

Provox HMEs and HMEFs  
Literature Review

# Provox HMEs and HMEFs

**Including Provox XtraHME and Provox Life product ranges**

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# 1. Summary

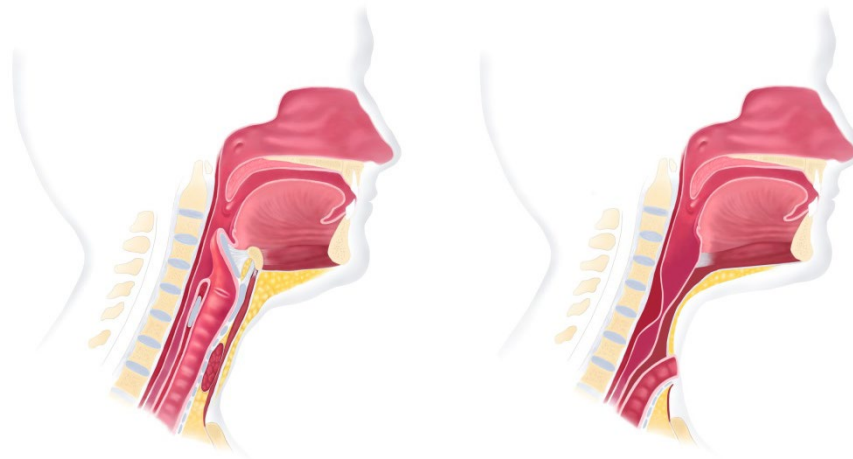
This literature review aims to provide an overview of the published work on the different generations of **Provox Heat and Moisture Exchangers (HMEs), attachments and accessories developed by Atos Medical**.

The Literature review includes an introduction to the physiological and pulmonary consequences of a total laryngectomy and introduces pulmonary rehabilitation with HMEs in general. Then, it describes the different HMEs, and attachments manufactured by Atos Medical. After that, clinical evidence on Provox HMEs and attachments is presented. The searches were conducted using product names and their generic names as keywords in the PubMed search engine and Cochrane library, covering a period between 1990 and July 2024. Additionally, Atos's own company database with publications on these products was screened for relevant publications.

Atos Medicals HMEs and attachments have been extensively studied. Due to this, in the laryngectomized population, HMEs are considered the gold standard for pulmonary rehabilitation. Use of HMEs have shown short-term effects such as reduced dispersion of droplets, containment of secretions, decreased tracheal dryness and irritation, increased tracheostoma hygiene, easier and more hygienic stomal occlusion, and improved intelligibility of speech. Long-term effects seen, after more than 2 weeks of compliant use, were significant decreases in mucus production and plugging, coughing, forced expectorations, shortness of breath, stomal cleaning, and pulmonary infections. Significant improvements were also seen in sleep, fatigue, psychosocial aspects, and improved Quality of Life. HMEs have been shown to reduce complications in the post-operative phase. Use of HMEs has also been shown to be cost-effective, both in post-operative in-patient setting and during long-term use.

## 2. Physiological and pulmonary consequences of total laryngectomy

During a total laryngectomy, the entire larynx is irreversibly removed, which leads to a permanent disconnection of the upper and lower airways. The patient breathes in and out through a permanent tracheostoma in the neck instead of through the nose and mouth (see Figure 1). Therefore, the functions of the upper airways are affected. These include warming, humidifying, and filtering of inhaled air and providing upper airway resistance (1).



**Figure 1.** Schematic drawing of normal anatomical situation (left) and the anatomical situation after total laryngectomy (right). In the normal situation the patient can inhale and exhale through the nose and mouth. After total laryngectomy, the upper airways are bypassed, and breathing takes place through the tracheostoma in the neck.

In addition, these anatomical changes lead, among other things, to changes in voice production, breathing, and olfaction. In the following sections, clinical evidence pertaining to the impact of breathing through a tracheostoma on tracheal climate, filtration, breathing resistance, pulmonary health and quality of life will be described.

### 2.1 Tracheal climate (temperature and humidity)

During normal nasal inspiration in a healthy individual with unaltered anatomy, ambient air of, for example, 22°C and 40% Relative Humidity (RH) is conditioned to 29°C and 21 mg H<sub>2</sub>O/L (70% Relative Humidity (RH)) in the nose and is further heated to approximately 32°C and 35 mg H<sub>2</sub>O/L (98% RH) at the subglottic level(2-5). The point where the inspired gas reaches 44 mg H<sub>2</sub>O/L (100% RH) at 37°C, is known as the isothermal saturation limit (ISB).

During nasal inspiration the air passes further through the respiratory tract and it reaches these conditions in the small peripheral airways(6). During inspiration through a tracheostoma the ISB moves towards more peripherally located airways and humidification takes place in regions of the airways that only have limited suitability for exchange of heat and moisture

leaving a large part of the airways with a humidification deficit(5). Therefore, in patients breathing through a tracheostoma ambient air of, for example, 22°C and 40% RH is only conditioned to 27-28°C and 50% RH at the level of the upper trachea (7), see Figure 2 .

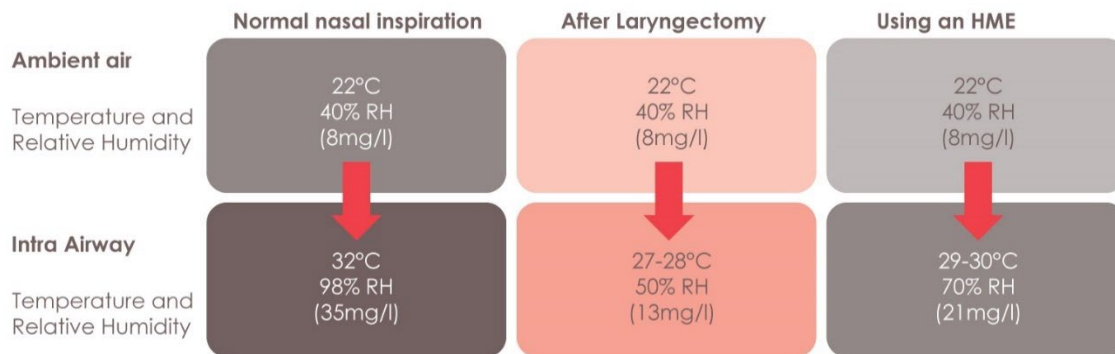


Figure 2. Description of intra-airway tracheal climate in different breathing conditions accordingly to Scheenstra et al., 2011. The end-inspiratory relative air humidity (RH) and temperature (C) are given. The measurements were made at room temperature conditions.

Both temperature and humidity have a significant impact on the ciliary activity in the trachea. During normal conditions the cilia move to clear the surface of mucus and impurities or particles that have been deposited in the peripheral regions of the lungs towards the mouth, where the secretion is swallowed, expectorated or aspirated (8, 9). Studies in a rabbit model have shown that at body temperature (37°C) the cilia stop beating when the RH drops below 50%. When RH lowers to 60% there already is a reduction in the mucociliary frequency of 30% (7, 10, 11). The preservation of the mucociliary clearance, together with the filtration function of the nose, as described in the following section, are important for defense against infections.

## 2.2 Filtration

Apart from warming and humidification, filtration of the air is one of the most important functions of the nose. During normal breathing, the nose not only humidifies and heats the inhaled air but it also filters the air of airborne particles (12). Filtration is important for multiple reasons. One is that the airborne spread of viral and bacterial disease requires, among other things, that infectious particles are inhaled by susceptible individuals and deposited at effective sites within the respiratory system (13). The risk of infection is directly related to the infectious dose of a pathogen, i.e. the number of particles needed to start an infection (14).

Filtration can help prevent the number of particles inhaled, thus reducing the chance the infectious dose is reached. The other reason that filtration by the upper airways is important, is that not only airborne bacteria and viruses are filtered, but also other particles such as

allergens, pollen, dust and Particulate Matter (PM)(12). PM refers to small ambient airborne particles from various sources (15-18) and is the pollutant that affects the most people worldwide (19, 20). It is the most harmful fraction of air pollution(20) and has no threshold below which it is not harmful (21). Even exposure at levels below the latest standards contributes to hospital admissions, ER visits, and is linearly associated with all-cause mortality (22-26). Literature suggests that a reduction in exposure to PM can be expected to improve health almost immediately and states that this should be taken into account for cost-benefit analyses, as PM has been shown to place a heavy burden on worldwide healthcare financially (26, 27).

The filtration of air is a complicated subject and depends on tidal volume, breathing pattern, air flow velocity, airway geometry as well as on numerous other parameters including particle mobility, density, hygroscopicity, shape and chemical composition and diameter of particle size (13, 28, 29). The deposition rate and location within the nose depends on the particle diameter. More than 80% of particles of 1-3  $\mu\text{m}$  deposited within the entire nasal airways were held back at the nasal part. About 90% of particles larger than 4  $\mu\text{m}$  were held back in the anterior nasal airways (30).

In laryngectomized patients, the filtration function of the upper airway is entirely lost as the upper airways are completely and permanently bypassed and the patient only breathes through the tracheostoma. Therefore, neck breathers are more susceptible to a much higher deposition of all types of airborne particles in the lower airways. As a result of this lack of filtration as well as the humidification deficit resulting from the loss of the conditioning of the inhaled air in the upper airways, laryngectomized patients experience increased respiratory infections (31-33).

### **2.3 Breathing resistance**

Upper airway resistance accounts for 50-75% of total airway resistance during quiet breathing in normal individuals, of which two thirds is caused by nasal resistance (34, 35). Resistance of the upper airways is an important mechanical respiratory parameter for the optimal alveolar function and gas exchange in the respiratory system. It determines the effort it takes to breathe. Additionally, resistance ensures a difference in pressure between the alveoli and the outside, the transpulmonary pressure that causes the small airways to stay open.

The resistance of the upper airways is dynamic and changes depending on the airflow needs in case of temporary requirement of higher oxygenation. This can be achieved by widening the respiratory tract or switching to oral breathing (36). As a result of a total laryngectomy, this dynamic ability to adapt breathing resistance is lost, since breathing takes place via the 'resistance-free' tracheostoma. This implies that the work of breathing reduces and resistance becomes less dynamic.

It has been hypothesized that the loss of upper airway resistance increases dynamic airway compression by shifting the equal pressure point toward a more peripheral airway region, where the airway has less elasticity and is more easily flattened (37). Because of a decrease

in transpulmonary pressure, these airways might then be compressed, which may cause atelectatic collapse of small airways (38).

Furthermore, it has been suggested that a reduced resistance to expiration indirectly decreases arterial oxygen saturation by reduced expiratory lung volumes, resulting in suboptimal pulmonary gas exchange (37, 39, 40).

## 2.4 Pulmonary health and quality of life

The loss of respiratory conditioning by the upper airways has a negative impact on the tracheobronchial system, which in response to the humidification deficit greatly increases mucus production. The humidification deficit also causes increased viscosity of the mucus. This increased mucus production leads to symptoms such as increased coughing and forced expectoration which tends to exacerbate during dry and cold seasons. In patients unable to cough up secretions themselves this may also lead to a need for tracheal suctioning. The combination of increased mucus production and increased viscosity can lead to mucus plugs and the dried secretions can form into crusts. Increased nasal discharge and shortness of breath have also been reported (1, 37, 41-46).

Furthermore, tracheobronchial irritation produces extensive histological changes: squamous metaplasia of the respiratory ciliary epithelium and chronic inflammatory changes of the lamina propria have been observed in the trachea at the level of the carina in laryngectomized and tracheostomized patients (47, 48). This leads to excessive sputum production, frequent involuntary coughing, and repeated forced expectorations to clear the airway (49, 50). These pulmonary symptoms generally develop and increase within the first 6 to 12 months after initial surgery and then tend to stabilize (41, 51).

Laryngectomized patients experience the physical consequences of having a stoma (frequent sputum production from the stoma and its interference with social activities) as the most severe side effect of their surgery (43) (37). The pulmonary symptoms significantly affect the quality of life of the patient; perceived quality of voice, aspects of daily life, anxiety and depression (1, 52).

## 3. Pulmonary rehabilitation with Heat and Moisture Exchangers

Heat and moisture exchangers (HMEs) compensate for the loss of the natural humidification functions of the nose and are considered standard of care in laryngectomized patients (53, 54). In this section the basic properties and functions of HMEs and HMEFs (Heat and Moisture Exchangers with Filter) are described, followed by a historical overview of HME development and a description of the properties and functions of the HMEs, attachments and accessories in Atos Medical's portfolio.

### 3.1 HMEs and HMEFs properties and function

Pulmonary rehabilitation seeks to compensate for airway humidification deficits with the ultimate goal of reducing the adverse effects of total laryngectomy on pulmonary health. Heat and Moisture Exchangers (HMEs) are passive humidifiers that were developed to compensate for the loss of heating and humidification by the upper airways in neck breathers. In short, an HME has three physical properties: 1) heat and moisture exchanging capacity; 2) resistance; and to a small extent 3) filtering particles (55). The basic component of a heat and moisture exchanger is foam, paper, or another substance, which acts as a condensation and absorption surface. To enhance the water-retention capacity, the material is often impregnated with hygroscopic salts such as Calcium Chloride (56) (see Figure 3). The HMEs used for neck breathers are mostly hygroscopic and may also be impregnated with a bactericide solution (e.g. chlorine hexedine) to attempt to control bacterial colonization (57, 58).

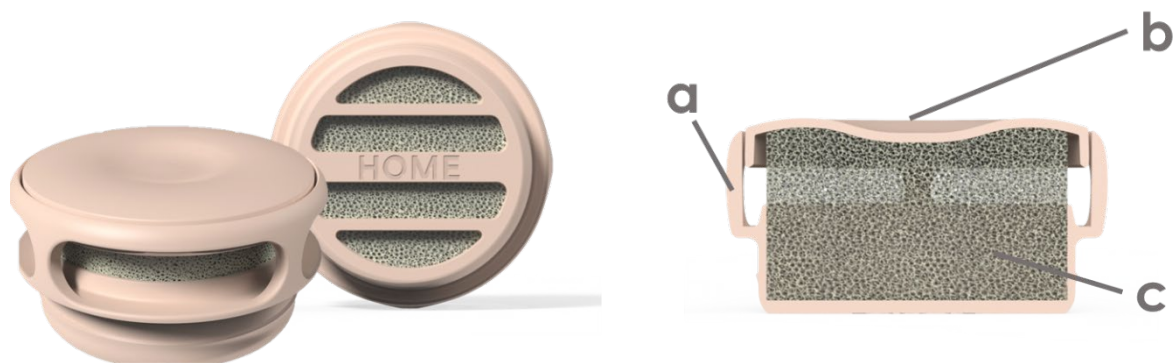


Figure 3. HME (HME pictured: Provox® Life™ Home HME) and its general components. On the left-hand side, an HME with manual occlusion function is shown from the top and bottom sides. On the right-hand side, a cross-section of an HME is shown including the plastic outside of the HME (a), the plastic lid that is pushed down to close the HME airtight for speaking (b), and the foam on the inside, treated with calcium chloride to retain heat and moisture from exhaled air (c).

An important feature of an HME is a mechanism to facilitate occlusion of the tracheostoma to generate tracheoesophageal speech. This can be accomplished via manual occlusion on the lid of the HME or 'automatically' with a handsfree speaking valve incorporating a membrane that closes automatically when exhaled airflow increases to generate speech (59). The basic functions of an HMEs are illustrated in Figure 4.



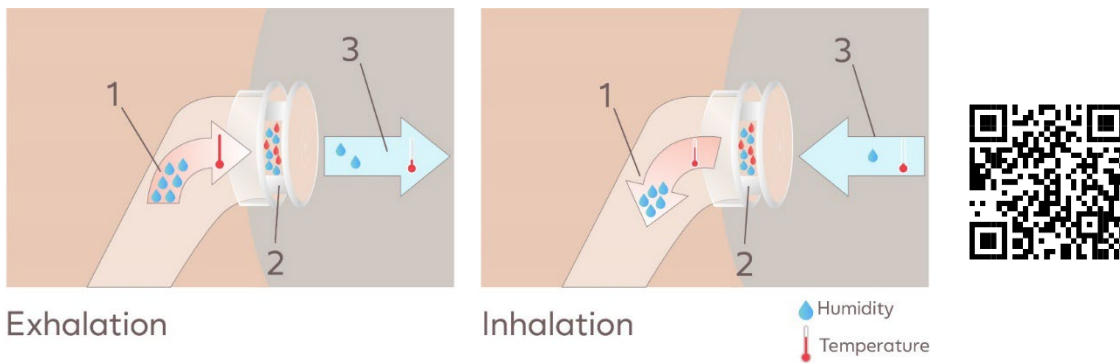


Figure 4. Working

principle of an HME. The illustration on the left-hand side shows the mechanism during exhalation (breathing out): Heat and humidity from the exhaled air (1) is being collected in the HME (2). Thus, there is limited loss of heat and moisture into the environment. The illustration on the right-hand side demonstrates how this heat and moisture is returned (1) to the air that passes through the HME (2) on inhalation of cold and dry air (3). QR code shows benefits of using an HME.

With regards to the filtering function, a standard HMEs act as a barrier to larger airborne particles, but due to their large pore size they do not filter microorganisms, pathogens or other small particles to a significant degree (55). On the other hand, HMEFs combine the humidification properties of an HME with the filtration properties of a highly effective electrostatic filter (>98% bacterial and viral filtration efficiency), which consist of a mat of fibers with electrostatic charges. Any opposing particle with charge is attracted and bound to the material and a hygroscopic layer is added to provide humidification. Electrostatic filters effectively filter small particles such as microorganisms and pathogens (See Figure 5) (60).

