Health technology assessment in head and neck cancer:

(Cost-)effectiveness evaluation is key to implementation of innovation and rehabilitation

Ann-Jean Chavelli Carla Beck

Health technology assessment in head and neck cancer: (Cost-)effectiveness evaluation is key to implementation of innovation and rehabilitation

Ann-Jean Chavelli Carla Beck

ISBN 978-94-6380-894-1

Cover Ramon Bruin | www.ramon-bruin.com

De omslag is door de auteur van het proefschrift samen ontworpen met en gemaakt door illustrator Ramon Bruin. Het is een optische illusie met diepte effect. De stapel biljetten is een representatie van het proefschrift, waarbij elk biljet een hoofdstuk weerspiegelt. Het laatste biljet bevat het sleutelgat in de hals – symbool voor de laryngectomie patiënt – en is terug te vinden in de algemene Discussie, waarin de '7 *key* points to implementation of innovation and rehabilitation' worden beschreven. Het €20 biljet werd gekozen vanwege het jaar van verdediging (2020) en omdat het proefschrift Europees onderzoek betreft.

Layout inside Bregje Jaspers | ProefschriftOntwerp.nl

Printed by Proefschirft Maken | www.proefschriftmaken.nl

Printing of this thesis was kindly supported by: ACTA, Atos Medical B.V., Castor EDC, Chipsoft, NKI-AVL, Patiëntenvereniging Hoofd-Hals (PVHH), Pfizer.

Health technology assessment in head and neck cancer: (Cost-)effectiveness evaluation is key to implementation of innovation and rehabilitation

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit

op woensdag 16 september 2020, te 11.00 uur

door

Ann-Jean Chavelli Carla Beck
geboren te Leiden

Promotiecommissie:

Promotor:	Prof. dr. W.H. van Harten	Universiteit Twente
	Prof. dr. M.B. van den Brekel	Universiteit van Amsterdam
Copromotores:	Dr. V.P. Retèl	Universiteit Twente
Overige leden:	Prof. dr. M.G.W. Dijkgraaf	Universiteit van Amsterdam
	Prof. dr. F.J.M. Hilgers	Universiteit van Amsterdam
	Prof. dr. L.E. Smeele	Universiteit van Amsterdam
	Prof. dr. C.R.N. Rasch	Universiteit Leiden
	Prof. dr. H.A.M. Marres	Radboud Universiteit Nijmegen
	Prof. dr. M.A. Joore	Universiteit Maastricht

Faculteit der Tandheelkunde

Voor mijn ouders,
Mike Beck en Jane Beck-Lie A Fat

Contents

Part I

Introduction

Chapter 1

General introduction and outline of the dissertation

Introduction

The aim of this dissertation was to contribute to the knowledge on the (cost-)effectiveness of innovations in head and neck cancer (HNC) treatment and rehabilitation. With this knowledge, the goal was to facilitate clinical and policy decision-making with the intention to optimize access to innovation and rehabilitation for HNC patients at an international level. To achieve this, we conducted a broad health technology assessment (HTA) including cost-effectiveness analyses and identification of barriers and facilitators. We studied several medical devices and device reimbursements, and also compared treatments and rehabilitation programs. We applied the HTA framework including legal/administrative, social (physician- and patient-related), organizational, hospital and economic aspects as guidance for the chapters.

In this introduction, we will first provide an overview on treatment and rehabilitation modalities in HNC care including innovative technologies (e.g. medical devices). Second, the general procedures and practices towards obtaining access to care for patients are explained. This part first describes the pathway towards patient access and thereafter explains the purpose of HTA assessment including cost-effectiveness analyses of innovations needed to obtain access. Third, issues related to accessing HNC treatment and rehabilitation, such as problems with reimbursement and coverage, are sketched internationally. Fourth, the research objectives are introduced. Fifth, the research projects and design, and general outline of this dissertation are described.

Head and neck cancer treatment and rehabilitation

Head and neck cancer incidence and etiology

Head and neck cancer is generally referred to as squamous cell carcinomas of the upper aerodigestive tract (HNSCC), thyroid, head and neck skin and salivary gland cancers. Cancer of the head and neck can origin from various tissue types such as the mucosa (most frequently squamous cell carcinoma (HNSCC), adenocarcinoma), skin (e.g. melanoma, SCC, basal cell carcinoma), salivary glands (e.g. mucoepidermoid carcinoma, salivary duct carcinoma), lymph nodes (e.g. B-cell lymphoma) and connective tissue (e.g. sarcoma) [1].

Annually, HNC accounts for over 650,000 patients worldwide [2]. In the Netherlands, the incidence is approximately 3200 patients per year [3]. The disease most often occurs in male patients aged above sixty. Excessive alcohol consumption, tobacco use and the human papilloma virus (HPV) are most prevalent predisposing risk factors in the western world [4-6]. The clinical presentation is dependent on the site of origin. In general, patients often present with symptoms such as a sore and painful spot in their mouth or throat, difficulty with swallowing, hoarseness, fatigue,

neck swelling or weight loss. Upon physical examination, the presence of a suspicious swelling, lesion, ulceration, and/or painless pathologically enlarged neck lymph nodes are frequently observed [6].

