who are obliged to keep the secret;

- not to use this documentation in any way, except for the purpose agreed upon with CROMSOURCE;

- to be aware, and to authorize accordingly since now, that the present Curriculum Vitae, with all the information contained, can be made available within the Company and to Competent Authorities, concerned Clients and Auditors in general.

I authorize the treatment of my data according to the applicable local regulation about data protection and any further amendments (Data Protection Act)

Signature: _____ **Date: 6 April 2014**

Dr. Malgorzata Kaczorowska was selected as the Expert Reviewer for this CER for the following reasons:

- Dr. Kaczorowska is an ENT Specialist who has almost 20 years of experience in the medical profession.
- Dr. Kaczorowska has extensive experience with and knowledge of medical devices used for the treatment of respiratory disease
- Dr. Kaczorowska was trained on the CROMSOURCE CER SOP on August 1, 2015

GENERAL INFORMATION	
Name and Surname	Malgorzata Kaczorowska
Date of birth	16/Oct/1970
Place of birth	Warsaw
Nationality	Polish
Mother tongue Language	Polish
Present Job Position	Medical Monitor

EDUCATION	
Education	Specialist in Audiology and Phoniatry; Board Certification in Audiology and Phoniatry Certificate No. 0733/2013.1/3
Institution – City (Country)	Ministry of Health, Poland
Date	2013
Education	ENT Specialist; Board Certification in Otorhinolaryngology Certificate No. 0721/2005.2/16
Institution – City (Country)	Ministry of Health, Poland
Date	2005
Education	PhD; Doctoral Thesis in Medicine, Clinical Immunology
Institution – City (Country)	Medical University of Warsaw, Poland
Date	2004
Education	MD; Faculty of Medicine Certificate No. L15800/28688/96
Institution – City (Country)	Medical University of Warsaw, Poland
Date	1996

LANGUAGE SKILLS			
Language	English	Level	4
Language	Spanish	Level	1
Language	Russian	Level	1

Level 1: Beginner understands read and spoken language, not able to clearly formulate his thoughts in the given language, makes grammar mistakes and uses very basic vocabulary when speaking or writing.

Level 2: Speaking skills are better but the vocabulary used and sentence structures are still basic; makes pronunciation mistakes, lacks fluency.

Level 3: Comfortable speaker and writer, can build more complex structures and formulate thoughts in a clear manner, makes some grammar mistakes.
Level 4: Experienced and fluent user, pronunciation & accent are correct, speaking rhythm is regular, writing skills are developed, language used is rich.

PROFESSIONAL EXPERIENCE/CAREER HISTORY	
Company	CROMSOURCE
Job Position	Medical Monitor
Date (from-to)	Sep/2014 - ongoing
Main tasks and Responsibilities:	Is clinical advisor for the entire lifecycle of the clinical trial by answering to medical questions Participates actively in the project meetings by giving his/her medical advice Reviews study data listing from a medical point of view Analyses and makes an independent interpretation of study data/results Writes and/or reviews protocol, Care Report Form (CRF) and Clinical Study Reports (CSR) Provides training in specific disease/therapeutic area
Company	COVANCE
Job Position	Clinical Research Associate
Date (from-to)	Nov/2013 – Aug/2014
Main tasks and Responsibilities, if relevant for your present position:	Responsible for all aspects of study site monitoring and management, CRF review, query generation and resolution, tracking and following-up on serious adverse events. Involved in the administration of clinical research project and managing investigator site budgets.
Company	ENT Department of The Children's Memorial Health Institute, Warsaw, Poland
Job Position	Physician
Date (from-to)	Feb/2012 – Nov/2013
Main tasks and Responsibilities, if relevant for your present position:	ENT/audiology consultant for patients of The Children's Memorial Health Institute, Warsaw, Poland. Providing evaluation and treatment of a board range of inborn and acquired ear, nose and throat disorders.