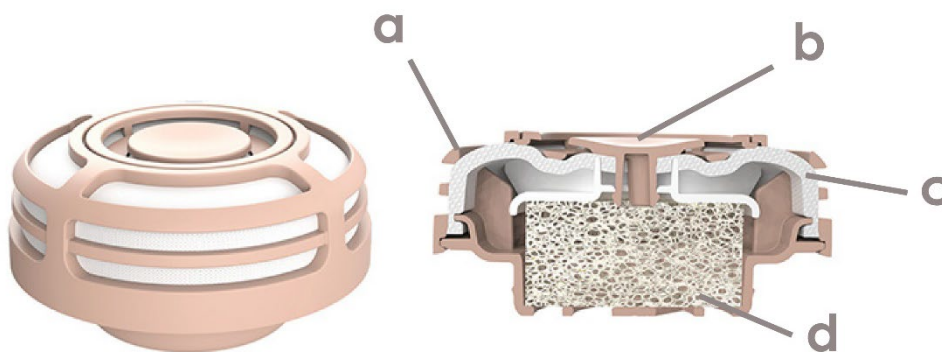


Figure 5. HMEF and its general mechanism. On the left-hand side, an HMEF for manual occlusion function is shown from the top and bottom side. On the right-hand side, a cross-section of an HMEF is shown. The plastic outside of the HMEF (a), the plastic lid that is pushed down to close the HME airtight for speaking (b), and the electrostatic filter inside (c) and the foam, treated with calcium chloride to retain heat and moisture from exhaled air (d).

In addition to heat- and moisture-retaining capabilities, HMEs and HMEFs partially restore the lost breathing resistance. It has been suggested that the breathing resistance provided by

HMEs create a positive end-expiratory pressure and thereby help to reduce alveolar collapse and improve lung volumes and gas exchange (39, 55, 61).

Another explanation is that HMEs increase extra-thoracic expiratory resistance comparable to the mechanism of purse lip breathing (PLB). This is a phenomenon familiar to patients with COPD, in whom PLB has been shown to improve arterial oxygenation (62-65). Use of PLB allows a reduction in dynamic airways compression. The positive effects of PLB are mainly attributed to enlarged transpulmonary pressures, reducing the tendency for alveoli to collapse (64-66).

Since a large percentage of laryngectomees present lung disorders in the form of COPD, similar positive effects can be expected by the partial restoration of breathing resistance provided by an HME (7, 37).

However, it is important to bear in mind that an HME also increases inspiratory resistance, in contrast to PLB, which can have clinically relevant effects since too high inspiratory resistance may cause patient discomfort and shortness of breath. It may not be tolerated for a longer period of time and can negatively affect adherence to HME use or the ability to use an HME during physical activity/exercise, impacting overall pulmonary rehabilitation (7, 8, 34).

### 3.2 History of pulmonary rehabilitation in laryngectomy patients

In 1960, Toremalm first described the benefits of HME use for laryngectomized and tracheotomized patients: in comparison to nasal breathing, a person breathing through a tracheostoma loses about 500 ml of water. Their results showed that by using an HME it was possible to retain 250 to 300 ml of this water loss in the respiratory system (67, 68). Additional studies have shown that the use of an HME reduced water loss of the inhaled air in anaesthetized patients (69, 70).

The use of HME also impacts the temperature in the respiratory system. Evidence shows that the tracheal climate can rapidly change after the application and removal of an HME. The use of an HME increases the temperature in the trachea from 27-28°C to 29-30°C and the relative humidity from 50% to 70% (as shown in Figure 2) after just 10 minutes of HME placement (71).

The temperature of inspired tracheal gases was significantly lower during breathing through an open stoma compared to breathing with an HME HCH, both at rest and during hyperventilation in tracheostomized patients (72). Furthermore, HMEs provided satisfactory heating and humidification of inspired gases, similar to a heated humidifier in spontaneously breathing tracheotomized patients (73). When comparing the humidification performance of an HME and a heating-and-humidification high-flow device in spontaneously breathing subjects with tracheostomy, the high-flow system achieved higher absolute humidity than the HME, however, both systems supplied an absolute humidity higher than the American Association for Respiratory Care requirements (HME >30 mg/L, heated-and-humidified high flow >33mg/L) (74).

Along with the temperature and humidification, the use of an HME was found to increase the capillary oxygen tension, which indicates the partial pressure of oxygen in the blood compared to a placebo (61).

In 1990, Ackerstaff and colleagues were the first to publish clinical results on the use of an HME in laryngectomized patients (75). The use of an HME ('StomVent') diminished the frequency of sputum production, forced expectorations and stoma cleaning (75). Additionally, short term effects after only 6 weeks of HME use were a reduction of respiratory symptoms and subsequently improved quality of life; a significant decrease in symptoms of fatigue and malaise and improved social contacts (76). The HME and baseplate tested in this study ('StomVent') were combined in one piece and could not be separated, which resulted in a relatively large number of problems with the adhesive loosening from coughing (76).

A subsequent clinical study tested a newer device where the HME and baseplate could be separated ('Freevent'). The results showed not only a reduction in the incidence of coughing but also the mean daily frequency of sputum production, forced expectorations, and stoma cleaning. The long-term HME user group (3 months of HME use) showed a significant improvement in shortness of breath, fatigue and malaise, sleeping problems, anxiety, depression and perceived voice quality (77). Furthermore, pulmonary function tests showed significant improvements in inspiratory flow and volume values following the use of an HME (77). Despite the fact that the HME and baseplate could be separated, loosening as a result of coughing still occurred frequently because the stoma was still not accessible for cleaning due to two crossed plastic bars blocking the entrance. In addition, this device was still difficult to occlude for tracheoesophageal speech as it did not include any mechanism for stoma occlusion.

The positive impact of HME use in laryngectomized patients was further confirmed in another study, in which patients were followed-up for 6 months. In that study, the use of the HME ('Freevent') showed significant improvement over time (from baseline to 3 and 6 months) in forced expectorations, perceived voice quality, social anxiety, social interactions and in feelings of anxiety and depression (78).

Respiratory parameters such as coughing, number of chest infections, mucus production and shortness of breath at rest improved in patients using an HME (Trachinaze) compared to a placebo (61). A literature review supported the use of HME devices and concluded they decrease the effect of sputum production, the need for ongoing suctioning, and the formation of stomal crusting as reported (79).

Two other extensive independent reviews (55, 80) concluded that the HME effectiveness on pulmonary rehabilitation is mainly due to the heating and humidification of inhaled air, and that is possibly that the added breathing resistance and slight particle filtration further benefit the respiratory system. However, it is not expected that an HME significantly compensates for the loss of upper airway filtration of smaller particles such as bacteria and viruses; the pores of the HME filter are large and there are no effective mechanisms to help capture and trap particles. Despite the fact that the use of HMEs does not effectively decrease colonization of the lower respiratory tract by pathogenic microorganisms, they do not endanger the health of patients with a tracheostoma through exposure to pathogenic microorganism either (81).

Although an HME cannot completely restore the physiological functions of the upper respiratory tract, depending on their humidification capacity they increase the temperature and humidity level of inspired air, helping to compensate for the humidification deficit in laryngectomized patients (82). Thus, having a positive effect on tracheal epithelium mucosa (82) and overall pulmonary health.

### 3.3 Provox HMEs and attachments

The impact of HME use on pulmonary health, humidification and heating of inspired air has been clearly demonstrated in initial clinical research and validated in several studies (76-78).

In 1995 Atos Medical developed the first generation of Provox HMEs. These first generation Provox HMEs were discontinued in 2016. They have been succeeded by the second generation, Provox XtraHMEs, in 2010 and the third generation, Provox Life HMEs, in 2020 (see Figure 6). The following sections briefly describe the Provox HMEs and their attachments and include performance characteristics (laboratory data) where relevant.

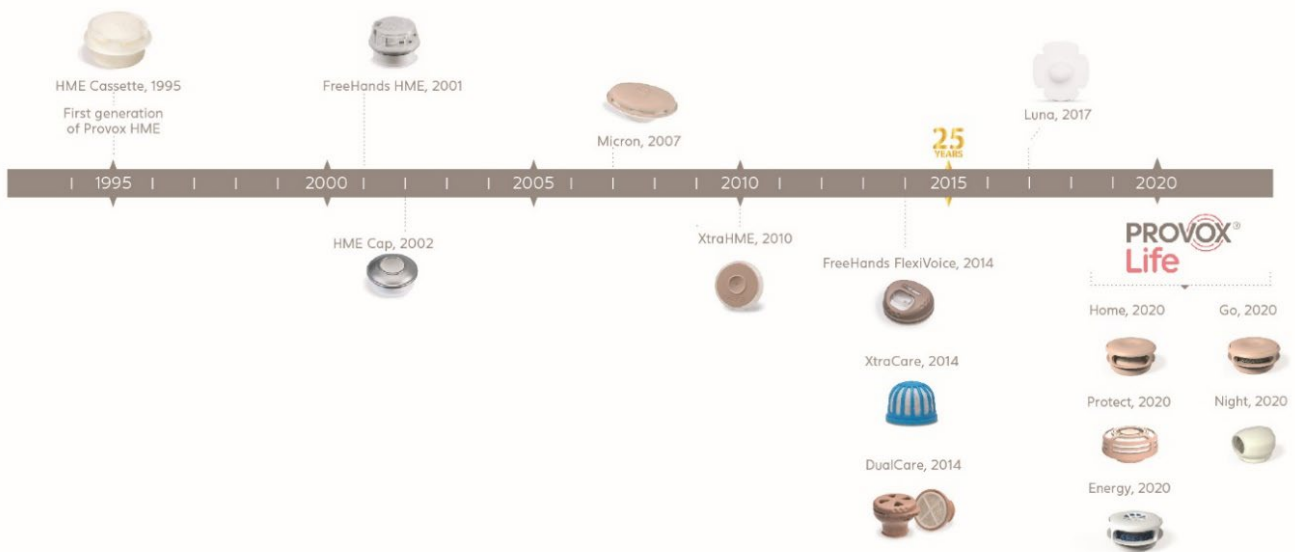


Figure 6. Timeline of the development of different Provox HMEs and HMEFs.

#### 3.3.1 Provox HMEs

##### Provox HME: Normal and HiFlow

The Provox HME development and design was guided by the remarks from patients in earlier HME studies (76, 77). The Provox HME consisted of a separate HME cassette and a self-adhesive baseplate available in two different shapes and four different materials to accommodate different skin types in stoma shapes (see Figure 7).

This first generation of Provox HMEs was available in Normal and HiFlow and was discontinued in 2016. The HiFlow cassette had a lower resistance than the Normal cassette.



Figure 7. Provox HME Normal (left) and Provox HME HiFlow (right).

### Provox XtraHMEs: XtraMoist and XtraFlow

Provox XtraHMEs were developed to provide improved performance in humidification capacity, an improved humidification capacity/airflow resistance ratio, and new design features to enhance usability in comparison to the first generation Provox HMEs. Provox XtraHMEs were introduced to the market in 2010 and are available in two versions: XtraMoist HME and XtraFlow HME (See Figure 8).



Figure 8. Provox XtraHME (XtraFlow and XtraMoist).

The XtraMoist HME Cassette, can be worn day and night under low to normal physical effort. The XtraFlow HME Cassette has a lower breathing resistance for use during increased physical effort and to enable adaptation to the increased breathing resistance associated with HME use in relation to open stoma breathing.

Compared to the Provox HMEs, the XtraHMEs have 50% more HME media (in volume), which acts as a spring. The XtraHME also has a 1.4 mm lower profile than the Provox HME, and a rim on the lid to guide the correct finger position for occlusion. In Figure 9 the differences between the Provox HME and the Provox XtraHME are shown.

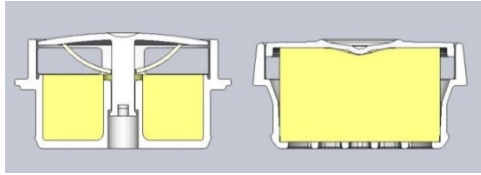


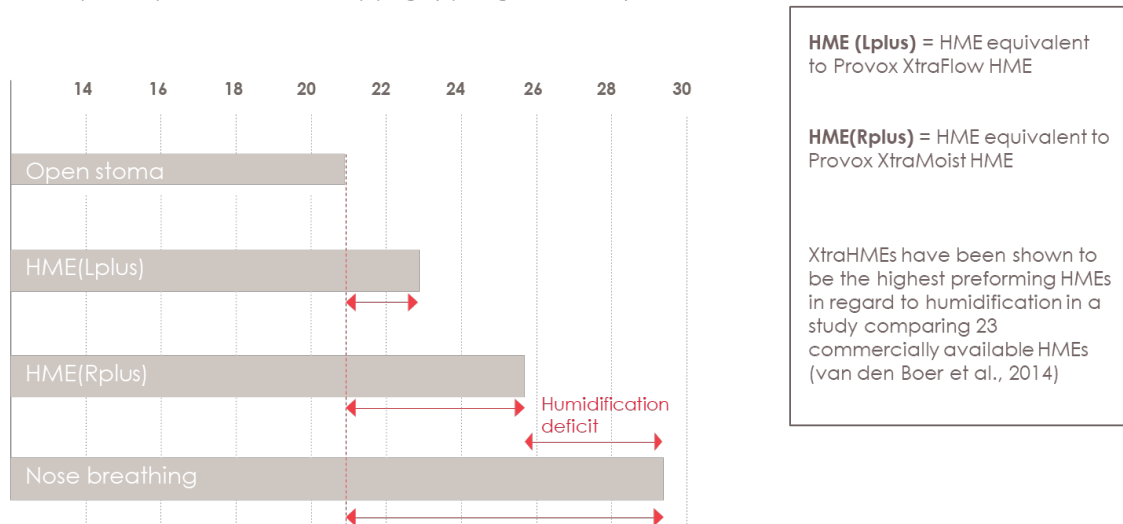
Figure 9. Schematic representation of Provox HME (left) and Provox XtraHME (right) in foam is shown in yellow.

The Provox XtraHMEs (XtraMoist and XtraFlow), which have a higher foam pore density to increase the surface area and binding capacity of hygroscopic salt in a similar size cassette, have been shown to have considerable heating and humidification improvement over Provox HME (83). Furthermore, Provox XtraMoist HME shows a significantly better water exchange performance than its predecessor according to a feasibility study (84) without decreasing the endotracheal temperature (85). Authors concluded that XtraHMEs show both heating and humidification improvement compared to the Provox HME.

In an ex vivo study comparing humidification performance of 23 commercially available HMEs for laryngectomized patients, Provox XtraMoist HME was shown to have a statistically significantly higher humidification capacity than all other tested HMEs (107). Thus, having a higher reduction of humidification deficit caused by breathing through an open stoma (see Figure 10).

Notably, these results are validated with absolute humidity outcomes. According to this study, humidification capacity correlates well with the end-inspiratory absolute humidity outcome. This means that the wet core weight of an HME is a predictor of its performance (107).

End inspiratory absolute humidity (mg/l) (subglottic level)



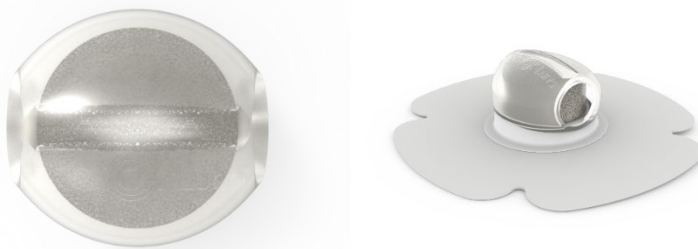
**Figure 10. HMEs increase end-inspiratory humidity levels versus open stoma breathing and reduce the humidification deficit versus nose breathing depending on their humidification capacity.**

Measuring the difference between wet and dry core weight in two different generations of HMEs (XtraMoist, XtraFlow, Normal and HiFlow). It has been demonstrated that the water uptake capacity of hygroscopic HMEs is no longer optimal after 24-hours of use due to condensation and secretion build up (86). Thus, from a pure humidification efficiency point of view, an HME should be used for no longer than 24 hours. However, in daily life the HME is replaced more frequently, (studies report 1.1 – 2.8 per day(87-89) <sup>1</sup>), owing to coughing up of secretions and variations in oxygen requirements throughout the day during different activity levels. More recently, COVID-guidelines for the management of laryngectomy care recommend also replacing the HME after community exposure (90).

### Provox Luna

An anthropological study conducted by Atos Medical with ReD Associates indicated that as many as 80% of the patients do not use an HME consistently during the night. Reasons cited include discomfort with the current solutions, lack of knowledge regarding the importance of compliant HME use, and the need for intermittent skin rest due to skin irritation. Consequently, compliant 24/7 HME use is not achieved by many patients, which has a negative effect on pulmonary rehabilitation<sup>2</sup>.

Launched in February 2017, Provox Luna HME and adhesive were developed to improve compliant HME use during night. Provox Luna consists of an adhesive and an HME. Provox Luna HME has a superior humidification capacity and comfort. Provox Luna adhesive is made



of skin friendly hydrogel material (See Figure 11).

**Figure 11. Provox Luna HME and adhesive.**

Provox Luna HME is a soft silicone HME with a pressure drop of 55Pa at 30L/min and a moisture loss of 21.4mg H<sub>2</sub>O/L air (according to device specification). With these values, the humidification properties of the Provox Luna HME are similar to Provox XtraMoist, whereas the pressure drop and hence the breathing resistance, is lower than for Provox XtraMoist (with a

<sup>1</sup> Pots-market surveillance activity conducted by Atos Medical in 2020-2021. Data on File.