The site of disease origin can be distinguished in several subsites in the head and neck area including the larynx (voice box), hypopharynx, nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, salivary glands and skin (Figure 1).

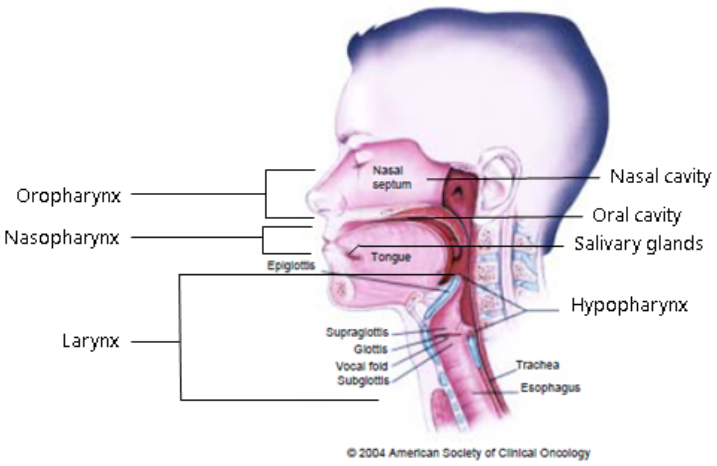

Figure 1. Head and neck cancer subsites [7].

Head and neck cancer treatment and survival

Treatment options are surgery, radiotherapy and/or systemic therapy. Systemic therapy can be chemotherapy (often Cisplatin based), targeted therapy or immunotherapy. For curative treatment of the most prevalent type, HNSCC, early stage disease (stage I and II) is treated with either surgery or radiotherapy, dependent on the subsite, operability of the tumor and the functional outcomes after treatment. Figures on the five-year survival rate have reported to be up to 90% in early stage HNSCC [7]. In advanced stage (stage III and IV), treatment modalities are often combined in order to achieve curation comprising of surgery, radiotherapy and/or systemic therapy. In patients with advanced disease, the five-year survival rate ranges from 15% to 60%, and therefore the prognosis is poor [7]. The recurrence rate and the prevalence of a second primary tumor localized in the head and neck area or lung is relatively high, often due to the continuation of carcinogenic exposure in these patients [8].

Nonetheless, the HNSCC rate has been decreasing by 0.22% annually and the number of survivors is estimated to be over a half a million patients in the United States. This increase in survivors is due to factors such as treatment advancements and decrease in tobacco use [5,9]. Besides the increase in the number of HNSCC survivors, the attention on survivorship and quality of life after treatment has followed this trend [10,11].

Head and neck cancer rehabilitation and quality of life

The importance of QoL as an outcome parameter has increasingly been recognized over the past years. This was also observed in the number of publications on QoL [12]. Disease and treatment of HNC can cause various problems related to QoL in terms of physical functioning, such as dysphagia, altered speech, but also on a psychosocial level, including anxiety, depression, and feeling insecure due to facial disfigurement. Surgical and organ preserving treatments both have influence on QoL, although they do affect physical and psychosocial functioning differently, e.g. in laryngeal cancer significantly more problems with dry mouth and dysphagia in the chemoradiation group compared to significantly more coughing, speech and sensory disturbances in smell and taste in the laryngectomy group [13]. These consequences have a substantial impact on a patients' social and work-related daily activities [14,15]. Study results have shown that HNC survivors have significantly worse QoL than the normal population especially on the disease-specific outcomes [16].

Rehabilitation care is of importance to patients to restore QoL, physical and psychosocial functioning, and subsequently resume daily activities and societal participation. HNC rehabilitation most frequently involves interventions of multiple healthcare professionals, e.g. speech-language pathologist, physiotherapist, dietician and psychologist [14,17]. In cancer rehabilitation, there has been a shift from monodisciplinary to multidisciplinary care, in which various disciplines set goals, align their interventions and have team meetings to evaluate the patient's rehabilitation [18-24]. In HNC patients, problems are often interrelated. Hence, the interdisciplinary approach in which disciplines not only work jointly but also set common goals together with the patient with the primary aim to regain participation in society. In our Institute, an interdisciplinary HNC rehabilitation (IHNR) program has been developed. Since 2011, this program is covered for patients by their health insurance [25]. A feasibility study of IHNR showed a decrease in distress and a significant improvement in QoL of patients after completing the rehabilitation program [14].

Innovative technologies in laryngectomy rehabilitation

After laryngectomy, patients have an altered anatomy; the vocal cords are removed and the nose and respiratory tract are disconnected (Figure 2). Patients have a stoma in the neck in which the respiratory tract ends. For these patients, restoration of voicing and diminishing pulmonary complaints is very important during rehabilitation [26].