Company	**8.1.1 Institute of Hearing Physiology and Pathology, Warsaw, Poland**
Job Position	Physician
Date (from-to)	Feb/2009 – Feb/2012
Main tasks and Responsibilities, if relevant for your present position:	Providing care for patients with problems related to hearing loss, tinnitus and hyperacusis, vertigo and balance disorders, speech and voice disorders.
Company	Medical Network CRO, Warsaw, Poland
Job Position	Medical Monitor
Date (from-to)	Dec/2009 – Nov/2010
Main tasks and Responsibilities, if relevant for your present position:	As medical monitor responsible for providing supervision and coordination of medical issues related to clinical research including: protocol clarifications, inclusion/exclusion determinations, issues of patient safety.

PROFESSIONAL EXPERIENCE/CAREER HISTORY	
Company	Medical Network CRO, Warsaw, Poland
Job Position	Clinical Research Associate
Date (from-to)	Mar/2007 – Jan/2009
Main tasks and Responsibilities, if relevant for your present position:	As CRA responsible for feasibilities, site selection, all aspects of study site monitoring and management, CRF review, query generation and resolution, track and follow-up on serious adverse events.
Company	Department of ENT, Medical University of Warsaw, Poland
Job Position	Physician
Date (from-to)	2000 – Mar/2007
Main tasks and Responsibilities, if relevant for your present position:	Providing evaluation and treatment for patients with ear, nose and throat disorders. Area of special interest Otology and neurootology. As a member of Cochlear Implant Program team involved in assessment of candidacy requirements, surgery, postoperative care, speech processor fitting and hearing rehabilitation in deaf patients. Rhinology- providing medical and surgical treatment of patients with diseases of the nose and sinuses including chronic rhino-sinusitis and Aspirin-exacerbated respiratory disease (AERD).
Company	Department of Pediatric ENT, Medical University of Warsaw, Poland
Job Position	Physician
Date (from-to)	1997-1999
Main tasks and Responsibilities, if relevant for your present position:	Providing care for pediatric patients with a board range of ear, nose and throat disorders.
Company	Department of Laboratory Diagnostics and Clinical Immunology, Medical University of Warsaw, Poland
Job Position	Researcher; Postgraduate Research Study
Date (from-to)	1997 – 2003
Main tasks and Responsibilities, if relevant for your present position:	Performing laboratory assays in haematology, chemistry and immunology. Area of special interest - diagnosis of immunodeficiency, diagnosis and monitoring of leukaemia and lymphoma by flow cytometry. Involved in research studies on primary immunodeficiency.

CLINICAL RESEARCH EXPERIENCE

Therapeutic area (pathology)	Countries Managed	Phase	Main responsibilities	
Asthma - long acting inhaled muscarinic antagonist	Europe	IIb	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ■ Medical Monitoring	☐ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
COPD –long acting inhaled muscarinic antagonist	Europe	II	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ■ Medical Monitoring	☐ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Preeclampsia - apheresis treatment with high affinity antibody adsorption column	Central Europe	I/II	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ■ Medical Monitoring	☐ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Cirrhosis with refractory and recurrent ascites – implantable alfa-pump system	USA, Canada	IV	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ■ Medical Monitoring	☐ Document management ☐ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Alzheimer's Disease - Tau Aggregation Inhibitor (TAI)	Americas, Europe, Asia, Australia	III	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ■ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Behavioral Variant Frontotemporal Dementia (bvFTD) - Tau Aggregation Inhibitor (TAI)	Americas, Europe, Asia, Australia	III	☐ Project management ☐ Feasibility ☐ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ■ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics

Breast cancer - antineoplastic monoclonal antibodies	Central Eastern Europe	III	☐ Project management ☐ Feasibility ■ All CRA activities ☐ Clinical Monitoring ■ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Breast cancer - antineoplastic monoclonal antibodies	Central Eastern Europe	II	☐ Project management ☐ Feasibility ■ All CRA activities ☐ Clinical Monitoring ■ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Renal transplantation: immunosuppressive - calcineurin inhibitor	Central Eastern Europe	III	☐ Project management ☐ Feasibility ■ All CRA activities ☐ Clinical Monitoring ■ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Pediatric renal transplantation: immunosuppressive - calcineurin inhibitor	Central Eastern Europe	II	☐ Project management ☐ Feasibility ■ All CRA activities ☐ Clinical Monitoring ■ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Prostate cancer - alpha particle emitting radiopharmaceutical	Central Eastern Europe	II	☐ Project management ■ Feasibility ■ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Hypercholesterolemia - CETP inhibitor	Central Eastern Europe	III	☐ Project management ☐ Feasibility ■ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics
Schizophrenia in adults - dopamine/serotonin stabilizer IM depot	Central Eastern Europe	III	☐ Project management ☐ Feasibility ■ All CRA activities	☐ Document management ■ Management of AE/SAE ☐ Safety reporting

			☐ Clinical Monitoring ☐ Regulatory submissions ☐ Medical Monitoring	☐ Auditing ☐ Data Management ☐ Statistics
Bipolar 1 Disorder - MT1/MT2 agonist	Central Eastern Europe	III	☐ Project management ☐ Feasibility ■ All CRA activities ☐ Clinical Monitoring ☐ Regulatory submissions ☐ Medical Monitoring	☐ Document management ■ Management of AE/SAE ☐ Safety reporting ☐ Auditing ☐ Data Management ☐ Statistics

PUBLICATIONS

Papers published under the name M.Kowalska till 2005 year

M.Kaczorowska MIFurmanek PKlimek HSkarżyński Iatrogenic internal carotid artery pseudoaneurysm as a complication of myryngotomy in 6-years-old boy Otolar. Pol. 2012; Vol.66; p368-372;

Kazimierz Niemczyk, Agnieszka Olejniczak, Malgorzata Kaczorowska, Lidia Mikolajewska, Katarzyna Pierchala, Krzysztof Morawski, Arkadiusz Paprocki Vestibular function in cochlear implant candidates Otolar. Pol. 2009; Vol.63; p168-170.

Kazimierz Niemczyk, Antoni Bruzgielewicz, Krzysztof F. Morawski, Malgorzata Kaczorowska, Lidia Mikolajewska, Olimpia Stanislawska-Sut Residual Hearing Status after Implantation of Various Types of Cochlear Implant Electrodes. Otolaryngology - Head and Neck Surgery 2005, Vol.133, Iss.2, Supplement, p P135

Maria Wąsik, M. Kaczorowska, U. Demkow. Altered expression of immune surface markers in children with recurrent infections of respiratory tract. J. Physiol. Pharmacol.2005; Vol.56; Supl.4; p.237-243;

R. Bartoszewicz, K Niemczyk, Andrzej Marchel, M. Kowalska Sudden deafness as a presentation of acoustic neuroma. Pol. Merk. Lek. 2005; Vol.19; nr 111; p.307-308;

K Pierchała, I Krzeska-Malinowska, M. Kowalska, R. Bartoszewicz, K Niemczyk. Long-term results of the transtympanic gentamicin treatment in Meniere's disease. Otolar. Pol. 2005; Vol.59; nr 3; p.409-413;

L. Mikołajewska, K Pierchała, M. Kowalska, K. Kochanek, K Niemczyk. Auditory neuropathy – diagnostics and therapy Otolaryngology – clinical review, 2004,Vol.3, nr 4; p.146-148

M. Kaczorowska, L. Mikołajewska, A Woźniak, J. Piotrowski, Z. Łukaszewicz-Moszyńska, K.Niemczyk Cochlear implants: qualification procedure in the pediatric population. New Medicine 2004, Vol.4; p.105-108