<sup>2</sup> Study conducted by Atos Medical with ReD Associates, 2015. Data on file.



pressure drop of 70Pa) and slightly higher than that of Provox XtraFlow (with a pressure drop of 40Pa).

Provox Luna Adhesive is made of a hydrogel material. Hydrogels are commonly used on a wide variety of wounds, such as skin tears, pressure ulcers, burn wounds and surgical wounds. Hydrogel dressings are water- or glycerine-based products, best suited for dry wounds or those with minimal to moderate exudates(91, 92). Hydrogel sheet dressings are reported to be comfortable and soothing, and to reduce pain because of their cooling effect(93-98).

### Provox Life HMEs

Throughout the course of innovation, Provox HMEs have continuously improved with regard to humidification, breathability and usability. The third generation, Provox Life HMEs, present superior breathability and humidification levels and a wider range of HMEs to improve usability.

A higher humidification capacity requires a larger foam volume, or higher foam pore density to increase the surface area and binding capacity of hygroscopic salt. This increases the airflow resistance through the device, which for patients is experienced as a higher breathing resistance (38). Breathing resistance is also increased by the inclusion of an electrostatic filter in HMEFs (38, 99). In a numerical HME model that calculates an HME's humidification and breathing resistance, it was shown that increasing the diameter of an HME is an effective way to improve the performance of an HME, as it increases humidification performance and at the same time lowers the breathing resistance (100).

An important modification made to achieve the high performance of the new Provox Life range of HMEs was to increase the HME diameter by 1 mm (4.5%), from the standard 22 mm to 23 mm. This seemingly small increase in diameter has a considerable impact on both humidification capacity and airflow resistance.

The different HME models are designed to provide the highest humidification while allowing breathability in various situations. Home HME, Go HME, Energy HME and Night HME were developed by optimizing parameters such as foam volume, foam porosity and air inlet/outlet area to accommodate different levels of physical activity (See Figure 12).



Figure 12. (From left to right) Provox Life Home HME, Provox Life Go HME, Provox Life Energy HME and Provox night HME.



The new Provox Life suite of HMEs was developed to provide the highest possible humidification while keeping the breathing resistance comfortable. Laboratory measurements of the Provox Life HMEs show a considerably higher humidification capacity (i.e. Moisture loss, measured in mg/l) and lower breathing resistance (i.e. Air Pressure Drop, measured in Pascal at 30 l/min (Pa)) in comparison to their functional equivalents in the second generation of Provox XtraHMEs (see Table 2 in Appendix and Figure 13). As seen in Figure 13, the breathing resistance represented by Go HME and Energy HME are 50% and 75% lower respectively compared to Home HME.

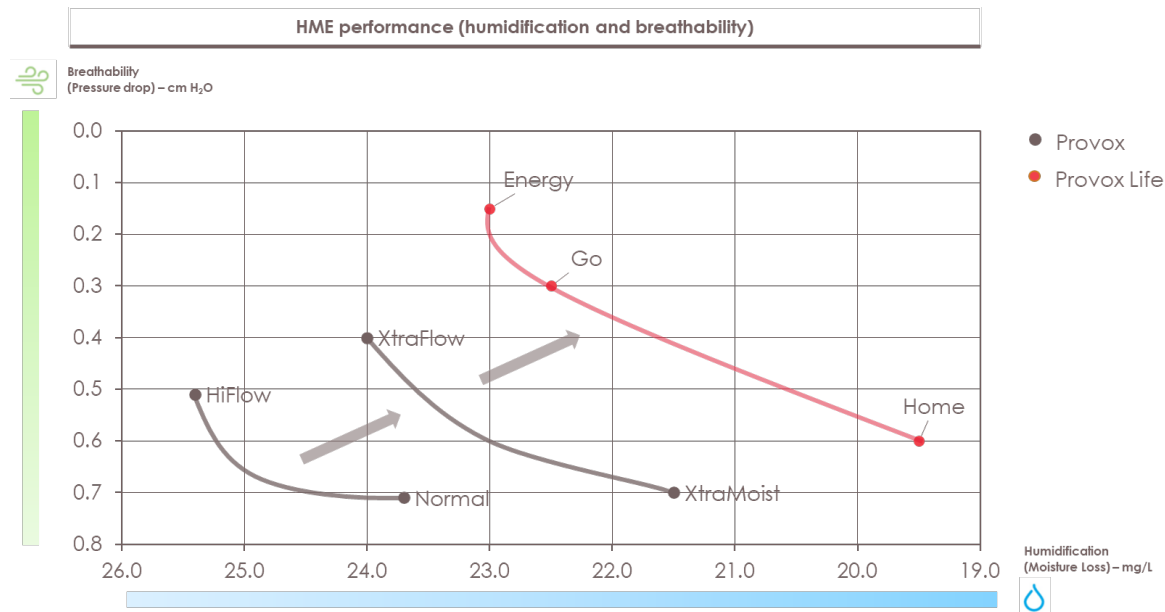


Figure 13. Provox Life optimizes HME performance for everyday situations.

### 3.3.2 Provox HMEFs

#### Provox Micron

Provox Micron HME is an HMEF that combines a Heat and Moisture Exchanger with a highly effective (>99% Viral and Bacterial Filtration Efficiency)\*<sup>3</sup> electrostatic filter (see Figure 14). The electrostatic filter is bidirectional, providing filtration of inhaled and exhaled air.

\*The VFE (Viral Filtration Efficiency) and BFE (Bacterial Filtration Efficiency) at an increased Challenge Level Test procedure adapted from ASTM F2101, was performed for Provox Micron HME and Provox Life Protect at Nelson Laboratories (US) in accordance with USFDA (21 CFR Parts 58, 210, 211 and 820) regulations. Mean VFE and BFE was >98%. Data on file.

<sup>2,3</sup> Since pathogens can enter and leave the human body in other ways (such as the mouth, nose, and eyes), Provox Micron and Provox Life Protect HME can never guarantee complete protection. Please read the instructions for use for guidance.



Figure 14. Provox Micron HME.

### Provox Life Protect

Provox Life Protect HME is an HMEF that combines an HME with a highly effective electrostatic filter (> 98% Viral and Bacterial Filtration Efficiency)\*<sup>2</sup> and is part of new Provox Life suite of HMEs (See Figure 15). Laboratory measurements demonstrate that Provox Life Protect HME presents 21% more breathability compared to Provox Micron HME and higher humidification capacity (See table in Appendix).



Figure 15. Provox Life Protect HME.

### 3.3.3 Provox Handsfree HMEs and Speaking Valves

#### Provox FreeHands and Provox FreeHands FlexiVoice

The legacy Provox FreeHands HME was developed to enable hands-free speech for tracheoesophageal speakers and was introduced in 2001. In 2014 it was replaced by its successor, the Provox FreeHands FlexiVoice HME.

The Provox FreeHands HME (see Figure 16 and Figure 17) is a system that combines the Provox FreeHands HME automatic speaking valve with the Provox FreeHands HME cassette.

Upon speech-exhalation, the membrane of the speaking valve closes off automatically, enabling the pulmonary air to be diverted through the voice prosthesis into the esophagus. This system is developed specifically for prosthetic tracheoesophageal speakers.

Although the Provox FreeHands HME is a discontinued device the published literature is still relevant due to the clinical equivalence of the device with the Provox FreeHands FlexiVoice speaking valve.



Figure 16. Provox FreeHands HME cassette.

### Provox FreeHands FlexiVoice

The Provox FreeHands FlexiVoice speaking valve has two settings. In one setting, the membrane of the speaking valve is always in the opened position, useful during physical activity (locked mode). In the other setting, the speaking valve is bias-open, meaning the membrane is normally in the opened position and only closes upon relatively strong exhalation (automatic speaking mode). The Provox FreeHands FlexiVoice comes in three different strengths to accommodate different speaking pressures (see Figure 17). The membrane also acts as a pressure relief valve, which allows the air to escape when coughing. The design of the speaking valve also allows for speech through manual occlusion, by placing a single finger over the front opening. The speaking valve cannot be used without an HME-cassette, meaning the system functions as a full-time HME.



Figure 17. Provox FreeHands FlexiVoice Light, Medium and Strong.

### Provox Life FreeHands FlexiVoice

The Provox Life FreeHands FlexiVoice speaking valve, similar to its predecessor, offers both hands-free speech and finger occlusion. For hands-free speech, Provox Life FreeHands FlexiVoice comes in three different strengths: light, medium, and strong.

## 3.3.4 Provox Attachments

### Adhesives properties and function

For peristomal attachment the Provox XtraHMEs can be attached with a variety of available Provox adhesives (Provox OptiDerm, FlexiDerm, XtraBase, StabiliBase and StabiliBase OptiDerm). Additionally, some patients may require the use of Provox Silicone Glue to

improve the seal of the adhesive to the skin. Other products that are recommended for proper application of the adhesive are Provox Cleaning Towel (to prepare and clean the skin) Provox Remove (to remove glue from the skin) and Provox Skin Barrier (to protect the skin). Using HMEs together with an adhesive provides a seal which makes the conditioning of air more reliable and facilitates tracheoesophageal speech.

**OptiDerm, FlexiDerm and XtraBase**

The hydrocolloid Provox OptiDerm is made of a hypoallergenic adhesive material that forms a gel in contact with water. The Provox OptiDerm adhesives are: Provox OptiDerm Round/Oval/Plus (see Figure 18)

Provox FlexiDerm is a very flexible material and has the strongest adhesive properties. It is a sticky, yet soft and flexible adhesive. The Provox FlexiDerm adhesives are: Provox FlexiDerm Round/Oval/Plus (see Figure 18)

Provox XtraBase with a concave shaped base was developed especially for hands-free speech. The base of this adhesive is more rigid and gives more support to the peristomal area. Both when used with a standard Provox HME and with the Provox FreeHands HME (see Figure 18).



**Provox XtraBase**

Figure 18. Provox OptiDerm, Provox FlexiDerm and Provox XtraBase Adhesives.

**Provox StabiliBase and Provox StabiliBase OptiDerm**

The peristomal adhesive baseplate Provox StabiliBase was introduced in 2012 and consists of a conically shaped, firm plastic base with vertical stabilizing bars providing support to tracheostoma during speech (see Figure 19). The base is welded on its outer rim to the adhesive material, which is similar to that of the existing Provox FlexiDerm and Provox XtraBase adhesives. The baseplate liner has three removable vertical strips and can be attached to the skin in three steps.

The design of the Provox StabiliBase adapter can be especially suitable for deep tracheostomas. The peel-off liner is divided into three sections to facilitate application to the skin.

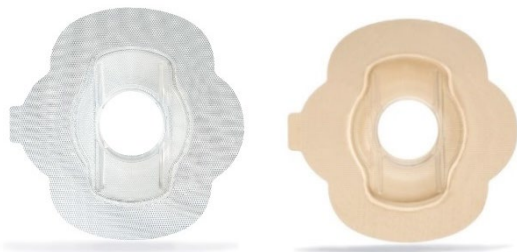


Figure 19. Provox StabiliBase (left) and Provox StabiliBase OptiDerm (right).

**Provox Life Adhesives**

Provox Life Adhesives are designed to be used together with Provox Life HMEs and accessories. Provox Life Standard Adhesive, Provox Life Sensitive Adhesive and Provox Life Stability Adhesive are flexible adhesives suitable for flat to moderately deep stomas. Provox Life Sensitive Adhesives (hydrocolloid) and Provox Life Night Adhesive (hydrogel) have an adhesive material with permanent skin contact that is hypoallergenic and suitable for sensitive skin (see Figure 20).

The adhesives have been developed to suit different situations and to satisfy patients' individual needs due to differences in skin type and stoma morphology. Parameters such as composition and thickness of the pressure sensitive adhesive material (the material closest to the skin) and the carrier (the outer layer of the adhesive) were optimized to balance adhesion and skin-friendliness for different purposes. For improved fit to a wide range of stoma morphologies, all Provox Life adhesives come in a clover shape. The clover shape was

introduced to prevent the occurrence of folds and creases of the adhesive when attached to concave stomas and thereby further contribute to an airtight adhesion.

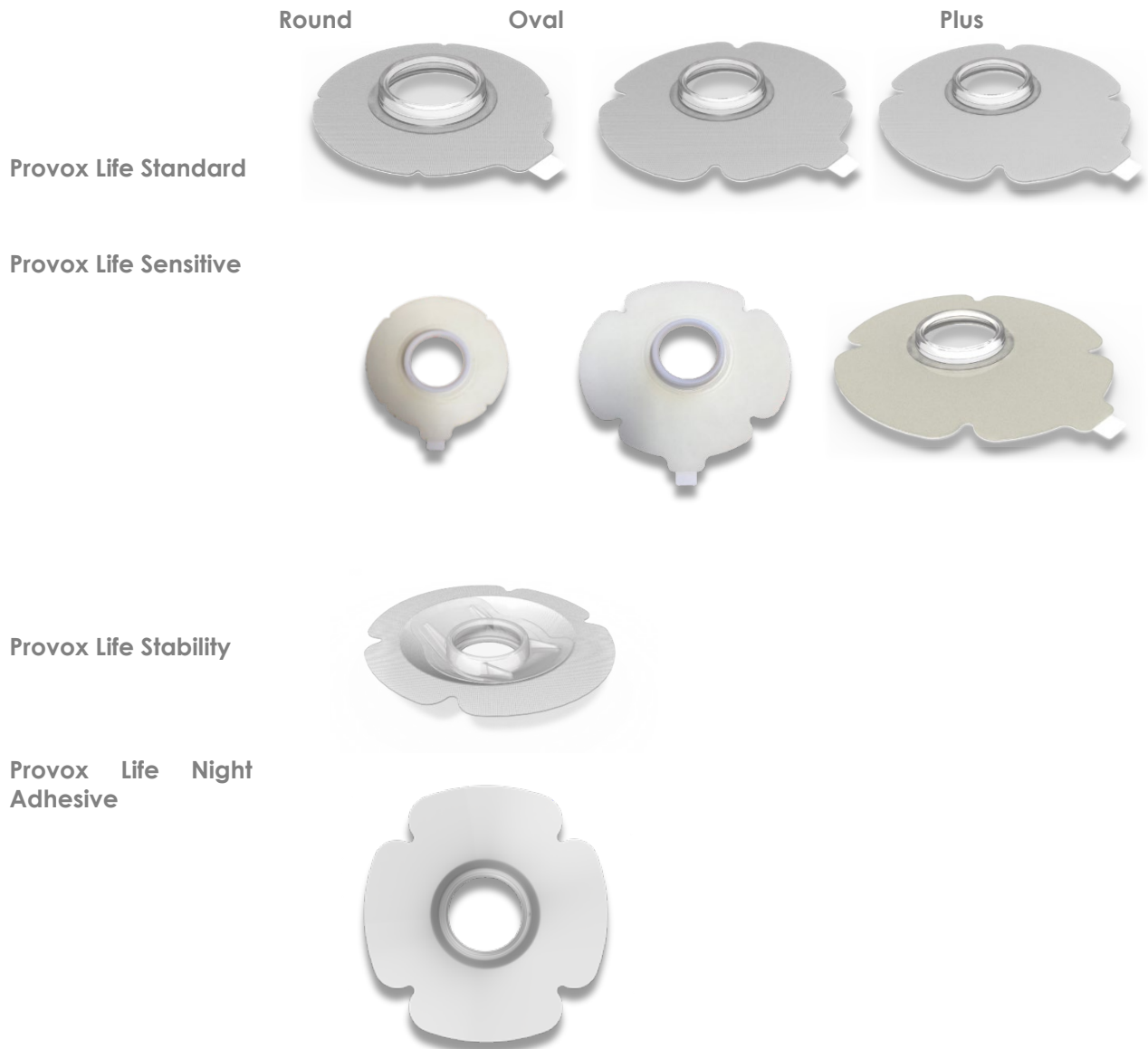


Figure 20. Provox Life Stability Adhesive.

### 3.3.5 Provox LaryTubes and LaryButtons

For intraluminal attachment the Provox HME can be attached with a Provox LaryTube or a Provox LaryButton. The primary reason for using a Provox LaryTube or Provox LaryButton is usually to maintain stoma patency, although a Provox LaryButton may also be beneficial in combination with a hands-free speaking valve.

### Provox LaryTubes

The Provox LaryTube is a so-called laryngectomy tube (see Figure 21). The Provox LaryTube can be used to attach Provox HMEs and Provox FreeHands FlexiVoice speaking valve (59, 101-106). The Provox LaryTube is held in place with a Provox TubeHolder (neck band) or it can be clicked into a baseplate (model with Blue Ring). For patients using a voice prosthesis, a fenestrated Provox LaryTube is available. The Provox LaryTube is well suited for immediate postoperative Provox HME use, when a laryngectomy tube is needed to maintain stoma patency, HME use during postoperative radiotherapy and HME use in patients with sensitive skin (107). Some patients experience permanent problems with stoma patency, requiring permanent use of a laryngectomy tube (107).



Figure 21. Three different types of Provox LaryTubes. Top: with blue ring; Middle: standard; Bottom: fenestrated.

### Provox Life LaryTube

Provox Life LaryTube can be used to attach Provox life HMEs and accessories. Provox Life LaryTubes are well suited for patient with a shrinking tracheostoma (See Figure 22). They are available in four types: Standard, Fenestrated Standard, With Ring and Fenestrated with Ring.