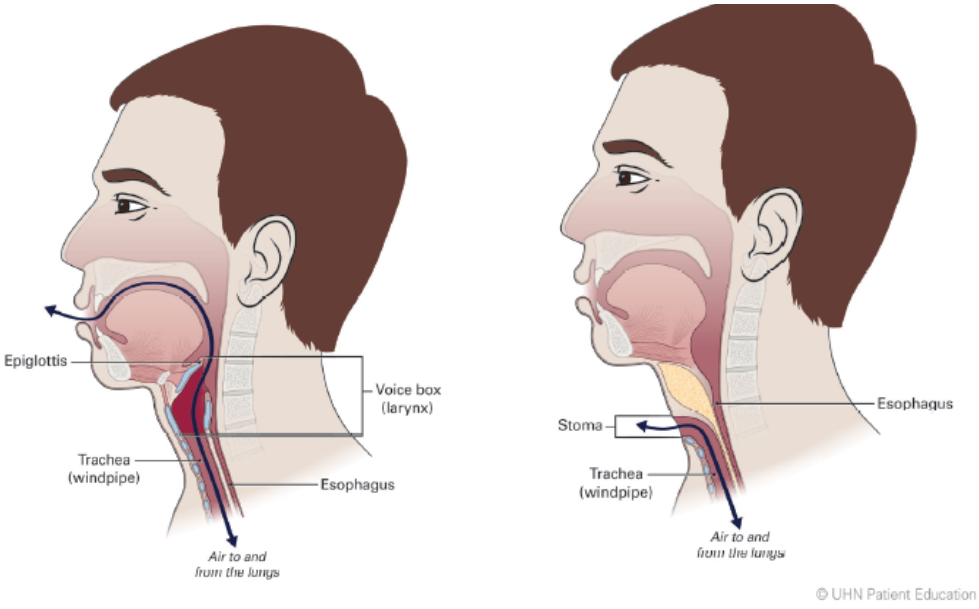

Figure 2a. **Figure 2b.**

Figure 2. Before (Figure 2a) and after (Figure 2b) total laryngectomy [27].

In voice and speech rehabilitation, several voice restoration methods can be applied including speech by means of the voice prosthesis, electrolarynx or esophageal speech. The voice prosthesis is the most frequently applied voice rehabilitation method in the Netherlands. With these valves, the speech is still pulmonary driven, as air from the lungs reaches the pharyngoesophageal segment (neoglottis) causing it to vibrate and thus creating a voice for speech. The indwelling prosthesis is placed in the tracheoesophageal wall, either directly postoperative or at a later time point (Figure 3a). Different types of voice prostheses are currently on the market varying in device lifetime (median ranging from 63 to 186 days) and price [28]. In the past years, novel prostheses were also developed adjusted to patients' needs including hands-free devices [29]. The electrolarynx, a battery operating machine, produces a mechanical monotonous voice sound (Figure 3b). Although a modulation of the tone is now possible (Trutone®), the popularity of the device has never been great. In the Netherlands, this device is more often used as a temporary option when speaking with other means is not possible. For the esophageal speech, the esophagus is used as a driving source in stead of the lungs

when air is injected into the esophagus to produce voicing by means of burbing up the air to initiate vibrations in the pharyngoesophageal segment [26,30,31]. This option is frequently applied in patients who do not prefer to use the voice prosthesis.

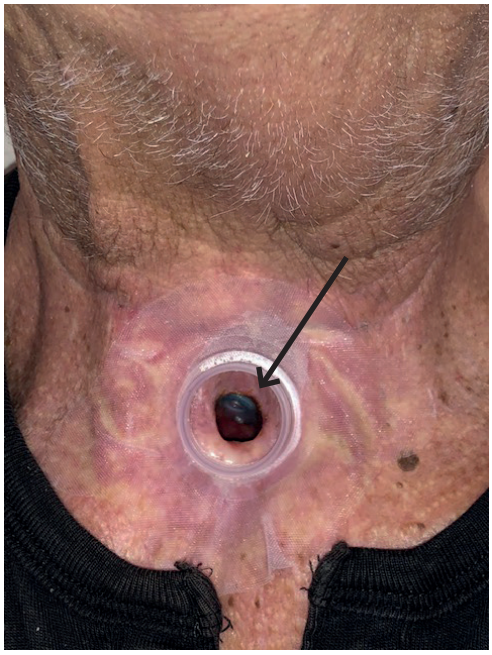

Figure 3a.

