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Cost-effectiveness of heat and moisture exchangers compared to usual care for pulmonary rehabilitation after total laryngectomy in Poland

Valesca P. Retèl1,2 · Cindy van den Boer3 · Lotte M. G. Steuten4 · Sławomir Okła5 · Frans J. Hilgers3,6 · Michiel W. van den Brekel3,6,7

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Abstract The beneficial physical and psychosocial effects of heat and moisture exchangers (HMEs) for pulmonary rehabilitation of laryngectomy patients are well evidenced. However, cost-effectiveness in terms of costs per additional quality-adjusted life years (QALYs) has not yet been investigated. Therefore, 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 was performed. Primary outcomes were costs, QALYs and incremental cost-effectiveness ratio (ICER). Secondary outcomes were pulmonary infections, and sleeping problems. The analysis was performed from a health care perspective of Poland, using a time horizon of 10 years and cycle length of 1 year. Transition probabilities were derived from various sources, amongst others a Polish randomized clinical trial. Quality of life data was derived from an Italian study on similar patients. Data on frequencies and mortality-related tracheobronchitis and/or pneumonia were derived from a Europe-wide survey amongst head and neck cancer experts. Substantial differences in quality-adjusted survival between the use of HMEs (3.63 QALYs) versus UC (2.95 QALYs) were observed. Total health care costs/patient were 39,553 PLN (9465 Euro) for the HME strategy and 4889 PLN (1168 Euro) for the UC strategy. HME use resulted in fewer pulmonary infections, and less sleeping problems. We could conclude that given the Polish threshold of 99,000 PLN/QALY, using HMEs is cost-effective compared to UC, resulting in 51,326 PLN/QALY (12,264 Euro/QALY) gained for patients after total laryngectomy. For the hospital period alone (2 weeks), HMEs were cost-saving: less costly and more effective.

Keywords Heat and moisture exchanger (HME) · Laryngectomy · Cost-effectiveness analysis · Pulmonary rehabilitation

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Introduction

The incidence of larynx cancer for men and women in Poland was around 2700 in 2012, and the mortality rate was 6.5 per 100,000 [1]. For many years, total laryngectomy (TLE) has been the standard of surgical treatment for advanced stage of laryngeal carcinoma [2].

It has been proven in many studies that a TLE, besides having an impact on voice and speech, has major pulmonary and other physical and psychosocial consequences [3–6]. Due to the disconnection of the lower and upper airways, the conditioning of inhaled air, for example, warming, humidifying and filtering is no longer possible. Significantly colder and dryer air will thus enter the trachea and bronchi, impacting mucociliary function and causing often-bothersome pulmonary problems [4, 5]. These problems consist of excessive phlegm production, involuntary coughing, and increased need to clear the airway from mucus by forced expectoration. Clinical research has shown that these problems can cause pulmonary infections, negatively affect many health-related quality of life (HRQoL) aspects, and also negatively influence voice quality, irrespective of the mode of communication (prosthetic trachea-esophageal or esophageal voice) [3–7]. These pulmonary problems correlate, for example, significantly with voice quality and several aspects of daily living, including fatigue, sleep problems, social contacts and psychological distress [3]. Although great progress has been achieved in the rehabilitation after laryngectomy, still a proportion of this population experience a long-term impact on HRQoL [8]. As the changes in the pulmonary physiology occur immediately after the TLE, it has long been become common practice to provide extraneous airway humidification directly following the surgery.

Most clinicians are well aware of the necessity to compensate for the loss of the upper airway function. Already in 1990, the first heat and moisture exchanger (HME) for laryngectomized patients was introduced [9]. The HMEs are applied to compensate for the lost functions of the upper airways, and have been found to diminish these symptoms and improve the HRQoL significantly [7, 10]. The specific HME evaluated in this study was proved clinically effective in several prospective studies in different countries and climates [11, 12] and has a positive effect on intra-tracheal temperature and humidity, and improvement of pulmonary function [10]. Initially the use of HME typically started several weeks to months after the TLE, but in recent years, evidenced by a randomized controlled trial, it has become increasingly common to start HME use immediately post-surgery and forego the use of external humidification systems [13].

Today, little is known about the costs and benefits of using HMEs compared to usual care (UC) for pulmonary rehabilitation after TLE. Though some studies do have additional information on costs [13, 14], a formal cost-effectiveness analysis has not yet been performed. The aim of the present study was to analyze the incremental cost-effectiveness for using HMEs compared to UC (stoma covers, suction systems and/or external humidifiers) for patients, who underwent TLE in Poland. Such information may help in taking reimbursement decisions concerning HMEs.