Figure 22. Provox Life LaryTubes. (left) standard, (right) fenestrated with Ring.

### Provox LaryButton

Provox LaryButton is a so-called stoma button (see Figure 23). A stoma button is primarily used in stomas that are shrinking and that have a tight 'lip' or 'rim' that holds the button in place(107)and patients with sensitive skin. The Provox LaryButton is a silicone stoma button, that maintains the opening of the stoma. It can be used to attach an HME, also in combination with the Provox FreeHands FlexiVoice speaking valve (88, 101, 102, 108, 109).

The Provox LaryButton has a retention collar but can also be held in place by using a Provox TubeHolder or Provox LaryClips (small adhesives combined with Velcro-attached hooks).



Figure 23. Provox LaryButton with LaryClips.

### Provox Life LaryButton

Provox Life LaryButton is a silicone stoma button that can be used to attach Provox Life HMEs and accessories, similar to the legacy Provox LaryButton it can be also used in combination with the Provox FreeHands FlexiVoice speaking valve (see Figure 24).






Figure 24. Provox Life LaryButton.









**3.3.6 Supporting Provox Accessories**

Provox Accessories were developed to provide protection to the tracheostoma during showering, taking care of peristomal skin when cleaning, improve the seal of the adhesive to the skin.

Table 1. Provox accessories.

Product name	Product Image	Intended use
Provox ShowerAid		Provox ShowerAid is a cover that protects the stoma from water when showering.
Provox Adhesive Strip		Provox Adhesive Strip is a single-use device that provides an additional seal. For use when using the Provox Luna Adhesive and Provox Life Night Adhesive when showering.
Provox Adhesive Remover		Provox Adhesive Remover is a wipe that helps make it easier to take off an adhesive at the end of the day.

<p>Provox Skin Barrier</p>		<p>Provox Skin Barrier leaves a protective layer on the skin, which can be helpful if the skin is sensitive. The barrier comes in a special wipe that leaves a protective layer on the skin.</p>
<p>Provox Cleaning Towel</p>		<p>Provox Cleaning Towel cleans the skin and removes oil from the skin before putting on an adhesive. It is alcohol-based and non-perfumed.</p>
<p>Provox Silicone Glue</p>		<p>Provox Silicone is a liquid glue that can be used to improve the adhesion between the skin and the adhesive.</p>
<p>Provox LaryClip</p>		<p>Provox LaryClip is an alternative to Provox TubeHolder (See Figure 23). Consist of two-piece system that helps to optimise the air-tight attachment of Provox LaryButtons and Provox Life LaryTubes to the stoma.</p>
<p>Provox FreeHands support</p>		<p>Provox FreeHands Support helps reduce stoma movement and is designed to improve voice quality when speaking hands-free.</p> <p>Consist of a transparent base with a discrete ring, and a fixation adhesive. The ring is placed over Provox FreeHands FlexiVoice. The base and ring support the stoma,</p>

		and the fixation adhesive attaches the base to the chest.
Provox Life Shower		Provox Life Shower protects the stoma from water when showering. Compatible across the range of Provox Life™ Adhesives.

## 4. Clinical evidence on Provox HMEs

Atos Medical's innovation and HME development are backed by strong clinical evidence as demonstrated by the amount of clinical and scientific studies conducted on Provox HMEs during the last 30 years. A total of 63 publications reporting clinical studies with laryngectomy HMEs have been published between 1990 and 2024. In 51 of those publications (81%) HMEs manufactured by Atos Medical are included, involving over 2000 patients (Figure 25 and 26).

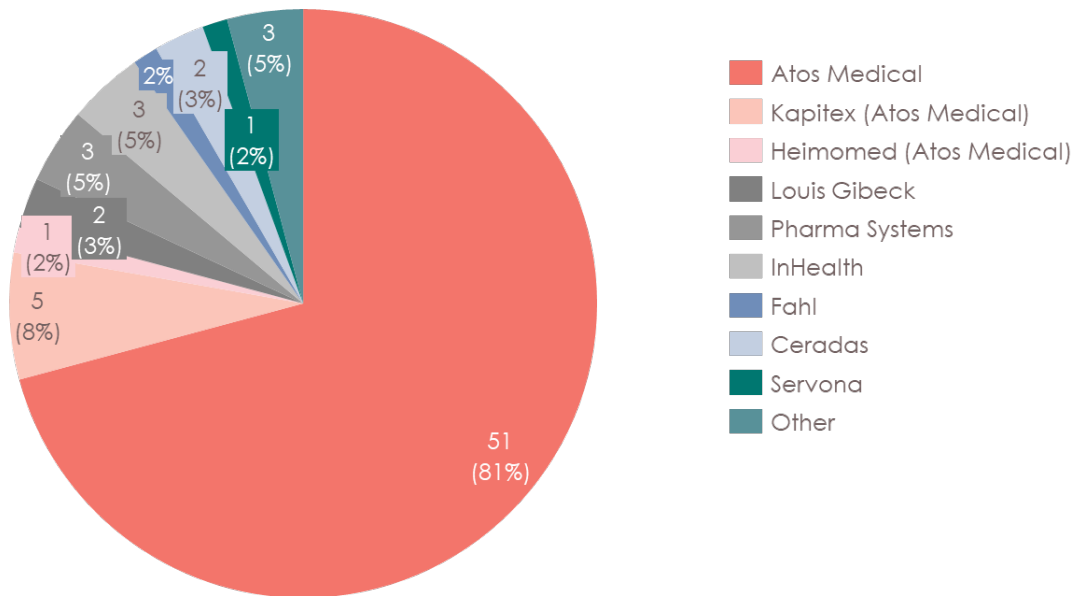


Figure 25. Pie-Chart including clinical evidence of HME use in laryngectomized patients per manufacturer, based on 63 identified peer-reviewed publications published between 1900 and 2024. Clinical evidence: refers to a clinical study where patients were included and an HME from a listed manufacturer has been studied. Some articles mention several brands and are therefore represented multiple times.

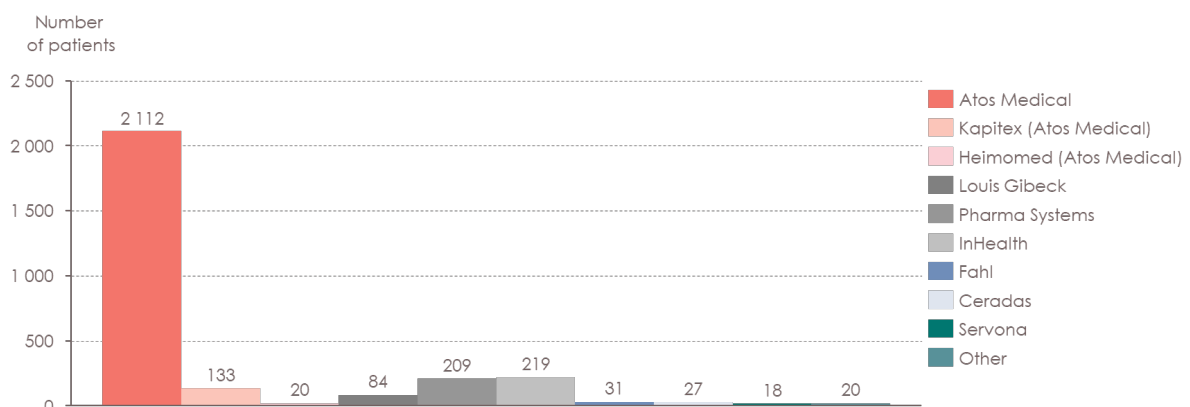


Figure 26. Bar-graph showing number of patients by manufacturer included in 63 identified HME peer-reviewed publications.

Since the development of the first HMEs, there has been increasing clinical evidence highlighting the importance of humidification performance and the adherent use of HMEs in pulmonary rehabilitation and related psychosocial aspects.

In the following sections, the clinical data that support the impact on pulmonary rehabilitation and the quality of life of laryngectomized patients with the different generations of Provox HMEs are presented chronologically.

## 4.1 Clinical Evidence for HMEs

### 4.1.1 Pulmonary physiology and tracheal climate

Measuring intra airway temperature and humidity during breathing is a very complex issue. To determine the effect of HME use in temperature and humidity in laryngectomized patients an Airway Climate Explorer tool was developed at the Netherlands Cancer Institute and validated *in vivo* (110). This tool made it possible to assess the influence of Provox HME in standard room conditions on tracheal temperature and humidity. In a study including 10 laryngectomized patients it was shown that the presence of Provox Normal HME increased the intra-tracheal mean humidity with 3.2 mg H<sub>2</sub>O/L (95% CI: 1.5–4.8 mg H<sub>2</sub>O/L;  $p < 0.001$ ), from 21.4 to 24.6 mg H<sub>2</sub>O/L and decreased the mean intra-tracheal temperature with 1.68C (95% CI: 0.9–2.48C;  $p < 0.001$ ) from 28.58C to 26.98C (111).

Interestingly, in a randomized crossover study conducted in 10 disease-free laryngectomized patients consisting of testing Provox HMEs in a cold environment, the presence of the Provox HME significantly increased both inspiratory and expiratory temperature with 3.9C (95% CI: 2.7–5.1C;  $p < 0.001$ ) and 1.2C to 26.98C (95% CI: 0.8–1.2C;  $p < 0.001$ ), respectively, and mean humidity minimum and maximum values increased with 4.2 mg H<sub>2</sub>O/L (95% CI: 3.3–5.0 mg H<sub>2</sub>O/L;  $p < 0.001$ ) and 2.4 mg H<sub>2</sub>O/L (95% CI: 1.7–3.1 mg H<sub>2</sub>O/L;  $p < 0.001$ ), respectively (50). Additionally, in a warm environment, the presence of an HME has a cooling effect on the temperature while it still humidifies the inspired air (6).

Breathing through an HME increases endotracheal minimum and maximum humidity values. During inhalation the minimum humidity values are dependent on the inhalation breath length (IBL). The lowest humidity occurs at the end of inspiration and decreases when the IBL is lengthened. A study conducted in 13-16 laryngectomized patients showed that the presence of Provox HME caused a significantly shorter inhalation breath length (1.05s) compared to breathing without HME (1.35s,  $p < 0.001$ ) (112). Furthermore, the decay of gradual evaporation of water took longer with the Provox HME in situ, so the air in the trachea stayed humid longer than without Provox HME (2.69 vs. 2.19s;  $P < 0.0001$ ) (112).

The humidification capacity and breathing resistance of an HME are inversely related. When comparing Provox Normal with Provox HiFlow (lower breathing resistance) it was shown that even though both HMEs prolonged exhalation breath length (EBL) by approximately +0.5 seconds ( $p < 0.001$ ); EBL without HME: 2.19 s, Normal HME: 2.61s, and HiFlow: 2.69s, Provox

Normal had better humidification properties than Provox HiFlow (+5.8 and 4.7 mg H<sub>2</sub>O/L, respectively) and showed a small but significant positive effect on tidal volume (0.07 L;  $p < .05$ ) (38). Therefore, the fact that Provox HiFlow has 25% lower breathing resistance, means that is a 25% less effective humidifier. However, the use of Provox Normal and Provox HiFlow both increased endotracheal humidity significantly compared to no-HME. Thus, an HME with higher humidification capacity is the better choice for regular daily use if the breathing resistance is tolerated. In circumstances when a lower breathing resistance is required a lower humidification capacity HME, is an acceptable alternative (38).

Additional efforts have been made to generate *ex vivo* methods to determine HME performance comparable to *in vitro* and *in vivo* results. A study has shown that HME humidification performance could be determined by measuring the weight difference between end-inspiration and end-expiration using a regular balance and a standard spirometer. The results obtained with this method for four Provox HMEs with known *in vivo* humidity and *in vitro* water loss correlated well with previous *in vivo* measurements ( $R^2 = 0.98$ ) and *in vitro* values provided by manufacturer ( $R^2 = 0.77$ ) based on 24-hour ISO 9360-2:2001 assessments (113).

As mentioned before, tracheal mucociliary activity is highly dependent on tracheal humidity. A multi-center case-control study looking at tracheal mucociliary clearance in detail in 3 different groups, 21 long-term HME users, 10 non-HME users and 16 non-HME users before and after 4-9 months HME use. Long-term use of XtraMoist and XtraFlow HMEs helped to restore tracheal ciliated cells and helped prevent their loss (114), highlighting the importance of compliant use of HME to have a positive impact on tracheal cilia.

#### 4.1.2 Pulmonary health/complaints

The positive impact on pulmonary symptoms resulting from **Provox HME** use, were first shown by Hilgers et al. in a prospective non-randomized clinical study (115). This study includes 19 patients and showed that they experienced improvement in their respiratory symptoms. The increased breathing resistance caused by Provox HME did not lead to a discontinuation of the device. However, some patients reported that they sometimes remove the HME during increased physical activity.

Similar results were observed in a short-term study in Denmark in 18 patients, in which 5 patients experienced less coughing and mucus production, 12 reported it was unchanged and 1 patient experienced more coughing after a trial period of 3 weeks. Eleven patients did not experience a change in breathing resistance and 7 found it to be increased (116).

These results were confirmed by similar studies in different countries including: Spain (117), the US (106), Poland (106) and Brazil (118). Thus indicating that results can be expected to be similar across cultures and climates. For example, the study performed in the US (106) showed that Provox HME adherence was 73% and that 68% of the patients reported a decrease in coughing, 73% reported decreased mucus production, 60% reported decreased forced expektoration, and 52% reported decreased need for stoma cleaning. The daily cough-expektoration frequency also decreased significantly. The study conducted in Poland by Bien

et al. (88) supports these results, showing that patients wearing an HME day and night have more significant improvements compared to those who use an HME less consistently, including better sleep. The study from Brazil showed that the use of Provox HME over a 6 week time period reduced cough and expectoration of patients (118).

Subsequently, to investigate long-term impact of Provox HME use, 69 patients using Provox HME were included in a study in The Netherlands. In this study the use of Provox HME improved respiratory symptoms in 65% of the patients, and 94% of the patients overall benefited from the device. Regarding adherence to HME use 78% of the patients used the device on a regular basis during the night and 53% of the patients also used the device at night, 6% used it irregularly and 16% did not use the device. There was an obvious relationship between the length of use of the device and pulmonary complaints. The longer the device was used, the more the pulmonary complaints (coughing, forced expectoration, sputum production) decreased (119).

In a long-term RCT with Provox HME including 60 patients, a notable improvement with regard to coughing ( $p=0.00174$ ) and to bronchorrhea ( $p=0.0031$ ) was reported after 3 months of Provox HME use compared with the non-HME group. A trend regarding breathing effort in the Provox HME group was also reported (89). Provox HME was used daily by 80% of the patients of whom 42% used it day and night at the end of the 3 months.

The improvement in humidification capacities in **Provox XtraHMEs** (XtraMoist and XtraFlow) resulted in a further reduction of mucus production just after three weeks of use in 13 patients in a prospective study using HMEs with the same foam media, yet different to the final appearance of the devices (120). During this observation period, 7/13 patients (54%) reported noticeably less mucus production than with their accustomed HME, including one patient who previously did not use an HME at night, but did so during the study period. Interestingly, that patient had the largest reduction in coughing frequency (from 20 times to 5 times daily).

In line with these results, a cross-over study with 45 patients showed that the improvement in tracheal climate translated into patients reporting significantly less tracheal dryness with the second generation Provox XtraHMEs compared to the first generation Provox HMEs ( $p=0.039$ ) after 6 weeks of use (87). They observed a trend towards less frequent coughing and forced expectoration. Furthermore, Provox XtraHME use compared to non-HME use was studied by Parrilla et al., (121). This multi-center time series study included 30 HME-naïve Italian patients who used Provox XtraHME for 12 weeks. For patients using Provox XtraHME for more than 20 hours during 12 weeks, already after just 2 weeks there was a significant positive effect of Provox XtraHME use on pulmonary complaints, with a significant decrease in daily coughs (from 8.8 at baseline to 4.6 with Provox XtraHME,  $p<0.0001$ ) and daily forced expectorations (from 6.3 at baseline to 3.0 with Provox XtraHME,  $p<0.0001$ ), which further improved after 6 weeks (3.5 and 3.0, respectively) and then stabilized at 12 weeks (2.4 and 1.9, respectively). After 2 weeks of Provox XtraHME use, 63% of patients reported less coughing and less mucus production.

A parallel study in the previous study population looked at how laryngectomized patients get accustomed to the use of an HME (both XtraMoist and XtraFlow) and attachments (102). Thirty patients were followed for 12 weeks. In the first 2 weeks, patients reported some

discomfort of HME use, such as increased breathing resistance (43.3%). A small proportion of patients experienced problems with increased coughing when starting HME use. However, after 6 weeks patients were generally accustomed to the breathing resistance and just one patient found it more difficult to breathe through the HME after 12 weeks of HME use. 72.4% of participants reported that breathing was less difficult, 24.1% found it equal and just 3.4% more strenuous compared to breathing through an open stoma ( $p=0.002$ ). The number of patients removing their HME due to breathing resistance dropped from 73% to 24.1% ( $p=0.001$ ) after 12 weeks of HME use.

A retrospective comparative cohort study performed by Ebersole et al., 2020 (122) compared Provox XtraHME use vs external tracheal humidification (ETH) during post laryngectomy hospitalization in 40 laryngectomized patients. Placement of Provox XtraMoist HME was initiated after medical clearance on postoperative day 1, or when the patient was able to put on or remove the HME independently. The rate of mucus plugs –which during post-operative recovery can be a potentially deadly airway complication– as well as the proportion of patients with one or more mucus plugs events was significantly reduced in the HME group compared with ETH (0.13 and 0.38 per 10 inpatient days, respectively,  $p=0.02$ ). The proportion of patients with one or more mucus plugs event was also significantly reduced in the HME group (50% ETH and 11% HME,  $p=0.01$ ).