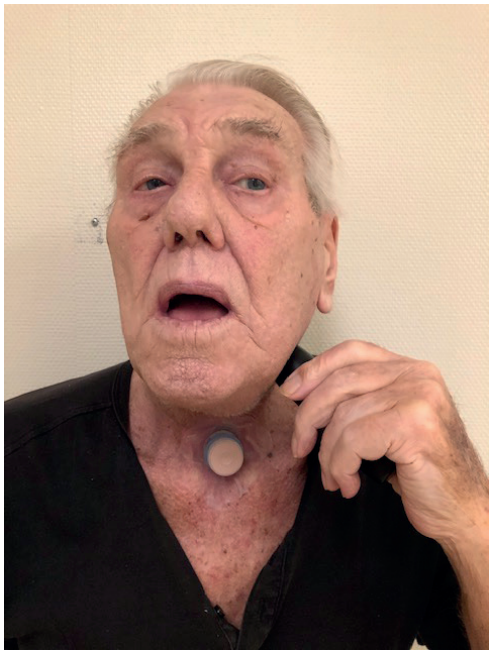

Figure 3b.

Figure 3. Speech rehabilitation after laryngectomy: a patient with a voice prosthesis (Figure 3a; see arrow) and electrolarynx (Figure 3b) (permission was obtained from the patient).

Internationally, there is no consensus on which method to use [31]. In Europe, speech rehabilitation varies per country due to e.g. differences in reimbursement, device-related factors and physicians' preferences. Voice restoration with the voice prosthesis has shown to be most favorable with regard to voice quality and this is also the preferred method in the Netherlands. However, for example, the proportion of patients applying the electrolarynx in the UK and US and esophageal speech in Poland is much higher due to a variety of factors including device costs and lack of coverage [26,32,33].

In pulmonary rehabilitation, various devices are used which cover the stoma and restore pulmonary functioning. The heat and moisture exchanger (HME) is a medical device compensating for the function of the upper respiratory tract (Figure 4a). The HME provides humidification, heating and filtering of inhaled air. There is ample evidence that the HME reduces airways infections and pulmonary complaints such as involuntary coughing [34-40]. In addition, the device positively affects patients' QoL by improving social contact and reducing fatigue complaints [34,36,41-44]. Novel HME

devices focus on improving pulmonary humidification, compliance, voicing, comfort and skin care [45,46]. Other alternatives are e.g. foam pads or cloth bibs, which also cover the stoma and can humidify and heat the inhaled air (Figure 4b). Although bibs are potentially superior HMEs, unfortunately the leaks of air diminish their efficacy and in general patients prefer the HME's for comfort and speech [47].

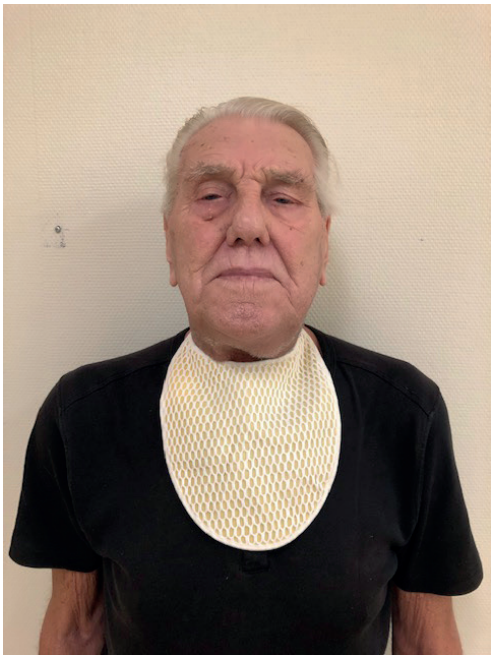

Figure 4a.

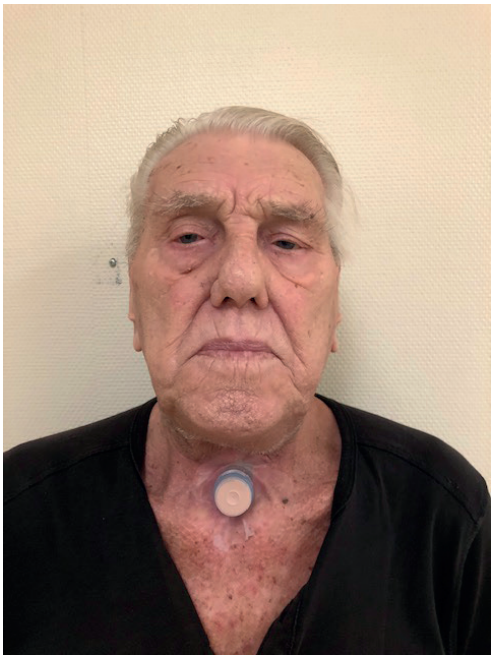

Figure 4b.

Figure 4. Pulmonary rehabilitation after laryngectomy: a patient with an heat and moisture exchanger (HME) (Figure 4a) and a bib Figure (Figure 4b) (permission was obtained from the patient).