Methods

Model description

A Markov decision model was developed to compare two strategies: UC and using HME. The model was constructed with three mutually exclusive health states: “complete remission”, “recurrent cancer” and “death” (death of cancer or other causes) (see Fig. 1). A disease model was chosen, in which several parameters were incorporated, such as pulmonary infection, tube feeding and sleeping problems. The study adopted a health care perspective from Poland, a time horizon of 10 years and cycle length of 1 year. The model simulated the course of events in a hypothetical cohort of 1000 patients with an average age of 65 years with larynx cancer who underwent TLE. The analyses are performed according to the guidelines of conducting Health Technology Assessment in Poland from the Agency for Health Technology Assessment (AOTM) [15] and reported following the CHEERS guideline [16].

Probabilities

To investigate the cost-effectiveness of using HMEs compared to UC for pulmonary rehabilitation after TLE, probabilities concerning sleeping problems and the usage of sleeping medication of a recent randomized clinical trial reported by Bien and colleagues in Poland were used [17]. Survival probabilities were based on the literature [18–20]. Progression of the cancer and probabilities for progression of cancer were assumed to be equal for the two strategies, except for the occurrence of tracheobronchitis and/or pneumonia. The probability of tracheobronchitis and/or pneumonia (further called pulmonary infection) and related mortality was derived from a European-wide survey [21]. The findings of the survey were in accordance to literature [6, 20, 22, 23]. UC in Poland during the direct postoperative period can be divergent; hospitals may use stoma covers, suction systems, external humidifier or nothing. A
range of possibilities is taken into account in the model. In the time period after hospitalization for the TLE, the patients are assumed to commonly use either a stoma cover or nothing when discharged to their homes (personal communication by Polish health care providers).

Costs

The costs were calculated after total laryngectomy, and excluding palliative costs, because these were assumed to be equal for both groups. The costs of the health state “complete remission” including medication, hospitalization, stoma covers and saline were based on data derived from several hospitals in different regions in Poland, using questionnaires (personal communication, see Supplementary Appendix). The content of UC can be very diverse, as not every country uses the same devices or equipment in the hospital setting or at home. The average annual costs of the HME package were provided by Atos Medical AB; Sweden. The average costs are based on estimated use of one HME cassette per day, one adhesive per 1.5 day, and 2 laryngectomy tubes or stoma buttons per year. All costs were expressed in new Polish Zloty (PLN), with the mean value of year 2012 (Table 1).

Health effects

Health-related quality of life was modeled by assigning utilities to the different health states. The utilities are expressed in quality-adjusted life years (QALYs). The QALY is a measure of disease burden, including both the quality and the quantity of life lived, where a correction factor is multiplied to the additional life years lived. The utilities regarding UC versus HME use were based on EuroQol 5D-5L (available at http://www.euroqol.com) [24] data derived from an HME versus non-HME study in Italy. This study has a time-series design, where not all patients did use an HME at the beginning of the study, and finally 38 patients ended the study using an HME regularly [25]. A QALY “weight” was applied for sleeping problems, as measured in the study of Bien et al. [17], by converting a 4-point Likert scale of questions regarding sleeping problems from a scale of 0–10 (by multiplying “most of the time” with 0, “a lot of the time” with 0.33, “time to time, occasionally” with 0.66 and “not at all” with 1; see Tables 1, 2).

Uncertainty analysis

The model was programmed in Microsoft Excel (Microsoft, Redmond, WA, USA) and the robustness of the model was tested by changes of several parameters using various sensitivity analyses. Future costs and effects were discounted to their present value by a rate of 3.5 % for both, according to European guidelines [26]. Incremental cost-effectiveness ratios (ICERS) were calculated by dividing the incremental costs by incremental quality-adjusted life years (QALYs). Uncertainty in the input parameters was handled probabilistically, by assigning distributions to parameters (Table 1) [27]. Parameter values were drawn at random from the assigned distributions, using Monte Carlo simulation with 5000 iterations. The results of the simulation of the hypothetical cohort of 1000 patients are illustrated in a cost-effectiveness (CE) plane, each quadrant indicates whether a strategy is more or less expensive and more or less effective [28]. To show decision uncertainty, cost-effectiveness acceptability curves (CEACs) are presented. CEACs show the probability that a pathway has the highest net monetary benefit, and thus is deemed cost-effective, given different cost per QALY ratios.