M Wąsik, B Jakubczak, M Kowalska Phenotypic and functional characteristic of peripheral blood neutrophiles. Laboratory 2004 Vol.7; p.23-27

K Niemczyk, M. Kowalska. Tumors of the ear and temporal bone. Therapy 2003 Vol.. 11 nr 6/1;p. 34-38

I Krzeska-Malinowska, P Podogrodzki, M. Kowalska, K Niemczyk.Transtympanic steroides application in sudden deafness. Otolar. Pol. 2003 Vol. 57 nr 4; p. 549-553

T. Kucharski, K Niemczyk, M. Kowalska, A Bruzgielewicz, R. Bartoszewicz. Overview of new methods of visualization in operating field in aspect of inner ear surgery.Otolar. Pol. 2003; Vo.l 57; nr 6; p. 881-887;

K Kądziela, H. Kowalska, B Rymkiewicz-Kluczyńska, M. Kowalska, G Miszkurka, J. Rybczyńska, M Wąsik, E Pańkowska. Changes in lymphocyte subsets in children with newly diagnosed type 1 diabetes mellitus. J. Pediatr. Endocrinol. Metab. 2003; Vol.16; nr 2; p.185-191

M. Kowalska, H. Kowalska, L Zawadzka-Głos, M Dębska, E. Szerszeń, M Chmielik, M Wąsik. Dysfunction of peripheral blood granulocyte oxidative metabolism in children with recurrent upper respiratory tract infections. Int. J. Pediatr. Otorhinolaryngol 2003; Vol. 67; nr 4; p. 365-371

PUBLICATIONS

I Krzeska-Malinowska, M Held-Ziółkowska, M. Kowalska, K Niemczyk The role of immunological factors in Meniere`s disease. Otolar. Pol.2002 Vol. 56 nr 5; p. 583-587

I Krzeska-Malinowska, K Pierchała, M Held-Ziółkowska, K Niemczyk, M. Kowalska Intratympanic gentamycin application for the treatment of Meniere`s disease. Otolar. Pol. 2001 Vol. 55 nr 6; p. 623-626

M Wąsik, H Kowalska, B. Gałązka, J Rybczyńska, M. Kowalska, E Wagiel. Flow cytometric detection of leukemia and lymphoma in the cerebrospinal fluid. Cent. Eur. J. Immunol. 1999 Vol.24 nr 3;p.191-195

M. Wąsik, M. Chmielik, M. Kowalska, L Zawadzka-Głos, J Rybczyńska, E Górska. Lymphocytes subpopulations disturbances in children with tonsillar hypertrophy. New Medicine 1999 Vol.3/17; p.246-249

OTHER CERTIFICATIONS RELEVANT FOR YOUR POSITION/ ORGANIZATIONS MEMBERSHIP

8.1.2 Member of Polish Association of Otolaryngologists/Head & Neck Surgeons
Member of Polish Association of Audiologists

TRAININGS AND COURSES: Professional Development Log – available on request as attachment to this CV

COMPUTER/TECHNICAL SPECIFIC COMPETENCES

Systems:	Windows 7, Vista, XP
Program Languages:	n/a
Software: (in addition to Microsoft Package)	Statistica

CROM SOURCE

CURRICULUM VITAE – *Malgorzata Kaczorowska*

I, the undersigned, in relation to all the projects and activities conducted within CROMSOURCE, to all the information and connected material and, furthermore, to the intellectual property rights,

Declare:

- to keep strictly confidential all information, data and strategies which will be communicated by CROMSOURCE;
- to maintain all the documentation and the materials strictly confidential and not to disclose their content, wholly or in part, to any third party;
- to strictly limit this documentation only to those collaborators who necessarily require access to it for the purpose of their job, who have been informed of its confidential nature and who are obliged to keep the secret;
- not to use this documentation in any way, except for the purpose agreed upon with CROMSOURCE;
- to be aware, and to authorize accordingly since now, that the present Curriculum Vitae, with all the information contained, can be made available within the Company and to Competent Authorities, concerned Clients and Auditors in general.