Procedures and practices of patient access to innovations in Europe

Access to innovations in healthcare

Health innovation is defined by the World Health Organization (WHO) as [48]:

'Health innovation identifies new or improved health policies, systems, products and technologies, and services and delivery methods that improve people's health and wellbeing. Health innovation responds to unmet public health needs by creating new ways of thinking and working with a focus on the needs of vulnerable populations. It aims to add value in the form of improved efficiency, effectiveness, quality, sustainability, safety and/or affordability. Health innovation can be preventive, promotive, curative and rehabilitative and/or assistive care.'

Access to innovations such as the voice prosthesis and HME have a different routing in the various European countries in terms of procedures and practices. In this thesis, we will focus on the process related to accessing innovative technologies in specific. To get the medical device from bench to bedside, several steps have to be undertaken (Figure 5).

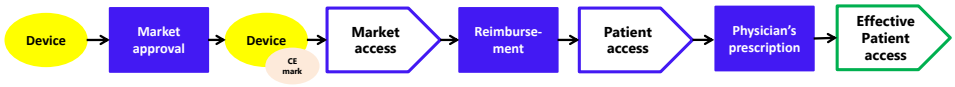

Figure 5. Global framework procedures and practices.

First, the safety and performance is assessed before the medical device is placed on the market. When the device meets the requirements, a Conformité Européenne (CE) mark is assigned to the device and it is approved to distribute on the market. Second, the device has to be assessed on certain requirements during the reimbursement in order to obtain coverage [49-51]. After the legal requirements, it is important that the physicians prescribe the device in order for it to be accessed by the patients. Prescription by the physician is an important step towards device diffusion and is influenced by internal and external factors [52,53].

The diffusion of innovations follow a normal curve, in which users, such as physicians can be distinguished in five categories of adopters (Figure 6). The 'innovators' are the ones who adopt the innovation first. They are willing to take the risk of the device failing at an early stage of implementation. Innovators most often have the finances to accomplish this. They are the gatekeepers by introducing the innovation into clinical practice. The 'early adopters' follow the innovators and are somewhat more careful. But as early adopters often have leadership roles, their positive experience with the innovation empower the diffusion. The 'early and late

majority' comprises of two third of the adopters. The early majority wait a significant time after the innovators and early adopters but are willing to adopt the innovation. In contrast, the late majority are more conservative and sometimes a bit skeptical towards the innovation. At last, the 'laggards' are very skeptical and bound to their traditions. They will stick to their old habits and wait until the innovation cannot be ignored anymore [54].

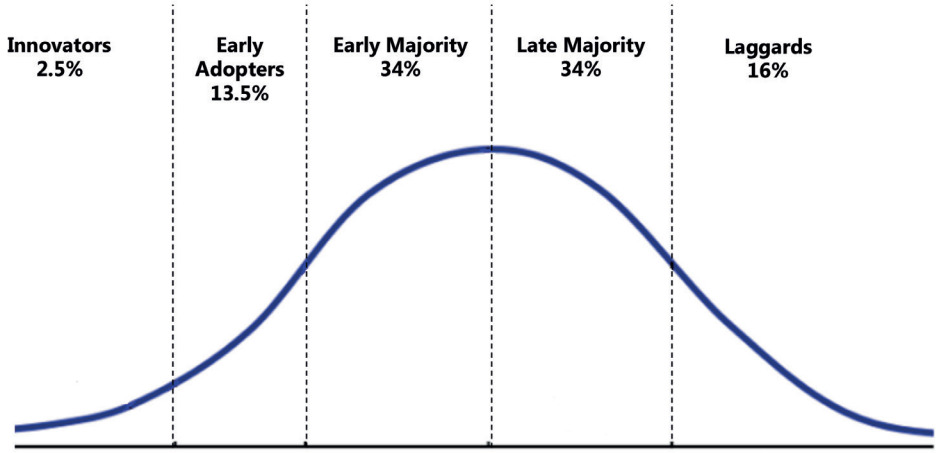

Figure 6. Rogers' adoption curve [54].

Finally, access is realized, known as *effective patient* access, when device utilization by the patient is made possible.

Assessment of innovations

Evaluation of innovations by means of a broad health technology assessment (HTA) is essential in obtaining patient access. HTA is a systematic evaluation which provides information on the (cost-)effectiveness of these technologies with the purpose to inform policy as well as clinical decision-making regarding reimbursement and implementation. HTA is a multidisciplinary framework considering ethical, organizational, social and economic aspects related to the innovation [55,56].

Preferably, a trial-based cost-effectiveness analysis is performed with data from a randomized controlled trial (RCT) [57]. However, RCT data is often not unavailable due to too long time lines, financial issues or too small samples. In these cases, a model-based economic evaluation (decision-analytical modeling) is conducted. This method allows e.g. for extrapolation of the data, synthesis of different sources, extrapolation of the time horizon and simulation of thousands of fictive patients in order to take into account decision uncertainty [58]. The latter can be beneficial in studies with small sample sizes, as is often the case in HNC. Also, a model-based economic

evaluation enables cost-effectiveness analyses in early developmental phases, taking into account dynamics o the technology and the uncertainty of the parameters.