Threshold

Whether a strategy is deemed efficient depends on how much society is willing to pay for a gain in effect (the maximum willingness to pay for one QALY), which is referred to as the ceiling ratio or threshold [28]. In Europe, several countries have an established range of ceiling ratios based on the societal willingness to pay for one QALY. In Poland, such a range does not formally exist. For such case,
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean</th>
<th>SE</th>
<th>Units</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS to DFS</td>
<td>0.763</td>
<td>0.030</td>
<td>Beta</td>
<td>[18]</td>
<td></td>
</tr>
<tr>
<td>DFS to DM</td>
<td>0.196</td>
<td>0.030</td>
<td>13/73</td>
<td>Beta [18]</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mort. related pulmonary infection UC</td>
<td>0.015</td>
<td>0.001</td>
<td>4.1/24.47/11 Beta [21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mort. related pulmonary infection HME</td>
<td>0.005</td>
<td>0.001</td>
<td>3.7/74.48/11 Beta [21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection UC</td>
<td>0.285</td>
<td>0.120</td>
<td>6.79/24.47 Beta [21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection HME</td>
<td>0.066</td>
<td>0.105</td>
<td>4.92/74.48 Beta [21]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of benzodiazepines UC</td>
<td>0.275</td>
<td>0.030</td>
<td>11/40 Beta [17]</td>
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<td></td>
</tr>
<tr>
<td>Use of benzodiazepines HME</td>
<td>0.110</td>
<td>0.030</td>
<td>2/18 Beta [17]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Utilities</th>
<th>Mean</th>
<th>SE</th>
<th>Lower/upper (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HME use</td>
<td>0.952</td>
<td>0.015</td>
<td>Beta</td>
<td>[25]</td>
</tr>
<tr>
<td>Usual care (UC)</td>
<td>0.830</td>
<td>0.015</td>
<td>Beta</td>
<td>[25]</td>
</tr>
<tr>
<td>Palliative period</td>
<td>0.500</td>
<td>0.015</td>
<td>Beta</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs in PLN</th>
<th>Mean (Zloty)</th>
<th>(Euros)</th>
<th>SE</th>
<th>Lower/upper (%)</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary infectiona</td>
<td>1,627</td>
<td>(2564)</td>
<td>207.55</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Including: 4 days admission</td>
<td>4 × 325</td>
<td>(4 × 575)</td>
<td>41.45</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Antibioticsb</td>
<td>49</td>
<td>(85)</td>
<td>6.21</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>229</td>
<td>(129)</td>
<td>29.15</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Plain X-ray</td>
<td>50</td>
<td>(50)</td>
<td>6.38</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Sleep medicationc</td>
<td>128</td>
<td>(672)</td>
<td>16.29</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>HME packaged</td>
<td>13,966</td>
<td>(5,575)</td>
<td>1,781</td>
<td>±25</td>
<td>Gamma</td>
<td>Atos Med.</td>
</tr>
<tr>
<td>Stoma covere</td>
<td>228</td>
<td>(365)</td>
<td>29.10</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Suction systemf</td>
<td>42</td>
<td>(50)</td>
<td>5.34</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Ultrasonic nebulizer-hospital</td>
<td>832</td>
<td>(2915)</td>
<td>106.14</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
<tr>
<td>Saline use at homeg</td>
<td>785</td>
<td>(2,035)</td>
<td>100.13</td>
<td>±25</td>
<td>Gamma</td>
<td>Hosp</td>
</tr>
</tbody>
</table>

Hosp: personal communication; data from several hospitals in different regions in Poland (see Supplementary Appendix), using questionnaires; Atos Medical: available at: http://www.atosmedical.com
SE standard error, HME heat and moisture exchanger, UC usual care, Mort. mortality, DFS disease-free survival, DM distant metastasis

a Including: 4 days of hospital admission, antibiotics, plain X-ray, outpatient clinic
b Antibiotics: Metromidazil; Cefalospomyn; Amoxiclavicaan; Zinnat 5–14 days
c Estazolan (noctal), estimation for daily consumption 0.20–0.50 PLN
d Including one HME cassette per day, one adhesive per 1–1.5 day, and 1 laryngectomy tube or stoma buttons per year
e Estimation 0.25-1 PLN/day;
f Container 7 PLN; Tubing 2.50 PLN/2 days; Suction tip 0.32 PLN approx. 6/day
g Sodium chloride ampules 9 mg/ml per 15 pieces (assumption 5 pieces per day)
the World Health Organization (WHO) has established a cost-effectiveness criterion indicating that a health care technology is cost-effective if the incremental cost-effectiveness ratio (ICER) is less than three times the per capita gross domestic product (GDP) for a given country \[29\]. Last GDP per capita has been announced by the President of Main Polish Office for Statistics (Główny Urząd Statystyczny) for the years 2007–2009 and equals 33,181 PLN, what means that 3 × GDP per capita results in a ceiling ratio of 3 × 33,181 is 99,543 PLN/QALY, according to the Agency for Health Technology Assessment in Poland (AOTM) \[15\].