Early postoperative adoption of Provox XtraHME helped the patient become accustomed to the device immediately after total laryngectomy which was shown to improve long-term adherence to HME use, thus positive impacting pulmonary health(46).

Another important factor impacting adherence is comfort and skin irritation. The Provox Luna system -skin friendly hydrogel adhesive and a soft silicone HME- effect on adherence has been studied in a multicenter, randomized crossover trial conducted in 3 centers in the Netherlands and including 46 laryngectomized patients. In this study it was shown that the use of the Provox Luna HME and adhesive increased the number of adherent patients (96% and 76%, respectively,  $p=0.02$ ), the average number of hours of daily HME use increased from 21 to 23.2 hours ( $p=0.003$ ) and frequency of skin improvement overnight increased (3.9 days with Provox Luna HME and 8.1 during usual care,  $p=0.008$ ) (123).

For a deeper insight into the lives and needs of patients in a contemporary context, and a better understanding of issues related to current HME products, Atos Medical initiated an extensive collaborative research project in 2015, which was completed in 2019. Parts of the results were published in Leemans et al. 2020 (52). The research by ReD Associates and the Netherlands Cancer Institute revealed that most patients struggled with issues related to pulmonary health and HME products. It was reported that many patients experienced issues related to insufficient humidification, including excess mucus and coughing. Situational issues reported included too high breathing resistance during physical activity, insufficient protection against airborne particles/pathogens and pulmonary problems at night. Attachments issues such as insufficient security, poor fit and skin irritation from adhesives were prevalent. Further, issues related to pulmonary health limited the lives of total laryngectomy patients. The in-depth analysis by Leemans et al., shown that pulmonary problems are an underlying cause of many issues experienced by total laryngectomized patients, including psychosocial and quality of life issues (Figure 27). The issues highlighted in this research were the starting point for the development of the third generation of HMEs, Provox Life.



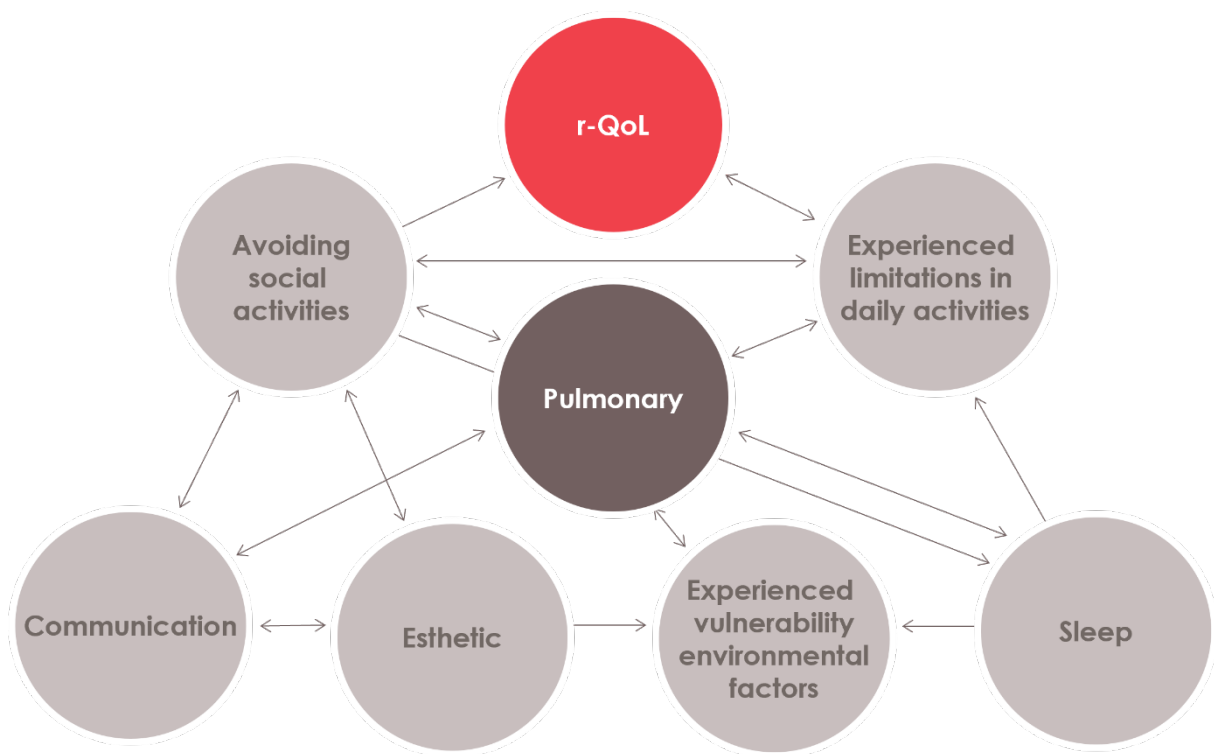


Figure 27. Pulmonary health issues are correlated to most other problems TL patients are experiencing. Figure modified from Leemans et al., 2020.

The introduction of **Provox Life** was expected to optimize pulmonary rehabilitation after total laryngectomy. A mixed-methods study including a rapid literature review, semi-structured expert interviews and an early Health Technology Assessment (HTA) using structured expert elicitation (SEE) with regards to Provox Life was conducted by Panaxea ([www.panaxea.eu](http://www.panaxea.eu)) ahead of the full launch of Provox Life. The expert interviews and the SEE showed that, on average, experts expected to see stronger effects in patients using Provox Life HMEs compared to the predecessors, Provox XtraHME and Provox HME and/or no HME use regarding improved breathing resistance, decreased shortness of breath, improved tracheal climate, reduced mucus production and plugging, reduced pulmonary infections, higher number of social contacts, improved overall Quality of Life (QoL) and improved satisfaction.

The first clinical study with Provox Life products was conducted by Longobardi et al. (124), and provided confirmation that Provox Life can improve pulmonary outcomes in laryngectomized patients. The study compared the Provox Life system with the legacy Provox XtraHME devices ('Usual Care') in this randomized, prospective cross-over study with 40 patients. An increased adherence to HME use was observed when using Provox Life, from 22.6 hours per 24 hours during usual care to 23.9 hours when using Provox Life ( $p=0.011$ ). This corresponded with an increase in HMEs used; an average of 1.7 HMEs was reported during the usual care period, and 2.0 HMEs during Provox Life ( $p=0.025$ ). A significant reduction in forced expectorations was observed during the Provox Life period (average 4.3 forced expectorations/24 hours) compared to usual care (6.7/24 hours) ( $p=0.0001$ ), as well as a significant reduction in the frequency of dry coughing (from 4.3 coughs/24 hours in the usual

care period and 3.1/24 hours in the Provox Life period ( $p=0.031$ ). All four domains of the Coughing and Sputum Assessment Questionnaire (CASA-Q) scored significantly higher (i.e. better) during the Provox Life period compared to the usual care period (COUS:  $p=0.007$ , COUI:  $p=0.002$ , SPUS:  $p=0.0004$ , and SPUI:  $p=0.000003$ ). Breathability through the HME improved when using Provox Life, patients reported a statistically significant reduction in shortness of breath when climbing stairs (or physical exercise) ( $p=0.046$ ) and when walking (on ground level) ( $p=0.005$ ) with Provox Life compared to usual care.

A multi-center prospective, two-phase clinical study in Australia, investigated the impact of establishing an optimal Day/Night HME and attachment regimen on pulmonary health and skin integrity (125). In Phase 1 (6 weeks), 42 post-laryngectomy HME users transitioned from their usual HME regime to equivalent new device/s (i.e. "like-for-like"). In Phase 2 (6 weeks) participants used the full range of HMEs to achieve an optimal day/night regimen. From baseline to end of Phase 2, cough symptoms and impact significantly improved, as did sputum symptoms, sputum impact, duration and types of HMEs used, reasons for HME replacement, involuntary coughs, and sleep. In conclusion, this clinical study supports previous findings that the Provox Life HME range enables optimal improved HME use, with pulmonary and related symptom benefits. Further, the study shows that switching to Provox Life on a like-for-like basis already improves pulmonary outcomes, which can be further improved when implementing an optimal day and night regimen.

In a prospective observational study conducted in Germany, 23 patients were followed for 12 weeks after being introduced to Provox Life. After 2 weeks, adherence to using HMEs was 22h per day, and a trend towards an increase in the CASA-Q domains was reported where the increase was more profound in the patients that used Provox Life as instructed. All of the patients rated their experience with Provox Life more than 3 out of 5 (126).

With Provox Life Energy, a HME specific for physical activity was introduced. This HME has been investigated in two studies (127, 128). In a feasibility study investigating whether breathing-gas-analysis during cardiopulmonary exercise testing is possible with an HME, Heirman et al., concluded that in principle, CPET is possible in laryngectomized patients with an HME. However, the protocol might not be appropriate. In their sample size of 10 patients, Heirman et al. did not report any differences in peak performance capacity between patients using a regular HME (Provox Life Home HME and Go HME) and a lower breathing resistance HME (Provox Life Energy). A study by Mesolella et al. 2024 investigated which HME might be most suitable for laryngectomized patients during physical activity. The performance of 31 laryngectomized patients was tested during medium-high physical effort. The authors reported that Provox Life Energy was a suitable HME for patients during physical activity. Provox Life Energy was the most appreciated HME by patients due to their perception of less dyspnea and fatigue during the performance tests.

### 4.1.3 The impact of HME use on psychosocial aspects and quality of life

As previously described, pulmonary symptoms significantly affect the well-being and quality of life of the patient. These include perceived quality of voice, participation in social activities, aspects of daily life, anxiety and depression (1, 52, 77, 129).

In the first **Provox HME** study by Hilgers et al, in addition to the pulmonary benefits it was shown that Provox HME facilitated voicing and improved intelligibility after 3-weeks of Provox HME use in 9 patients out of 19. Furthermore, patients were positive about the spring valve closure mechanism used for digital occlusion of the Provox HME (115). Improved speech ability, voice quality, pitch, loudness and intelligibility when using Provox HME have been reported in several studies (88, 106, 116, 119). It has been shown that maximum phonation time and dynamic loudness range improved when occluding on top of the Provox HME compared to finger occlusion directly on the stoma (130). This can probably be attributed to better, airtight, occlusion and better distribution of occlusal forces (reducing force on the voice prosthesis and voice producing segment in the esophagus).

Furthermore, most patients found stoma occlusion with Provox HME easier and more hygienic (116). Bien et al., reported on a trend towards less sleeping problems in patients that adherently used HMEs, and the authors suggested that due to less coughing during the night patients wake up less and hence have improved sleep quality (88).

In a multicenter time, series study including 41 patients, it has been shown that the adherent use of **Provox XtraHMEs** increased the general quality of life (measured by means of EQ-5D Index) from an average of 0.84 at baseline to 0.90 after 2 weeks of XtraHME use and this improved even further at 12 weeks (0.96,  $p<0.0001$ ). The EQ-5D VAS scale showed an increase from 61.3 at baseline to 69.8 after 2 weeks and 80.0 after 12 weeks of Provox XtraHME use ( $p<0.0001$ ). Additionally, patients showed a progressive reduction in shortness of breath, fatigue, and psychological stress over time.

Reduced frequency of cleaning of the stoma, improved voice quality, sleeping and a better appearance was also reported after 2 weeks of Provox XtraHME use (121).

The introduction of **Provox Life** led to a further improvement in quality of life as evidenced by a significant reduction in the number of nights sleeping medication was used (219 nights vs 108 nights ( $p=0.044$ )) and a significant reduction in the anxiety/depression domain for the EQ-5D (QoL assessment tool) when using Provox Life HMEs compared to usual care (70% compared to 55% reported "no problems", respectively,  $p=0.035$ ) (124).

Further, it was shown that an optimal Day/Night regime can improve sleep quality as seen in a significantly improved score of the validated Jenkins sleep questionnaire (125).

#### 4.1.4 Pulmonary complications and cost-effectiveness

The beneficial physical and psychosocial effects of HMEs for pulmonary rehabilitation have a positive impact on cost-effectiveness during postoperative stages and long-term stages. The immediate postoperative effects on pulmonary rehabilitation and impact in cost-effectiveness after total laryngectomy, were assessed in a study by Merol et al.(103). In this RCT, 53 patients were randomized into the standard external humidifiers (EH) or the experimental Provox HME arm. Adherence to 24/7 HME use when using Provox HME (Normal and HiFlow) was 87% (compared to 12% in the EH arm). Adherence and patient satisfaction were significantly higher in the Provox HME group ( $p<0.001$ ). Additionally, the number of

coughing episodes, mucus expectorations for clearing the trachea and sleeping disturbances were significantly less when using Provox HME ( $p < 0.001$ ). Even though the breathing resistance of the Normal HME is higher than that of the HiFlow none of the patients using the normal HMEs reported shortness of breath. An improved nursing staff satisfaction and preference was also reported. The daily humidification-related costs for the HME system were considerably lower than for the EH system coupled with a reduction for nursing time. Thus, the authors concluded that HMEs can be considered the better and more cost-effective option for early postoperative airway humidification after total laryngectomy.

Similarly, a case-control study in Canada including 48 patients in the early post-operative period reported that the use of a Provox HME reduced the occurrence of post-operative adverse events (mucus plugs) in patients using Provox XtraHMEs compared to patients using EH. Of those patients who experienced mucus plugs, only 12.5% (3/24) had used a Provox HME in contrast to 87.5% (21/24) who used EH ( $p = 0.002$ ). The odds ratio (OR) of having an adverse event if not using Provox HME was 8.27 (CI = 1.94 – 35.71). Provox XtraHME use significantly reduced the number of days requiring physiotherapy (1.75 days vs. 3.20 days,  $p = 0.034$ ), days in IC-unit, suctioning per day and in-hospital complications such as mucus plugging, and post-operative care requirements compared to EH. In all, these findings would suggest early post-operative HME use can positively impact hospital costs (46).

The effect on cost-effectiveness in long-term laryngectomized patients (average of 274 days after their surgery) when using Provox HME and Provox XtraHME have been reported in a survey study that includes answers from 75 patients. More than 85% of the respondents used an HME, of whom 77% were compliant users (use an HME at least 20 hours per day). Compliant HME users presented a reduced use of external humidifiers and vaporizers. Notably, HME users also tended to take less sleeping medication and had better pulmonary status and lower health-care costs. The incidence of pulmonary illnesses (either before or after surgery) was about 25%. More than 90% of the respondents were heavy smokers before laryngectomy. Chronic pulmonary problems were present in a quarter of the participants (131). In this study it was reported that the main reason for not using an HME 24 hours per day were skin irritation from the adhesive and no use of HME during the night or during physical activity (131). Similarly, another study showed that skin irritation and adhesion problems are the most common reasons for not using the HME in an adherent way (132). The study also reported that the use of a voice prosthesis and an early start with HME use after TLE are factors that significantly improve compliant use of Provox HME ( $p = 0.001$ ) (132).

According to a retrospective study, Provox HME users have a significantly lower incidence of severe tracheobronchitis and pneumonia episodes compared to non-HME users (4.92 vs 6.79,  $p = 0.047$ ), which has an impact on medical costs, quality of life and possibly survival related to tracheobronchitis and/or pneumonia (32).

In a recent study addressing the new generation of Provox Life HMEs, a significant reduction in the frequency of sleeping medication intake ( $p = 0.044$ ) was reported (124).

The cost-effectiveness of HME use in terms of costs per additional quality-adjusted life years (QALYs) has been addressed in a study including in a European setting (Poland). Using a model-based cost-effectiveness analysis of using HMEs versus usual care (UC) (including stoma covers, suction system and/or external humidifier) for patients after laryngectomy has

shown that HME use substantially incremented quality-adjusted survival (3.63 QALYs) compared to UC (2.95 QALYs). The total 10-year health care costs per patient yielded 9,465 Euro for the HME strategy, and 1,168 Euro for the UC strategy. Compared to the UC strategy, the HME strategy resulted in 12,264 Euro/QALY (95 % CI 18,037–51,517) gained, thus HME use was found to be more costly, but more effective. During the immediate postoperative period, the use of HMEs is more effective and less costly. The cost savings by HME use are resulting from less sleeping problems, less admissions due to tracheobronchitis/pneumonia (pulmonary infections) and no use of external humidifier or saline during hospital admission compared to UC. Additionally, HME use resulted in fewer pulmonary infections, and less sleeping problems (33).

From an American perspective (USA), Provox HME<sup>4</sup> use was more effective and less costly compared with some extent alternative stoma covers (ASCs, e.g., as foam pads or cloth bibs). Provox HME use resulted in a 0.14 QALY gain (5.30 vs 5.15) vs no HME-users. Total costs per patient (lifetime) were \$59 362 (HME) and \$102 416 (ASC). Provox HME use cost-effectiveness, expressed in costs was \$3770 in total. Patients using Provox HME reported to have less productivity loss postoperatively and reported fewer occurrences of pulmonary events (airway infections and tracheobronchitis) postoperatively compared with ASC-users (133).