An important element in the HTA is the decision-analytical modeling, in which the relative costs and effectiveness of the innovation are assessed compared to the gold standard [56]. A decision-analytical model is developed in multiple consecutive steps (Figure 7). A healthcare decision, clinically- and/or policy-oriented, is formulated into a problem statement by means of problem conceptualization. In framing the research question, the cost-effectiveness analysis can be evaluated from different perspectives, e.g. the perspective of the hospital (healthcare perspective) or the society (societal perspective), the latter including indirect societal costs such as productivity losses. With this information, the model is conceptualized by choosing a modeling method and collecting data sources. The results that come forth from the model (model output) is used to inform stakeholders in healthcare [59,60].

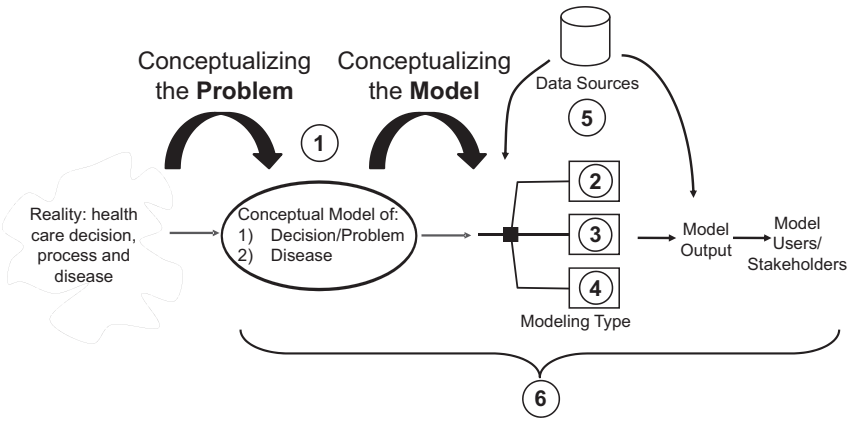

Figure 7. Development a cost-effectiveness model [59].

Despite the modeling method used, a model should adhere to number of requirements including transparency, internal consistency, reproducibility, interpretability and exploration of uncertainty [61]. In this thesis, the economic evaluations are conducted by means of a multistate-transition Markov simulation model. A Markov model is a stochastic model in which patients are transferred between health states (e.g. disease-free state, progression of disease state). Most often in oncology, the final state is death. The model consists of input parameters that have an influence on the costs, survival and/or QoL and can vary depending on the health state in which the patient is found to be in.

From the Markov model, two analyses are conducted: the deterministic and probabilistic analyses. In the deterministic analysis, model outcomes are generated without taking into

account the uncertainty of the parameters. To deal with the uncertainty of each parameter in the probabilistic analysis, certain distributions are used depending on the parameter type, such as gamma (above 0) for costs and beta distributions (between 0 and 1) for probabilities. For each simulation, random numbers are drawn from the distributions and with these values the model outcomes are calculated. Monte Carlo simulations are used to run individual patient simulation (e.g. 1000 patients) [58,62].

The primary outcome of the cost-effectiveness analysis, resulting from the deterministic analysis, is the incremental cost-effectiveness ratio (ICER). The ICER reflects the difference in costs of the "new" intervention and the "old" intervention (ΔC) divided through the difference in effects (ΔE):

$$\text{ICER} = \frac{\Delta C}{\Delta E}$$

The effects are preferably expressed in quality-adjusted life years (QALYs). A QALY is calculated by multiplying life years gained times the utilities. An utility is a number ranging from 0 (death) to 1 (full health) to reflects patients' health status. Utilities are calculated by using preference-based measures such as the EuroQol five-dimensional questionnaire (EQ-5D) [63-65]. However, the fact that the EQ-5D is a generic measurement tool based on preferences can be an issue because disease-specific symptoms of HNC patients are often not addressed in these generic measurements. In this way, one can hypothesize that a disease-specific questionnaire would be necessary to evaluate QoL in these patients [11]. A questionnaire that is often used to assess HNC-specific symptoms impacting QoL is the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) combined with the disease-specific EORTC QLQ module for HNC (QLQ-H&N35). HNC-specific issues are addressed by the EORTC QLQ-H&N35 such as opening of the mouth, speech problems and trouble with social eating [66,67]. Nonetheless, the outcomes result in subscale scores ranging from 0 to 100. These QoL scores have to be translated into utilities (preference-based scores) for utilization as model input parameters. One way to achieve this is by using a mapping model, in which the QoL outcomes are mapped into utilities by means of a statistical regression model [68].

Subsequently, the ICER is expressed in cost per QALY gained (cost/QALY). The innovation is cost-effective when the cost/QALY is below the willingness-to-pay threshold, reflecting the costs the society is willing to pay in order to gain one QALY. In the Netherlands, there are three severity-based thresholds at €20,000/QALY, €50,000/QALY and €80,000/QALY based on the severity of the illness. This threshold differs among countries [69,70]. For example, the threshold lies at £20,000-300,000/QALY in the United Kingdom (UK) and at $100,000/QALY in the United States [71,72].