### Sensitivity analysis

Tree one-way sensitivity analyses were performed, to test the robustness of the model. First, the utility rate of pulmonary infection was changed from 0.50 to 0.70, because this was an assumption and could have impact on the results. Second, because Poland has no formal discount rates, the range on discount rates was changed from 1 to 5 % for costs and utilities. Third, we calculated the maximum HME package price for a “less costly and more effective” situation. Additionally, we calculated a two-way sensitivity analyses, combining variations on the HME package price (from 10,000 to 20,000 PLN) and the probability of pulmonary infection for the non-HME user group (from 0.15 to 0.32), based on the results of the European-wide survey \[30\]. Finally, we estimated the ICER per payer for the period in the hospital (shorter time horizon; during 2 weeks), because during hospital admission, very different materials are used in the usual care group, such as the more expensive external humidifiers and suction \[13\].

### Results

#### Mean results

Using HMEs resulted in fewer pulmonary infections (including less re-admissions), less sleeping problems (less use of medication), less or no use of external humidifiers in the hospital or stoma covers at home, and a higher quality of life and social life compared to usual care. The total 10-year health care costs per patient yielded 39,553 PLN for the HME strategy, and 4889 PLN for the UC strategy. (Table 3) The QALYs amounted to 3.63 and 2.95, respectively. Compared to the UC strategy, the HME strategy resulted in 51,326 PLN/QALY (95 % CI 18,037–51,517) gained, and thus was found to be more costly, but more effective. The budget impact was the total costs for the HME strategy (39,553 PLN) multiplied by the target population (1500), 5.9 million PLN.

#### Uncertainty analysis

Figures 2 and 3 show that the HME group has a higher probability of being cost-effective compared to the UC group, as long as the willingness to pay threshold for 1 additional QALY is at least 51,000 PLN/QALY. At the prevailing threshold of 99,000 PLN/QALY the probability for HME being cost-effective compared to UC was 100 %.

#### Sensitivity analysis

The first sensitivity analysis using lower and higher utilities for pulmonary infection and the second sensitivity analysis regarding changing the discount rates did not have any significant effect of the results. Third, to derive a cost-saving result, the HME package costs had to be decreased to 2000 PLN per HME package. In the two-way analysis, the range of possible ICERs could be from 34,000 to 77,000 (See Table 4). All scenarios in the sensitivity analyses showed that the cost-effectiveness of the HME package remains, within a certain range of ICERs. For the hospital period alone (during 2 weeks), using HMEs was dominant: less costly, and more effective, compared to UC. For the period at home, the overall conclusion (HME being more effective but more costly) did not change.
Discussion

This is the first study investigating the cost-effectiveness of HME use versus UC. The results show that substantial differences occurred in QoL, in favor of HME use for pulmonary rehabilitation in laryngectomized patients. HME use resulted in 51,326 PLN/QALY gained and thus was found to be more costly, but more effective. Concluded, the HME group has a higher probability of being cost-effective compared to the UC group, as long as the willingness to pay threshold for 1 additional QALY is at least 51,326 PLN/QALY.

Table 3 Results of the base case and sensitivity analyses; incremental (difference) in life years (Lys), quality-adjusted life years (QALYs), and incremental costs and the incremental cost-effectiveness ratio (ICER) of the comparison between UC and HME use

<table>
<thead>
<tr>
<th></th>
<th>Costs</th>
<th>QALYs</th>
<th>Incremental costs (95 % CI)</th>
<th>Incremental QALYs (95 % CI)</th>
<th>ICER cost/QALY (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HME</td>
<td>39,553</td>
<td>3.63</td>
<td>34,664 (20,630–53,081)</td>
<td>0.68 (0.45–0.95)</td>
<td>51,326a (18,037–51,517)</td>
</tr>
<tr>
<td>UC</td>
<td>4889</td>
<td>2.95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a The numbers might not add up to 100 % because of rounding

Fig. 2 Cost-Effectiveness (CE)-plane; scatter plot showing the mean differences in costs and outcomes from the data using 5000 bootstrap replicates

Fig. 3 Cost-effectiveness Acceptability Curves (CEAC) presenting the probability of cost-effectiveness of the two alternatives for a range of values of thresholds (ceiling ratios, willingness to pay for one QALY)
Table 4 Results of the cost/QALY in two-way sensitivity analysis: range of variables of utilities versus different HME tariffs versus different pneumonia probabilities for the HME strategy