I authorize the treatment of my data according to the applicable local regulation about data protection and any further amendments (Personnel Protection Act 29.08.1997 Journal of Laws no 133 position 883)

Signature: _____ **Date:** 29 Апрель 2015

Appendix K: Clinical Investigation Documents

There are no relevant clinical investigation documents.

Appendix L: Regulatory References

Active Implantable Medical Device Directive (AIMDD) 90/385/EEC

Global Harmonisation Task Force GHTF/SG5/N4: 2010 Post Market Clinical Follow-up studies

Global Harmonisation Task Force SG5-N2R8: 2007 Clinical evaluation

MEDDEV 2.12.2 rev 2 (Jan 2012) Post Market Clinical Follow-up studies

MEDDEV 2.7.1 rev 3 (Dec 2009) Clinical evaluation: a guide for manufacturers and notified bodies

Medical Device Directive (MDD) 93/42/EEC (consolidated by the 2007/47/CE)

Others (eg. National regulations)

Procedures

Proposal for a Regulation of the European Parliament and of the Council on Medical Devices, and Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009; issued 26 Sep 2012

Appendix M: References

BALFOUR-LYNN, I. M., FIELD, D. J., GRINGRAS, P., HICKS, B., JARDINE, E., JONES, R. C., MAGEE, A. G., PRIMHAK, R. A., SAMUELS, M. P., SHAW, N. J., STEVENS, S., SULLIVAN, C., TAYLOR, J. A., WALLIS, C. & PAEDIATRIC SECTION OF THE HOME OXYGEN GUIDELINE DEVELOPMENT GROUP OF THE, B. T. S. S. O. C. C. 2009. BTS guidelines for home oxygen in children. *Thorax,* 64 Suppl 2**,** ii1-26.

BOLTON, C. E., ANNANDALE, J. A. & EBDEN, P. 2006. Comparison of an oxygen concentrator and wall oxygen in the assessment of patients undergoing long term oxygen therapy assessment. *Chron Respir Dis,* 3**,** 49-51.

CHATBURN, R. L., LEWARSKI, J. S. & MCCOY, R. W. 2006. Nocturnal oxygenation using a pulsed-dose oxygen-conserving device compared to continuous flow. *Respir Care,* 51**,** 252-6.

EATON, T. E., GREY, C. & GARRETT, J. E. 2001. An evaluation of short-term oxygen therapy: the prescription of oxygen to patients with chronic lung disease hypoxic at discharge from hospital. *Respir Med,* 95**,** 582-7.

HARDINGE, M., SUNTHARALINGAM, J. & WILKINSON, T. 2015. Guideline update: The British Thoracic Society Guidelines on home oxygen use in adults. *Thorax,* 70**,** 589-91.

JOHNS, D.P., ROCHFORD, P.D., STREETON, J.A. 1985. Evaluation of six oxygen concentrators. Thorax. 40:806-10.

LEBLANC, C. J., LAVALLEE, L. G., KING, J. A., TAYLOR-SUSSEX, R. E., WOOLNOUGH, A. & MCKIM, D. A. 2013. A comparative study of 3 portable oxygen concentrators during a 6-minute walk test in patients with chronic lung disease. *Respir Care,* 58**,** 1598-605.

LOBATO, S. D., RODRIGUEZ, E. P. & ALISES, S. M. 2011. Portable pulse-dose oxygen concentrators should not be used with noninvasive ventilation. *Respir Care,* 56**,** 1950-2.

NASILOWSKI, J., PRZYBYLOWSKI, T., ZIELINSKI, J. & CHAZAN, R. 2008. Comparing supplementary oxygen benefits from a portable oxygen concentrator and a liquid oxygen portable device during a walk test in COPD patients on long-term oxygen therapy. *Respir Med,* 102**,** 1021-5.