Probabilistic analyses are conducted through a cost-effectiveness plane (CE plane), cost-effectiveness acceptability curve (CEAC) and one-way sensitivity analyses. The CE plane

comprises of the incremental QALYs on the x-axis plotted against the incremental costs of the two treatment modalities on the y-axis (Figure 8). The dots in the CE plane reflect the simulated patients, whom fall into one of the four quadrants of the CE plane: less costly and more effective (dominate); less costly but less effective; more costly but more effective (cost-effective) and more costly and less effective (dominated) [58,73].

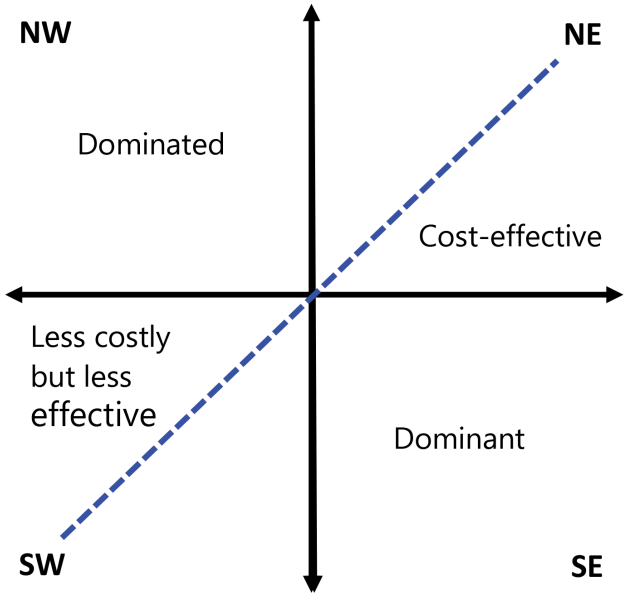

Figure 8. Cost-effectiveness plane (CE plane).

The CEAC is a graph showing the probability of the innovation being cost-effective (y-axis) at various thresholds (x-axis) (Figure 9) [74]. Furthermore, one-way sensitivity analyses look into the influence of individual parameters on the ICER, costs and QALY [75].

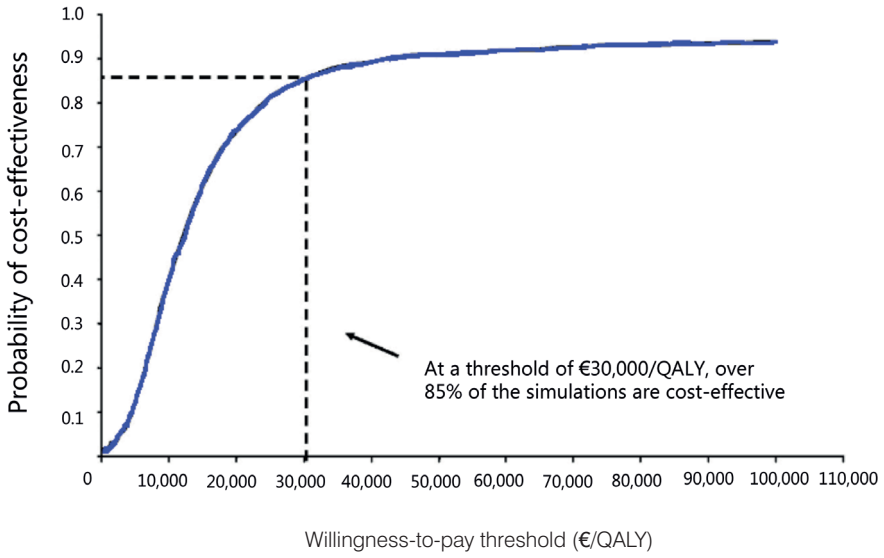

Figure 9. Cost-effectiveness acceptability curve (CEAC) [76].

Clinical case: issues in head and neck cancer innovation and rehabilitation

Worldwide, access to treatment and rehabilitation for HNC patients is not always provided. Examples are immunotherapy – for treatment of HNC – and the voice prosthesis, HME and supportive such as physiotherapy and speech-language therapy – for the purpose of rehabilitation. We observe variations in practice, but it is also frequently stated in literature [77-79]. Restriction in access is often multifactorial and caused by barriers in the procedures and practices related to the process towards patient access. However, certain barriers have not yet been identified and may vary among countries. Another problem is that HNC patients often suffer from financial toxicity as there are a relatively low educated patient group with low income which makes it even harder for them to access healthcare [80].