## 4.2 Clinical Evidence for Provox HMEFs

The clinical effect of the Provox Micron HME with filter (HMEF) in laryngectomized patients was investigated by Scheenstra et al. (134) in a short-term feasibility study. They assessed the Provox Micron HME with filter (HMEF) for short-term endotracheal climate changes and feasibility in daily practice. Compared to open stoma breathing, Provox Micron HME with filter (HMEF) HMEF increased endotracheal minimum humidity values (4.7 mgH<sub>2</sub>O/L,  $p < 0.0001$ ) compared with open stoma and increased end-inspiratory and end-expiratory temperature values. Patients spontaneously reported a further reduction in pulmonary complaints compared to the use of the normal Provox HME, 31% of patients reported remarkably decreased sputum production (134).

HMEFs are commonly used in ventilator dependent patients and during anesthesia. Their use has been found to decrease the incidence of Ventilator Associated Pneumonias (VAPs) in ventilated patients on the intensive care unit (ICU) in comparison with Heated Humidifiers (135, 136). Moreover, it has been reviewed that HMEFs decrease the rate of nosocomial pneumonias in comparison with heated humidifiers (137). In a study that was carried out in guinea pigs, a bacterial and viral filter was found to successfully protect the pigs from sensitization to aerosolized Natural Rubber Latex (138). Also, the use of HMEFs during anesthesia prevents bacterial migration from the patient to anesthesia circle systems (139, 140).

<sup>4</sup> Authors have confirmed that majority of patients in the study used Provox HMEs.

Additionally, patients using Provox Micron HME have reported reduced frequency in common cold symptoms, flu symptoms, asthmatic symptoms and allergy symptoms, and stated that they had a reduction in the amount of secretions and coughing frequency since they started using Provox Micron. One third of the patients reported using Provox Micron when they were involved in a hobby in a dusty environment, when working in dusty environment, when in a hospital environment, around sick individuals, when flying, when in large crowds or during allergy season. Compliant HME users tended to make less use of external humidifiers, vaporizers, and sleeping medication, and had better pulmonary status and lower health-care costs (131).

The COVID-19 pandemic has highlighted the need for an HMEF for protection of laryngectomized patients and health care professionals. Clinical guidelines recommended the regular use of a surgical face mask to prevent contact with mouth and nose mucosal surfaces and adhesive stomal support with highly efficient HMEFs such as Provox Micron for laryngectomized patients (141-144). An online survey conducted in the US during July and August 2020 completed by 173 TL patients showed that shifting to using Provox Micron HME was the most reported self-implemented HME change during the pandemic (145). Using Provox Micron HME was also the most frequently given HME change advice from SLPs and ENTs.

According to laboratory tests\* Provox Micron has a viral and bacterial filtration efficiency of >98%<sup>5</sup>. A recent study has reported the different filtration efficiency for face masks used during the COVID-19 pandemic, showing that a KN95/FFP2 mask during coughing and exhalation presents a range of filtration efficiency from 83%-99% (146).

These studies illustrate the relevance of Provox HMEFs in providing the most appropriate protection and humidification of the airways depending on the environment.

### 4.3 Clinical Evidence on Provox FreeHands speaking valves

One of the most important features of the Provox FreeHands HME speaking valves is that they provide an automatic mechanism to facilitate occlusion of the tracheostoma to generate tracheoesophageal speech.

A first feasibility study using Provox FreeHands speaking valve and including 20 patients showed that maximum phonation time using the Provox FreeHands HME was shorter than with manual occlusion on a regular Provox HME (15.2 s and 17.9 s, respectively;  $p=0.044$ ) but longer than with another hands-free device (11.6,  $p=0.006$ ). These can be attributed to the fact that when using a hands-free device, some of the speaking air is consumed for closing the valve mechanism, and more air pressure is required to closing the valve. Provox Hands-

\*The VFE (Viral Filtration Efficiency) and BFE (Bacterial Filtration Efficiency) at an increased Challenge Level Test procedure adapted from ASTM F2101, was performed for Provox Micron HME at Nelson Laboratories (US) in accordance with USFDA (21 CFR Parts 58, 210, 211 and 820) regulations. Mean VFE and BFE was >98%. Data on file.  
<sup>5</sup> Since pathogens can enter and leave the human body in other ways (such as the mouth, nose, and eyes), Provox Micron and Provox Life Protect HME can never guarantee complete protection. Please read the instructions for use for guidance.



free speaking valve showed a larger dynamic loudness range compared to Provox HME (33.0 dB and 28.2 dB, respectively;  $p=0.029$ ) and other hands-free devices (24.8,  $p<0.001$ ). The availability of voice with Provox HME and Provox FreeHands was always immediate, with no time lag noted, in contrast to other hands free devices where there was a time lag of 1-2 s, caused by a difficulty in closing the valve to speak (59).

Similar results regarding subjective voice quality and loudness range comparing Provox FreeHands HME with Provox HME and other hands-free devices have been reported in different studies (147, 148). However, it has been shown that even though speaking characteristics were better with manual occlusion patients continued to use Provox FreeHands HME device after the study period. Indicating that they would continue to use it either on a daily basis (average of 5 hours) or for special occasions or a limited number of hours per day (147).

Additional objective perceptual and acoustic analysis of 4 patients comparing Provox HME with Provox FreeHands HME have shown higher intensity of read speech (39.1 dB) with Provox FreeHands HME when compared with Provox HME (34.5 dB). Decreased pause time (23% vs. 27% respectively,  $p=0.033$ ) when using the Provox FreeHands HME compared to Provox HME. Additionally reduced maximum phonation time was reported when using Provox FreeHands vs Provox HME (8.3 vs 14.3 respectively;  $p=0.034$ ) (149).

Despite its limitations, the ability to speak hands-free when performing a manual task has been reported as the main advantage of Provox FreeHands HME and that it is useful and an easy-to-use additional device for special occasions when both hands are needed for tasks other than closing the stoma (driving a car, dining, fishing) (148, 149).

On the other hand fixation of the adhesive to the peristomal skin has been reported as the main disadvantage (149), followed by aspects such as voicing being too tiresome, diminished intelligibility and increased breathing resistance (147), adhesive seal problems (105) have been also been reported as reasons for not using the Provox FreeHands HME on a daily basis and to discontinue its use.

In a study involving 17 patients who used the Provox FreeHands HME it was found that phonation time was long, dynamic range wide, and a short lag time was needed for closing the valve which enabled patients to produce more natural-sounding speech (according to external phoneticians). Patients also reported that it was a great advantage to be able to speak hands-free (150).

The possibility to speak hands-free with Provox FreeHands HME has been shown to allow patients greater ease in communication, and to have more frequent social contacts ( $r=0.251$ ,  $p=0.030$ ), which can impact positively in quality of life (131).

Lansaat et al. (101) evaluated the short- and long-term feasibility of the second-generation automatic speaking valve, Provox FreeHands FlexiVoice HME, in a prospective multi-center study including 40 laryngectomized patients. At baseline few patients used the Provox FreeHands HME daily and a big proportion didn't use handsfree speech. After 6 months patients using the Provox FreeHands FlexiVoice increased to 37.5% of patients using Provox FlexiVoice on a daily basis, for a mean of 12.64 h/day. Twenty-five percent were using it on a

non- daily basis, for a mean of 3.76 h/day. Patients that stopped using the FlexiVoice reported this was due to the unpredictable fixation of the adhesive. The additional manual closure option of the FlexiVoice was experienced as beneficial for maintaining the adhesive seal longer. It was concluded that Provox FreeHands FlexiVoice HME allows for hands-free speech in a larger proportion of laryngectomized patients.

Longobardi et al., (151) described the percentage of Automatic Speaking Valve use in a cohort of 110 patients. They showed that only 17.3% (19/110) of patients used free-hands speech every day without problem. The main problems described were excessive fatigue and limited durability of the adhesive. In a second step, the study investigated the implementation of a specific handsfree rehabilitation training. Patients reported a high compliance to and satisfaction with the training program. After the training program, the percentage of patients using handsfree speech increased by 43% to 60% (66/110 patients)

## 4.4 Clinical Evidence on Provox attachments

### 4.4.1 Adhesives

The most reported problems with the adhesives are that they can cause skin irritation, and that device life is too short, especially when used with a hands-free speaking device. Successful use of the adhesive depends on stoma characteristics, on how the patient uses the adhesive and with what device the adhesive is used. A detailed study of (peri)stomal geometry in relation to adhesive use revealed a mismatch between patients and adhesives. This data could be used to develop new adhesives that help improve rehabilitation after laryngectomy (152).

Whilst most clinical studies investigate the HMEs and their impact on pulmonary symptoms, outcomes with regards to attachments are often reported as they are considered critical for adherence to HME use. This section provides an overview of results for HME attachments.

In an initial study, Provox OptiDerm, Regular and FlexiDerm adhesives were used by 19 patients. Initially patients experienced difficulty with loosening of the baseplate due to phlegm, however this decreased and was resolved after 3 weeks of use. Interestingly, the availability of OptiDerm, a hydrocolloid plaster, was considered useful for patients who have had recent surgery. Using this adhesive, some patients were able to start speaking within a shorter time limit following total laryngectomy (115).

A prospective non-randomized clinical study where 18 patients participated showed that the majority of patients used one adhesive and 1-2 Provox HME cassettes per day. Most patients did not experience a change in airway resistance and a small group found it to be increased. Interestingly, less skin irritation and easier removal was reported when using OptiDerm adhesive (116).

Subsequent studies have been performed in different countries/climates. A study in Spain has shown that 93% of the patients reported an adhesive removal without pain. Just 10% of the patients reported having skin irritation, 5% a mild skin irritation and 85% of the patients did not



report skin irritation at all. The possibility of having different adhesives with different shapes was reported as an advantage. Thirty two percent of the patients preferred to use the adhesives in combination (148). In another study conducted in the Netherlands skin irritation problems were resolved by alternating between the OptiDerm, Regular and FlexiDerm adhesives (106). During a clinical study in Poland it was shown that about half of the patients used a round shaped adhesive and the other half an oval shape. Most patients used a combination of various types of adhesives (Regular, FlexiDerm, OptiDerm, XtraBase). Just 6% of the patients reported to have 'very much' skin irritation and 77% 'none' or 'very little'. Removal of the adhesive was not painful in 94% of the patients (88).

In a study performed in Brazil, it was shown that the amount of Provox HMEs and Provox adhesives used decreased over time when comparing the first and the sixth weeks of the study. When asked about this decrease, patients related it to a reduction on the frequency of cough and forced expectoration. It is important to mention that during weeks of very hot weather the mean amount of adhesives used was higher due to patients' perspiration which generated troubles with adherence of the adhesives on the skin (153).

Provox XtraBase adhesive was developed especially for hands-free speech. The base of this adhesive is more rigid and gives more support to the peristomal area. It was studied in a study including 14 laryngectomized patients who had used the HME successfully before receiving the FreeHands HME. Both when used with a Provox HME and with the Provox FreeHands HME, on average the patients rated by VAS scale that the skin adherence of the XtraBase was better than that of the 'conventional' (OptiDerm, Regular, FlexiDerm) adhesives (148).

In a prospective clinical crossover study including 32 laryngectomized patients using OptiDerm and StabiliBase OptiDerm it was shown that 43% of the users preferred the StabiliBase OptiDerm over the OptiDerm when compared. Therefore, it was concluded that the StabiliBase OptiDerm is a valuable addition to the existing adhesive range for HME users(154).

Thirty patients who were at least 3 months post-laryngectomy and previously did not use an HME, were followed for 12 weeks to determine how they adapted to the use of Provox XtraHME and Provox attachments. The use of adhesives increased over time, although over 80% used an adhesive as attachment (Provox OptiDerm, Regular, FlexiDerm, XtraBase and StabiliBase), in the first weeks of HME use, patients tended also to use either a LaryTube or LaryButton. The number of patients that used an adhesives to attach the HME increased from 60% to 82% after 12 weeks ( $p=0.014$ ) (102).

In a first study, Ratnayake et al. (123) compared the relative compliance and dermatological outcomes in patients using the Provox Luna during the night. This multicenter, randomized crossover trial was conducted in 3 centers in the Netherlands and included 46 laryngectomized patients. The authors found that in the group using the Provox Luna during the night, the number of compliant users significantly improved and the intervals of daily HME use were longer in comparison to the group that used their 'usual care'. Additionally, there was a significantly increased frequency in self-reported skin improvement overnight when using the Provox Luna. At the end of the study, 56% of the patients wanted to continue using the Provox Luna.

Mayo-Yáñez et al. (155) conducted a randomized crossover trial aimed to investigate possible differences in dermatological symptoms between the use of Provox FlexiDerm adhesive day and night and the use of Provox FlexiDerm adhesive during the day only, in combination with Provox Luna adhesive during the night in twenty-eight laryngectomized HME users. Results showed that dermatological problems were significantly less frequent when the study participants used the Provox FlexiDerm Adhesive in combination with Provox Luna (hydrogel) Adhesive compared to using Provox FlexiDerm Adhesive alone (14.3% vs 46.4%).

A randomized cross-over clinical study comparing Provox Life with the legacy Provox XtraHME devices ('usual care') in 40 laryngectomized patients showed that most patients used Provox StabiliBase during the usual care period, and Provox Life Stability during the Provox Life period. No statistically significant difference was reported regarding adhesive device life between Provox Life (19.3 hours) and usual care (20.3 hours,  $p=0.456$ ) and patients experienced skin irritation less frequently during the Provox Life period ( $p=0.013$ ). Based on the diary, patients experienced skin irritation an average on 4.25 days within 14 days with their usual care versus 2.60 days in the Provox Life period ( $p=0.013$ ) (124).

#### 4.4.2 Tubes and Buttons

Studies have shown that the use of a stoma button increases successful use of a hands-free speaking valve (108, 156). A study on the use of the LaryButton and LaryClips (108) demonstrated that the system was appreciated by the majority of the patients and that its use led to increased success with usage of hands free speaking valves. One study described that LaryButton and other stoma buttons have become a preferred method for securing hands-free speaking valves to the stoma (157). These are effective because they eliminate the need for adhesives and glues that are often ineffective in sustaining a peristomal seal during hands-free TE speech production.

During the COVID pandemic, aerosol generation was greatly discussed and investigated. A study from Hungary investigated the impact of LaryTubes on Aerosol distribution by velocity measurements and thermal imaging in 23 laryngectomized patients. Their results showed that laryngectomized patients without a laryngeal tube have lower risk for spreading viral aerosols due to reduced velocity of aerosols. They conclude that patients after a total laryngectomy should wear HMEs with viral filter in combination with dermal adhesives, to reduce aerosol spreading (158).

## 5. Perspectives and conclusion

The performance of Provox HMEs and their impact on tracheal climate and therefore beneficial effect on integrative pulmonary rehabilitation are supported by abundant and robust clinical and scientific evidence. Continuous innovation has enabled significant improvements in humidification and breathability performance of HMEs and technological advances in adhesives materials. Clinical data demonstrate that these technological improvements further reduce the humidification deficit and improve quality of life.

## 6. References

1. Hilgers FJ, Ackerstaff AH, Aaronson NK, Schouwenburg PF, Van ZN. Physical and psychosocial consequences of total laryngectomy. *Clin Otolaryngol Allied Sci.* 1990;15(5):421-5.
2. McFadden ER, Jr., Denison DM, Waller JF, Assoufi B, Peacock A, Sopwith T. Direct recordings of the temperatures in the tracheobronchial tree in normal man. *J Clin Invest.* 1982;69(3):700-5.
3. Ingelstedt S. Studies on the conditioning of air in the respiratory tract. *Acta Otolaryngol Suppl.* 1956;131:1-80.
4. Keck T, Leiacker R, Heinrich A, Kuhnemann S, Rettlinger G. Humidity and temperature profile in the nasal cavity. *Rhinology.* 2000;38(4):167-71.
5. Scheenstra RJ, Muller SH, Hilgers FJ. Endotracheal temperature and humidity in laryngectomized patients in a warm and dry environment and the effect of a heat and moisture exchanger. *Head Neck.* 2011;33(9):1285-93.
6. Scheenstra RJ, Muller SH, Hilgers FJ. Endotracheal temperature and humidity in laryngectomized patients in a warm and dry environment and the effect of a heat and moisture exchanger. *Head Neck.* 2011;33(9):1285-93.
7. Zuur JK, Muller SH, de Jongh FH, Van ZN, Hilgers FJ. The physiological rationale of heat and moisture exchangers in post-laryngectomy pulmonary rehabilitation: a review. *Eur Arch Otorhinolaryngol.* 2006;263(1):1-8.
8. Lorenz KJ. *Pulmonary Rehabilitation after Laryngectomy.* 1st edition - Bremen: UNI-MED Verlag AG; 2013 (UNI-MED SCIENCE). 86 p.
9. Williams R, Rankin N, Smith T, Galler D, Seakins P. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med.* 1996;24(11):1920-9.
10. Mercke U. The influence of varying air humidity on mucociliary activity. *Acta Otolaryngol.* 1975;79(1-2):133-9.
11. Mercke U, Toremalm NG. Air humidity and mucociliary activity. *Ann Otol Rhinol Laryngol.* 1976;85(1 Pt 1):32-7.
12. Schwab JA, Zenkel M. Filtration of particulates in the human nose. *Laryngoscope.* 1998;108(1 Pt 1):120-4.
13. Hatch TF. Distribution and deposition of inhaled particles in respiratory tract. *Bacteriol Rev.* 1961;25:237-40.
14. Tellier R. Aerosol transmission of influenza A virus: a review of new studies. *J R Soc Interface.* 2009;6 Suppl 6:S783-90.
15. Kelly FJ, Fussell JC. Air pollution and airway disease. *Clin Exp Allergy.* 2011;41(8):1059-71.
16. Particulate matter: Basic Information: US EPA (United States Environmental Protection Agency); 2014 [updated 2014. Available from: <http://www.epa.gov/pm/basic.html>.
17. McGarry P, Morawska L, He C, Jayaratne R, Falk M, Tran Q, et al. Exposure to particles from laser printers operating within office workplaces. *Environ Sci Technol.* 2011;45(15):6444-52.
18. Invernizzi G, Ruprecht A, Mazza R, Rossetti E, Sasco A, Nardini S, et al. Particulate matter from tobacco versus diesel car exhaust: an educational perspective. *Tob Control.* 2004;13(3):219-21.
19. Air quality and health - Fact sheet No 313 2014 [updated 2014. Available from: <http://www.who.int/mediacentre/factsheets/fs313/en/>.
20. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. 2002 [updated 2002. Available from: <http://whalibdoc.who.int/publications/2002/9241562072.pdf>.
21. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide, Global update 2005, Summary of risk assessment. 2005 [updated 2005. Available from: [http://whalibdoc.who.int/hq/2006/WHO\\_SDE\\_PHE\\_OEH\\_06.02\\_eng.pdf](http://whalibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf).
22. Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, et al. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J.* 1997;10(5):1064-71.
23. Brunekreeff B, Holgate ST. Air pollution and health. *Lancet.* 2002;360(9341):1233-42.
24. Jongeneel WP, Straatsen BAM, van Kempen EEMM, Fischer PH. Gezondheidseffecten van wegverkeer: een quickscan 2008 [updated 2008. Available from: [http://www.ggdkenisnet.nl/?file=5785&m=1319011665&action=file\\_download](http://www.ggdkenisnet.nl/?file=5785&m=1319011665&action=file_download).
25. Villeneuve PJ, Chen L, Rowe BH, Coates F. Outdoor air pollution and emergency department visits for asthma among children and adults: a case-crossover study in northern Alberta, Canada. *Environ Health.* 2007;6:40.
26. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect.* 2012;120(7):965-70.

27. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J Med Toxicol.* 2012;8(2):166-75.
28. Heyder J, Rudolf G. Deposition of aerosol particles in the human nose. *Inhaled Part.* 1975;4 Pt 1:107-26.
29. Londahl J, Moller W, Pagels JH, Kreyling WG, Swietlicki E, Schmid O. Measurement techniques for respiratory tract deposition of airborne nanoparticles: a critical review. *J Aerosol Med Pulm Drug Deliv.* 2014;27(4):229-54.
30. Keck T, Leiacker R, Klotz M, Lindemann J, Riechelmann H, Rettinger G. Detection of particles within the nasal airways during respiration. *Eur Arch Otorhinolaryngol.* 2000;257(9):493-7.
31. Jay S, Ruddy J, Cullen RJ. Laryngectomy: the patient's view. *J Laryngol Otol.* 1991;105(11):934-8.
32. van den Boer C, van Harten MC, Hilgers FJ, van den Brekel MW, Retel VP. Incidence of severe tracheobronchitis and pneumonia in laryngectomized patients: a retrospective clinical study and a European-wide survey among head and neck surgeons. *Eur Arch Otorhinolaryngol.* 2014;271(12):3297-303.
33. Retel VP, van den Boer C, Steuten LM, Okla S, Hilgers FJ, van den Brekel MW. Cost-effectiveness of heat and moisture exchangers compared to usual care for pulmonary rehabilitation after total laryngectomy in Poland. *Eur Arch Otorhinolaryngol.* 2015;272(9):2381-8.
34. McRae D, Young P, Hamilton J, Jones A. Raising airway resistance in laryngectomees increases tissue oxygen saturation. *Clin Otolaryngol Allied Sci.* 1996;21(4):366-8.
35. Ferris BG, Jr., Mead J, Opie LH. Partitioning of respiratory flow resistance in man. *J Appl Physiol.* 1964;19:653-8.
36. Recinto C, Efthymeou T, Boffelli PT, Navalta JW. Effects of Nasal or Oral Breathing on Anaerobic Power Output and Metabolic Responses. *Int J Exerc Sci.* 2017;10(4):506-14.
37. Togawa K, Konno A, Hoshino T. A physiologic study on respiratory handicap of the laryngectomized. *Arch Otorhinolaryngol.* 1980;229(1):69-79.
38. Scheenstra RJ, Muller SH, Vincent A, Sinaasappel M, Hilgers FJ. Influence of breathing resistance of heat and moisture exchangers on tracheal climate and breathing pattern in laryngectomized individuals. *Head Neck.* 2010;32(8):1069-78.
39. McRae RD, Jones AS, Young P, Hamilton J. Resistance, humidity and temperature of the tracheal airway. *Clin Otolaryngol Allied Sci.* 1995;20(4):355-6.
40. Swift AC, Campbell IT, McKown TM. Oronasal obstruction, lung volumes, and arterial oxygenation. *Lancet.* 1988;1(8577):73-5.
41. Harris S, Jonson B. Lung function before and after laryngectomy. *Acta Otolaryngol.* 1974;78(3-4):287-94.
42. Natvig K. Influence of different climates on the peak expiratory flow in laryngectomees. *J Laryngol Otol.* 1984;98(1):53-8.
43. Todisco T, Maurizi M, Paludetti G, Dottorini M, Merante F. Laryngeal cancer: long-term follow-up of respiratory functions after laryngectomy. *Respiration.* 1984;45(3):303-15.
44. Torjussen W. Airway obstructions in laryngectomized patients. A spirometric investigation. *Acta Otolaryngol.* 1968;66(1):161-70.
45. Usui N. Ventilatory function in laryngectomized patients. *Auris Nasus Larynx.* 1979;6(2):87-96.
46. Foreman A, De Santis RJ, Sultanov F, Enepekides DJ, Higgins KM. Heat and moisture exchanger use reduces in-hospital complications following total laryngectomy: a case-control study. *J Otolaryngol Head Neck Surg.* 2016;45(1):40.
47. Griffith TE, Friedberg SA. Histologic Changes in the Trachea Following Laryngectomy. *Ann Otol Rhinol Laryngol.* 1964;73:883-92.
48. Roessler F, Grossenbacher R, Walt H. [Condition of the tracheobronchial mucous membrane in patients with long-term tracheostomy. A scanning electron microscopy study]. *Laryngol Rhinol Otol (Stuttg).* 1988;67(2):66-71.
49. Zuur JK, Muller SH, Sinaasappel M, Hart GA, Van ZN, Hilgers FJ. Influence of heat and moisture exchanger respiratory load on transcutaneous oxygenation in laryngectomized individuals: a randomized crossover study. *Head Neck.* 2007;29(12):1102-10.
50. Zuur JK, Muller SH, Vincent A, Sinaasappel M, de Jongh FH, Hilgers FJ. The influence of a heat and moisture exchanger on tracheal climate in a cold environment. *Med Eng Phys.* 2009;31(7):852-7.
51. Ackerstaff AH, Hilgers FJ, Balm AJ, Van Zandwijk N. Long-term pulmonary function after total laryngectomy. *Clin Otolaryngol Allied Sci.* 1995;20(6):547-51.
52. Leemans M, van Sluis KE, Van Son R, Van den Brekel MM. Interaction of functional and participation issues on quality of life after total laryngectomy. *Laryngoscope Invest Otolaryngol.* 2020;5(3):453-60.

53. Hilgers FJ, Ackerstaff AH. Comprehensive rehabilitation after total laryngectomy is more than voice alone. *Folia Phoniatr Logop.* 2000;52(1-3):65-73.
54. Brook I. *The Laryngectomy Guide* 2013. 90 p.
55. Zuur JK, Muller SH, de Jongh FH, van Zandwijk N, Hilgers FJ. The physiological rationale of heat and moisture exchangers in post-laryngectomy pulmonary rehabilitation: a review. *Eur Arch Otorhinolaryngol.* 2006;263(1):1-8.
56. Thomachot L, Viviani X, Arnaud S, Boisson C, Martin CD. Comparing two heat and moisture exchangers, one hydrophobic and one hygroscopic, on humidifying efficacy and the rate of nosocomial pneumonia. *Chest.* 1998;114(5):1383-9.
57. Grolman W, Blom ED, Branson RD, Schouwenburg PF, Hamaker RC. An efficiency comparison of four heat and moisture exchangers used in the laryngectomized patient. *Laryngoscope.* 1997;107(6):814-20.
58. Brusasco C, Corradi F, Vargas M, Bona M, Bruno F, Marsili M, et al. In vitro evaluation of heat and moisture exchangers designed for spontaneously breathing tracheostomized patients. *Respir Care.* 2013;58(11):1878-85.
59. Hilgers FJ, Ackerstaff AH, Van As CJ, Balm AJ, Van den Brekel MW, Tan IB. Development and clinical assessment of a heat and moisture exchanger with a multi-magnet automatic tracheostoma valve (Provox FreeHands HME) for vocal and pulmonary rehabilitation after total laryngectomy. *Acta Otolaryngol.* 2003;123(1):91-9.
60. Raynor PC, Kim BG, Ramachandran G, Strommen MR, Horns JH, Streifel AJ. Collection of biological and non-biological particles by new and used filters made from glass and electrostatically charged synthetic fibers. *Indoor Air.* 2008;18(1):51-62.
61. Jones AS, Young PE, Hanafi ZB, Makura ZG, Fenton JE, Hughes JP. A study of the effect of a resistive heat moisture exchanger (Trachinaze) on pulmonary function and blood gas tensions in patients who have undergone a laryngectomy: a randomized control trial of 50 patients studied over a 6-month period. *Head Neck.* 2003;25(5):361-7.
62. Thoman RL, Stoker GL, Ross JC. The efficacy of pursed-lips breathing in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1966;93(1):100-6.
63. Tiep BL, Burns M, Kao D, Madison R, Herrera J. Pursed lips breathing training using ear oximetry. *Chest.* 1986;90(2):218-21.
64. Motley HL. The effects of slow deep breathing on the blood gas exchange in emphysema. *Am Rev Respir Dis.* 1963;88:484-92.
65. Mueller RE, Petty TL, Filley GF. Ventilation and arterial blood gas changes induced by pursed lips breathing. *J Appl Physiol.* 1970;28(6):784-9.
66. Schmidt GB, Bombeck CT, Bennett EJ, Kotb KM. Continuous positive airway pressure in the prophylaxis of the adult respiratory distress syndrome (ARDS). *Langenbecks Arch Chir.* 1975;Suppl:439-42.
67. Toremalm NG. A heat-and-moisture exchanger for posttracheotomy care. An experimental study. *Acta Otolaryngol.* 1960;52:461-72.
68. Toremalm NG. The daily amount of tracheo-bronchial secretions in man. A method for continuous tracheal aspiration in laryngectomized and tracheotomized patients. *Acta Otolaryngol Suppl.* 1960;158:43-53.
69. Shanks CA, Sara CA. A reappraisal of the multiple gauze heat and moisture exchanger. *Anaesthesia and intensive care.* 1973;1(5):428-32.
70. Steward DJ. A disposable condenser humidifier for use during anaesthesia. *Can Anaesth Soc J.* 1976;23(2):191-5.
71. Keck T, Durr J, Lejacker R, Rettinger G, Rozsasi A. Tracheal climate in laryngectomees after use of a heat and moisture exchanger. *Laryngoscope.* 2005;115(3):534-7.
72. Vitacca M, Clini E, Foglio K, Scalvini S, Marangoni S, Quadri A, et al. Hygroscopic condenser humidifiers in chronically tracheostomized patients who breathe spontaneously. *Eur Respir J.* 1994;7(11):2026-32.
73. Thomachot L, Viviani X, Arnaud S, Viallet R, Albanese J, Martin C. Preservation of humidity and heat of respiratory gases in spontaneously breathing, tracheostomized patients. *Acta Anaesthesiol Scand.* 1998;42(7):841-4.
74. Nakanishi N, Oto J, Itagaki T, Nakataki E, Onodera M, Nishimura M. Humidification Performance of Passive and Active Humidification Devices Within a Spontaneously Breathing Tracheostomized Cohort. *Respir Care.* 2018;64(2):130-5.
75. Ackerstaff AH, Hilgers FJ, Aaronson NK, Schouwenburg PF, van ZN. [Physical and psychosocial sequelae of total larynx extirpation and the use of a heat and moisture exchanger]. *Ned Tijdschr Geneesk.* 1990;134(50):2438-42.
76. Hilgers FJ, Aaronson NK, Ackerstaff AH, Schouwenburg PF, van ZN. The influence of a heat and moisture exchanger (HME) on the respiratory symptoms after total laryngectomy. *Clin Otolaryngol Allied Sci.* 1991;16(2):152-6.
77. Ackerstaff AH, Hilgers FJ, Aaronson NK, Balm AJ, Van ZN. Improvements in respiratory and psychosocial functioning following total laryngectomy by the use of a heat and moisture exchanger. *Ann Otol Rhinol Laryngol.* 1993;102(11):878-83.

78. Ackerstaff AH, Hilgers FJ, Aaronson NK, De Boer MF, Meeuwis CA, Knegt PP, et al. Heat and moisture exchangers as a treatment option in the post-operative rehabilitation of laryngectomized patients. *Clin Otolaryngol Allied Sci.* 1995;20(6):504-9.
79. Icuspit P, Yarlagadda B, Garg S, Johnson T, Deschler D. Heat and moisture exchange devices for patients undergoing total laryngectomy. *ORL Head Neck Nurs.* 2014;32(1):20-3.
80. Lorenz KJ, Maier H. [Pulmonary rehabilitation after total laryngectomy using a heat and moisture exchanger (HME)] in German. *Laryngorhinootologie.* 2009;88(8):513-22.
81. Kramp B, Donat M, Dommerich S, Pau HW, Podbielski A. Prospective controlled study of microbial colonization of the trachea in tracheotomized and laryngectomized patients with HME (heat and moisture exchanger). *Acta Otolaryngol.* 2009;129(10):1136-44.
82. Rosso M, Prgomet D, Marjanovic K, Puseljic S, Kraljik N. Pathohistological changes of tracheal epithelium in laryngectomized patients. *Eur Arch Otorhinolaryngol.* 2015;272(11):3539-44.
83. van den Boer C, Muller SH, Vincent AD, Zuchner K, van den Brekel MW, Hilgers FJ. Ex vivo water exchange performance and short-term clinical feasibility assessment of newly developed heat and moisture exchangers for pulmonary rehabilitation after total laryngectomy. *Eur Arch Otorhinolaryngol.* 2014;271(2):359-66.
84. van den Boer C, Nulle SH, Vincent AD, van den Brekel MW, Hilgers FJ. Ex vivo assessment and validation of water exchange performance of 23 heat and moisture exchangers for laryngectomized patients. *Respir Care.* 2014;59(8):1161-71.
85. Scheenstra RJ, Muller SH, Vincent A, Ackerstaff AH, Jacobi I, Hilgers FJ. A new heat and moisture exchanger for laryngectomized patients: endotracheal temperature and humidity. *Respir Care.* 2011;56(5):604-11.
86. van den Boer C, Vas Nunes JH, Muller SH, van den Brekel MW, Hilgers FJ. Water Uptake Performance of Hygroscopic Heat and Moisture Exchangers after 24-Hour Tracheostoma Application. *Otolaryngol Head Neck Surg.* 2014;150(6):999-1004.
87. Herranz J, Espino MA, Morado CO. Pulmonary rehabilitation after total laryngectomy: a randomized cross-over clinical trial comparing two different heat and moisture exchangers (HMEs). *Eur Arch Otorhinolaryngol.* 2013;270(9):2479-84.
88. Bien S, Okla S, van As-Brooks CJ, Ackerstaff AH. The effect of a Heat and Moisture Exchanger (Provox HME) on pulmonary protection after total laryngectomy: a randomized controlled study. *Eur Arch Otorhinolaryngol.* 2010;267(3):429-35.
89. Dassonville O, Merol JC, Bozec A, Swierkosz F, Santini J, Chais A, et al. Randomised, multi-centre study of the usefulness of the heat and moisture exchanger (Provox HME(R)) in laryngectomised patients. *Eur Arch Otorhinolaryngol.* 2011;268(11):1647-54.
90. Hennessy M, Bann DV, Patel VA, Saadi R, Krempl GA, Deschler DG, et al. Commentary on the management of total laryngectomy patients during the COVID-19 pandemic. *Head Neck.* 2020.
91. Hess CT. When to use hydrogel dressings. *Adv Skin Wound Care.* 2000;13(1):42.
92. Sarabahi S. Recent advances in topical wound care. *Indian J Plast Surg.* 2012;45(2):379-87.
93. Williams C. Hydrogel dressings: their role in dry and sloughy wounds. *Community Nurse.* 1998;4(9):42-4.
94. Sood A, Granick MS, Tomaselli NL. Wound Dressings and Comparative Effectiveness Data. *Adv Wound Care (New Rochelle).* 2014;3(8):511-29.
95. Hampton S. A focus on ActiFormCool in the reduction of pain in wounds. *Br J Community Nurs.* 2007;12(9):S37-42.
96. Rippon M, White R, Davies P. Skin adhesives and their role in wound dressings. *Wounds UK.* 2007;3(4):76-86.
97. Blumenstein I, Borger D, Loitsch S, Bott C, Tessmer A, Hartmann F, et al. A glycerin hydrogel-based wound dressing prevents peristomal infections after percutaneous endoscopic gastrostomy (PEG): a prospective, randomized study. *Nutr Clin Pract.* 2012;27(3):422-5.
98. Francesko A, Petkova P, Tzanov T. Hydrogel Dressings for Advanced Wound Management. *Curr Med Chem.* 2017;25(41):5782-97.
99. Scheenstra RJ, Muller SH, Vincent A, Ackerstaff AH, Jacobi I, Hilgers FJ. Short-term endotracheal climate changes and clinical effects of a heat and moisture exchanger with an integrated electrostatic virus and bacterial filter developed for laryngectomized individuals. *Acta Otolaryngol.* 2010;130(6):739-46.
100. Leemans M, van Alphen MJA, Vallenduuk W, Dirven R, van den Brekel MWM, Muller SH. Understanding and predicting the performance of passive heat and moisture exchangers using a numerical model. *Head Neck.* 2023;45(4):993-1005.
101. Lansaat L, de Kleijn BJ, Hilgers FJ, van der Laan BF, van den Brekel MW. A prospective multicenter clinical feasibility study of a new automatic speaking valve for postlaryngectomy voice rehabilitation. *Eur Arch Otorhinolaryngol.* 2017;274(2):1005-13.