<table>
<thead>
<tr>
<th>Tracheobronchitis and/or pneumonia probabilities for non-HME</th>
<th>0.15</th>
<th>0.28</th>
<th>0.32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HME tariffs in PLN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10,000</td>
<td>35,699</td>
<td>34,837</td>
<td>34,614</td>
</tr>
<tr>
<td>13,966</td>
<td>52,188</td>
<td>51,326</td>
<td>51,103</td>
</tr>
<tr>
<td>20,000</td>
<td>77,275</td>
<td>76,414</td>
<td>76,190</td>
</tr>
</tbody>
</table>

* Base case

When only focusing on the admission period (2 weeks), the use of HMEs is even cost-saving; 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. QoL savings by HME use are resulting from less sleeping problems, less pulmonary infection events and a general higher QoL.

Factors influencing the results were the HME package, and the probability of pulmonary infections. The latter probability has an important impact on both costs and QoL, as already described in the literature [3, 5]. Tracheostomized patients have been shown to have more respiratory tract infections than those without a tracheostoma, both in the hospital [22] and at home [23]. Since there is no scientific literature available of monitoring pulmonary infection rates and the correlation between pneumonia and mortality for laryngectomees with or without HMEs, first a retrospective chart review was conducted at the NKI-AVL as a part of this project. As this study was retrospective and from the beginning of the 1970, there was a documentation bias. Therefore, a survey amongst head and neck cancer clinicians in Europe was developed to test the expert opinion regarding the risk of pneumonia in the usual care group [30]. Because these data are not from the highest level of evidence, sensitivity analyses were performed. Based on the sensitivity analyses, the probability of pneumonia was changed between 0.15 and 0.32, and the HME package from 10,000 PLN to 20,000 PLN, the ICER would then result between 34,000 and 77,000 PLN/QALY. Another point of attention would be the combination of the data from the Dutch and Polish population, which is not optimal. However, as we did not have the specific data in the Polish setting, the data of the Dutch population in the 1990s, in the early days of HME use, were in our opinion the best available option. An alternative solution to investigate the pulmonary infection rates between HME and non-HME users would have been a comparison between HME users from the NKI-AVL and non-HME users from another EU country where HME use is less common among laryngectomized patients. However, this would also have its difficulties in the design, especially with regard to differences in treatment and lifestyle between the countries.

The QALY data were derived from an Italian study concerning the use of HME versus non-HME. The most optimal way is to derive also the QALYs in a Polish setting, but, unfortunately, these data were not available. The data from Italy are the best available data for now, for in the future it would be best to focus on local Polish data in further research.

Compliance with HME use was not incorporated in the analysis; this could have some impact on the results, on both costs and outcomes. Jones et al. stated in their article that the longer patients had had a tracheostoma without HME, the less likely they were able to use the high-resistant filter [6]. This could mean that the earlier start with HME, the higher the compliance can be. Bien et al. [17] showed data where the compliant users (24/7 use) did have more pulmonary benefits compared to the reduced compliant group. This is also likely because immediate postoperative HME use during the hospital stay has been shown to further increase compliance and to reduce and prevent the development of pulmonary problems significantly [12, 13, 31].

The cost parameters in this study were modeled fixed. If we modeled them probabilistic, the probabilistic ICER was equal to the deterministic ICER (51,000 PLN/QALY). We realize that the content of UC, the costs and amounts are very country specific. As known from the literature, Polish hospital costs are relatively low compared to other countries, which could explain the rather high ICER [32]. If one beholds the costs of the HME package (13,000 PLN) versus costs for consequences, e.g., hospital admission for pneumonia (1500 PLN), this is almost a factor 10 difference. In, for example, the Netherlands, this difference is much smaller (2500 Euros for hospital admission and 5000 Euros for the HME package). This will lead to a much lower ICER. For the future, it is interesting to investigate this in more detail and in more countries, to see if this has any impact on the results.

Considering the limitations of the mainly retrospective nature of the current data in the analysis, compared with other studies, this is the first full cost-effectiveness analysis concerning HME use for laryngectomized patients. Other studies mentioning costs in this regard already are pointing out the importance of using HMEs versus usual care [13, 14]. To conclude the current study, the use of HMEs for pulmonary rehabilitation after TLE in Poland is cost-effective compared to usual care. These results implicate for health policy decisions that HMEs should be considered for reimbursement in the Polish setting, as the ICER falls below the Polish threshold for new medical technologies.

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**References**


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