102. Macri GF, Bogaardt H, Parrilla C, Minni A, D'Alatri L, de Vincentiis M, et al. Patients' experiences with HMEs and attachments after total laryngectomy. *Clin Otolaryngol.* 2016;41(6):652-9.
103. Merol JC, Charpiot A, Langagne T, Hemar P, Ackerstaff AH, Hilgers FJ. Randomized controlled trial on postoperative pulmonary humidification after total laryngectomy: External humidifier versus heat and moisture exchanger. *Laryngoscope.* 2012;122(2):275-81.
104. Lorenz KJ, Huverstuhl K, Maier H. [Finger-free speech with the Provox FreeHands HME Automatic Tracheostoma Valve system. Clinical long-term experience]. *HNO.* 2009;57(11):1090-8.
105. Lorenz KJ, Groll K, Ackerstaff AH, Hilgers FJ, Maier H. Hands-free speech after surgical voice rehabilitation with a Provox voice prosthesis: experience with the Provox FreeHands HME tracheostoma valve system. *Eur Arch Otorhinolaryngol.* 2007;264(2):151-7.
106. Ackerstaff AH, Fuller D, Irvin M, Maccracken E, Gaziano J, Stachowiak L. Multicenter study assessing effects of heat and moisture exchanger use on respiratory symptoms and voice quality in laryngectomized individuals. *Otolaryngol Head Neck Surg.* 2003;129(6):705-12.
107. Ward EC, Acton LM, Morton A-L. Stoma Care and Appliances. In: Ward EC, van As-Brooks CJ, editors. *Head and Neck Cancer: Treatment, Rehabilitation, and Outcomes.* San Diego: Plural Publishing; 2007. p. 289-311.
108. Hilgers FJ, Ackerstaff AH. Development and evaluation of a novel tracheostoma button and fixation system (Provox LaryButton and LaryClip adhesive) to facilitate hands-free tracheoesophageal speech. *Acta Otolaryngol.* 2006;126(11):1218-24.
109. Moreno MA, Lewin JS, Hutcheson KA, Bishop Leone JK, Barringer DA, Reece GP. Tracheostomoplasty: A surgical method for improving retention of an intraluminal stoma button for hands-free tracheoesophageal speech. *Head Neck.* 2010;32(12):1674-80.
110. Zuur JK, Muller SH, de Jongh FH, van der Horst MJ, Shehata M, van Leeuwen J, et al. A newly developed tool for intra-tracheal temperature and humidity assessment in laryngectomized individuals: the Airway Climate Explorer (ACE). *Med Biol Eng Comput.* 2007;45(8):737-45.
111. Zuur JK, Muller SH, Vincent A, Sinaasappel M, de Jongh FH, Hilgers FJ. Assessment of tracheal temperature and humidity in laryngectomized individuals and the influence of a heat and moisture exchanger on tracheal climate. *Head Neck.* 2008;30(8):1072-82.
112. Scheenstra RJ, Muller SH, Vincent A, Sinaasappel M, Zuur JK, Hilgers FJ. Endotracheal temperature and humidity measurements in laryngectomized patients: intra- and inter-patient variability. *Med Biol Eng Comput.* 2009;47(7):773-82.
113. van den Boer C, Muller SH, Vincent AD, Zuchner K, van den Brekel MW, Hilgers FJ. A novel, simplified ex vivo method for measuring water exchange performance of heat and moisture exchangers for tracheostomy application. *Respir Care.* 2013;58(9):1449-58.
114. van den Boer C, Muller SH, van dN, V, Olmos RA, Minni A, Parrilla C, et al. Effects of heat and moisture exchangers on tracheal mucociliary clearance in laryngectomized patients: a multi-center case-control study. *Eur Arch Otorhinolaryngol.* 2015;272(11):3439-50.
115. Hilgers FJ, Ackerstaff AH, Balm AJ, Gregor RT. A new heat and moisture exchanger with speech valve (Provox stomafilter). *Clin Otolaryngol Allied Sci.* 1996;21(5):414-8.
116. Balle VH, Rindso L, Thomsen J. Speech rehabilitation by Provox voice prosthesis combined with heat and moisture exchange filters. *Acta Otolaryngol Suppl.* 1997;529:251-3.
117. Herranz Gonzalez-Botas J, Suarez T, Garcia Carreira B, Martinez Moran A. [Experience with the HME-Provox Stomafilter in laryngectomized patients]. *Acta Otorrinolaringol Esp.* 2001;52(3):221-5.
118. Masson AC, Fouquet ML, Goncalves AJ. Tracheostoma humidifier: influence on secretion and voice of patients with total laryngectomy. *Pro Fono.* 2008;20(3):183-9.
119. Ackerstaff AH, Hilgers FJ, Balm AJ, Tan IB. Long-term compliance of laryngectomized patients with a specialized pulmonary rehabilitation device: Provox Stomafilter. *Laryngoscope.* 1998;108(2):257-60.
120. Scheenstra RJ, Muller SH, Vincent A, Ackerstaff AH, Jacobi I, Hilgers FJ. A new heat and moisture exchanger for laryngectomized patients: endotracheal temperature and humidity. *Respir Care.* 2011;56(5):604-11.
121. Parrilla C, Minni A, Bogaardt H, Macri GF, Battista M, Roukos R, et al. Pulmonary Rehabilitation After Total Laryngectomy: A Multicenter Time-Series Clinical Trial Evaluating the Provox XtraHME in HME-Naive Patients. *Ann Otol Rhinol Laryngol.* 2015;124(9):706-13.
122. Ebersole B, Moran K, Gou J, Ridge J, Schiech L, Liu JC, et al. Heat and moisture exchanger cassettes: Results of a quality/safety initiative to reduce postoperative mucus plugging after total laryngectomy. *Head Neck.* 2020.

123. Ratnayake CBB, Fles R, Tan IB, Baijens LWJ, Pilz W, Meeuwis CA, et al. Multicenter randomized crossover trial evaluating the provox luna in laryngectomized subjects. *Laryngoscope*. 2019;129(10):2354-60.
124. Longobardi Y, Galli J, Di Cesare T, D'Alatri L, Settini S, Mele D, et al. Optimizing Pulmonary Outcomes after Total Laryngectomy: Crossover study on new Heat and Moisture Exchangers. *Otolaryngol Head Neck Surg*. 2022.
125. Ward EC, Hancock K, Boxall J, Burns CL, Spurgin AL, Lehn B, et al. Post-laryngectomy pulmonary and related symptom changes following adoption of an optimal day-and-night heat and moisture exchanger (HME) regimen. *Head Neck*. 2023;45(4):939-51.
126. Almajali O, Balk M, Rupp R, Allner M, Sievert M, Iro H, et al. The Effects of a "New Generation" of Heat and Moisture Exchangers in Laryngectomized Patients with Previous Heat and Moisture Changer Experience. *Ear Nose Throat J*. 2023;1455613231200769.
127. Heirman AN, Groen WG, van der Molen L, Dirven R, van den Brekel MWM, Stuijver MM. Maximal cardiopulmonary exercise testing in laryngectomized patients using different heat and moisture exchangers - feasibility and exercise responses. *J Laryngol Otol*. 2023:1-8.
128. Mesolella M, Allosso S, Mormile M, Quaremba G, Errante V, D'Aniello R, et al. Quality of Life and Respiratory Performance in the Laryngectomized Patient: Role of the HME Filters during Physical Activity. *J Clin Med*. 2024;13(11).
129. Mohide EA, Archibald SD, Tew M, Young JE, Haines T. Postlaryngectomy quality-of-life dimensions identified by patients and health care professionals. *Am J Surg*. 1992;164(6):619-22.
130. van As CJ, Hilgers FJ, Koopmans-van Beinum FJ, Ackerstaff AH. The influence of stoma occlusion on aspects of tracheoesophageal voice. *Acta Otolaryngol*. 1998;118(5):732-8.
131. Brook I, Bogaardt H, van As-Brooks C. Long-term use of heat and moisture exchangers among laryngectomees: medical, social, and psychological patterns. *Ann Otol Rhinol Laryngol*. 2013;122(6):358-63.
132. Pedemonte-Sarrias G, Villatoro-Solagaistoa JC, Ale-Inostroza P, Lopez-Vilas M, Leon-Vintro X, Quer-Agusti M. Chronic adherence to heat and moisture exchanger use in laryngectomized patients. *Acta Otorinolaringol Esp*. 2013;64 4:247-52.
133. Beck ACC, Retel VP, Bunting G, Sethi R, Deschler DG, van den Brekel MWM, et al. Cost-effectiveness analysis of using the heat and moisture exchangers compared with alternative stoma covers in laryngectomy rehabilitation: US perspective. *Head Neck*. 2020.
134. Scheenstra RJ, Muller SH, Vincent A, Ackerstaff AH, Jacobi I, Hilgers FJ. Short-term endotracheal climate changes and clinical effects of a heat and moisture exchanger with an integrated electrostatic virus and bacterial filter developed for laryngectomized individuals. *Acta Otolaryngol*. 2010;130(6):739-46.
135. Kirton OC, DeHaven B, Morgan J, Morejon O, Civetta J. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest*. 1997;112(4):1055-9.
136. Kranabetter R, Leier M, Kammermeier D, Just HM, Heuser D. [The effects of active and passive humidification on ventilation-associated nosocomial pneumonia]. *Anaesthesist*. 2004;53(1):29-35.
137. Subayi L, Chergui K, Beydon L. [Heat and moisture exchanging filters for conditioning of inspired gases in adult anesthesia and resuscitation]. *Ann Fr Anesth Reanim*. 1998;17(7):699-708.
138. Barbara J, Santais MC, Levy DA, Ruff F, Leynadier F. Prevention of latex sensitization in guinea pigs by a bacterial and viral filter used in anaesthesia. *Br J Anaesth*. 2005;95(3):349-54.
139. Boots RJ, Howe S, George N, Harris FM, Faoagali J. Clinical utility of hygroscopic heat and moisture exchangers in intensive care patients. *Crit Care Med*. 1997;25(10):1707-12.
140. Rathgeber J, Kietzmann D, Mergeryan H, Hub R, Zuchner K, Kettler D. Prevention of patient bacterial contamination of anaesthesia-circle-systems: a clinical study of the contamination risk and performance of different heat and moisture exchangers with electret filter (HMEF). *Eur J Anaesthesiol*. 1997;14(4):368-73.
141. Parrinello G, Missale F, Sampieri C, Carobbio ALC, Peretti G. Safe management of laryngectomized patients during the COVID-19 pandemic. *Oral Oncol*. 2020;107:104742.
142. Brook I. Prevention of COVID-19 Infection in Neck Breathers, Including Laryngectomees. *Int Arch Otorhinolaryngol*. 2020;24(3):e253-e4.
143. Yeung DCM, Lai R, Wong EWY, Chan JYK. Care of Patients With a Laryngectomy During the COVID-19 Pandemic. *Otolaryngol Head Neck Surg*. 2020:194599820933185.
144. Varghese JJ, Aithal VU, Rajashekhar B. Self-care and clinical management of persons with laryngectomy during COVID-19 pandemic: a narrative review. *Support Care Cancer*. 2021.









145. Searl J, Kearney A, Genoa K, Doyle PC. Clinical Experiences of People With a Laryngectomy During the SARS COVID-19 Pandemic. *Am J Speech Lang Pathol*. 2021;1-16.
146. Lindsley WG, Blachere FM, Beezhold DH, Law BF, Derk RC, Hettick JM, et al. A comparison of performance metrics for cloth face masks as source control devices for simulated cough and exhalation aerosols. *medRxiv*. 2021.
147. Op de Coul BM, Ackerstaff AH, van As-Brooks CJ, van den Hoogen FJ, Meeuwis CA, Manni JJ, et al. Compliance, quality of life and quantitative voice quality aspects of hands-free speech. *Acta Otolaryngol*. 2005;125(6):629-37.
148. Tervonen H, Back L, Juvas A, Rasanen P, Makitie AA, Sintonen H, et al. Automatic speaking valve in speech rehabilitation for laryngectomized patients. *Eur Arch Otorhinolaryngol*. 2005;262(10):816-20.
149. Hamade R, Hewlett N, Scanlon E. A quantitative and qualitative evaluation of an automatic occlusion device for tracheoesophageal speech: the Provox FreeHands HME. *Clin Linguist Phon*. 2006;20(2-3):187-93.
150. Lorenz KJ, Huverstuhl K, Maier H. [Finger-free speech with the Provox FreeHands HME Automatic Tracheostoma Valve system. Clinical long-term experience] in German. *HNO*. 2009;57(11):1090-8.
151. Longobardi Y, D'Alatri L, Brandi VF, Mari G, Marenza ME, Marchese MR, et al. Automatic speaking valve in tracheoesophageal speech: treatment proposal for a widespread usage. *Eur Arch Otorhinolaryngol*. 2024;281(6):3197-205.
152. van der Houwen EB, van Kalkeren TA, Post WJ, Hilgers FJ, van der Laan BF, Verkerke GJ. Does the patch fit the stoma? A study on peristoma geometry and patch use in laryngectomized patients. *Clin Otolaryngol*. 2011;36(3):235-41.
153. Masson AC, Fouquet ML, Goncalves AJ. Tracheostoma humidifier: influence on secretion and voice of patients with total laryngectomy. *Pro Fono*. 2008;20(3):183-9.
154. Lansaat L, Kleijn B, Hilgers F, Laan BV, Brekel MVD. Comparative Study Between Peristomal Patches in Patients with Definitive Tracheostomy. *Int Arch Otorhinolaryngol*. 2018;22(2):130-5.
155. Mayo-Yanez M, Balboa-Barreiro V, Lechien JR, Calvo-Henriquez C, Chiesa-Estomba C, Herranz Gonzalez-Botas J, et al. Improving heat and moisture exchanger therapy with a hydrogel base adhesive in laryngectomized patients: an open randomized crossover trial. *J Laryngol Otol*. 2022;1-20.
156. Lewin JS, Lemon J, Bishop-Leone JK, Leyk S, Martin JW, Gillenwater AM. Experience with Barton button and peristomal breathing valve attachments for hands-free tracheoesophageal speech. *Head Neck*. 2000;22(2):142-8.
157. Lewin JS, Montgomery PC, Hutcheson KA, Chambers MS. Further experience with modification of an intraluminal button for hands-free tracheoesophageal speech after laryngectomy. *J Prosthet Dent*. 2009;102(5):328-31.
158. Iszlai Z, Fodor B, Szabo R, Szekanecz Z, Karosi T. [Thermal imaging and velocity measurements of the exhaled airflow in total laryngectomized patients during COVID-19 pandemic.]. *Orv Hetil*. 2023;164(34):1327-36.







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## 7. Appendix

Table 1. Humidification capacity and breathability comparison of the different HMEs and HMEFs generations. Moisture loss and Air pressure drop values are according to device specification<sup>6</sup>.

	Provox HMEs	Provox XtraHMEs	Provox Life HMEs
	Normal	XtraMoist	Home
<b>Moisture loss</b> 	23.7 mg/L	21.5 mg/L	19.5 mg/L 9.3 % higher humidification compared to XtraMoist
<b>Air pressure drop</b> 	70 Pa	70 Pa	60 Pa 14% higher breathability compared to XtraMoist
	HiFlow	XtraFlow	Go
<b>Moisture loss</b> 	25.4 mg/L	24 mg/L	22.5 mg/L 6.3% higher humidification compared to XtraFlow
<b>Air pressure drop</b> 	50 Pa	40 Pa	30 Pa 25% higher breathability compared to XtraFlow
	HiFlow	XtraFlow	Energy
<b>Moisture loss</b> 	25.4 mg/L	24 mg/L	23 mg/L 4.2% higher humidification compared to XtraFlow
<b>Air pressure drop</b> 	50 Pa	40 Pa	15 Pa 63% higher breathability compared to XtraFlow
		Micron	Protect

<sup>6</sup> Data on file.

<b>Moisture loss</b> 		22 mg/L	23 mg/L 4.5% higher humidification compared to Micron
<b>Air pressure drop</b> 		70 Pa	55 Pa 21% higher breathability compared to Micron
		FreeHands	FreeHands
<b>Moisture loss</b> 		Moist: 24 mg/L Flow: 25 mg/L	23 mg/L 4% better humidification compared to FreeHands
<b>Air pressure drop</b> 		Moist: 70 Pa Flow: 65 Pa	56 Pa 14% better breathability compared to FreeHands
		Luna	Night
<b>Moisture loss</b> 		21.5 mg/L	18.5 mg/L 14% better humidification compared to Luna
<b>Air pressure drop</b> 		55 Pa	65 Pa

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