Achieving access to HNC care and rehabilitation is not only of importance for patients' chances of survival, but also for QoL after treatment, return to work and participation in society. For example, after laryngectomy, a voice prosthesis is crucial to patients to speak again in order to regain their work activities, their hobbies (e.g. sing in a choir) and participate in group interaction [81]. Supportive care including the speech-language pathologist, dietician and psychologist are needed to learn patients how to swallow safely with a different anatomy after laryngectomy; inform on what they can eat and drink in every phase of rehabilitation and to overcome their fear

of swallowing solid food again. This is not only important for patients to gain strength by means of increasing their intake, but also to eat and drink at work or on social occasions.

To access HNC treatment and rehabilitation care, more evidence is needed to prove the (cost-) effectiveness of innovations, and thereby support reimbursement and clinical decision-making. Also, providing country-specific barriers and facilitators related to patient access could bring forth policy- as well as clinically-oriented recommendations.

Aim and objectives of this dissertation

The aim of this dissertation was to provide more evidence on the (cost-)effectiveness of innovations in HNC treatment and rehabilitation to formulate clinical and policy implications with the goal to optimize access to innovation and rehabilitation for HNC patients at an international level. We have conducted a broad HTA including cost-effectiveness analyses and identification of barriers and facilitators on different levels of patient access. This work addresses health policy decision makers, the device industry, healthcare professionals and researchers in the field.

From the aim, a research question was framed for each project analyzing one of the aspects within the HTA framework, comprising of the evaluation of:

1) Legal/administrative aspects in **Chapter 2**
2) Social aspects with focus on the physician in **Chapter 3**
3) Organizational aspects in **Chapter 4**
4) Hospital aspects in **Chapter 5**
5) Economic aspects in **Chapter 6 and Chapter 7**
5) Social aspects with focus on the patient in **Chapter 8**

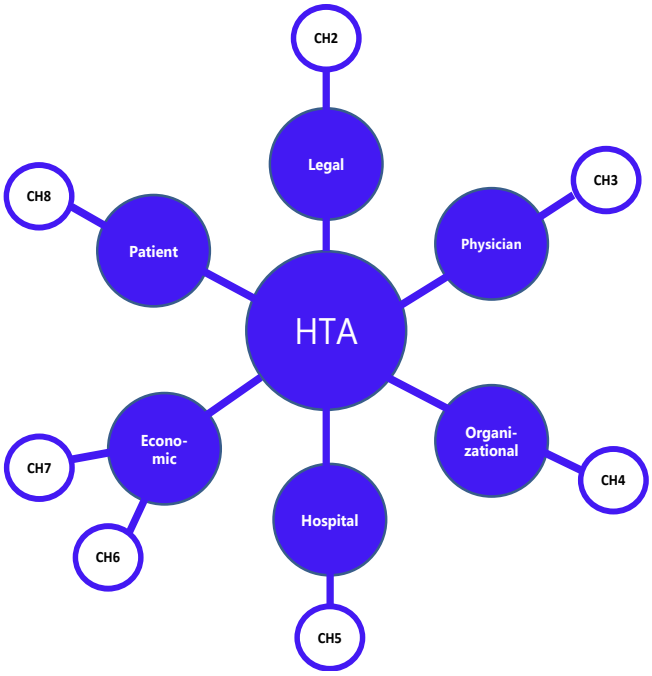

Figure 10. Outline of dissertation; each of the chapters (=CH) address one of the aspects of the health technology assessment (HTA) framework.

Research projects and design

Chapter 2 provides insight into the legal procedures of market approval and reimbursement of medical devices in eight European countries, and identifies barriers of and facilitators to early patient access to innovative medical devices. The study was conducted by means of a systematic review of literature and validated with representatives involved in reimbursement of medical devices of each country.

After market approval and reimbursement, physician's prescription of the medical device is required to realize access to the patient. **Chapter 3** evaluates factors influencing the physicians' prescription practices and reimbursement of the voice prosthesis and HME in eight European countries, and barriers of and facilitators to effective patient access. In this mixed-methods study, physicians (head and neck surgeons) and representatives of a device industry participated to an online survey. In addition, semi-structured interviews with the device industry representatives took place.

The provision of rehabilitation care involves a variety of interventions that depend on the type and the complexity of the problems HNC patients can have. In the Netherlands, the organizational

structure, content and funding of HNC rehabilitation care varies among different centers. In **Chapter 4**, an overview of the organization, content and funding of HNC rehabilitation in the 14 Dutch centers is given, and barriers of and facilitators to provision of HNC rehabilitation were explored. To achieve this, an online survey was sent to a representative of each discipline within the dedication HNC rehabilitation team and of the Financial Department.

Because treatment- and disease-related problems are often interrelated, more attention has been paid in recent years to stimulate disciplines to work together in a multidisciplinary and interdisciplinary rehabilitation program. The effectiveness and cost-effectiveness of the interdisciplinary HNC rehabilitation (IHNR) program in the Netherlands Cancer Institute (NKI-AVL) compared to usual supportive care in six other centers is currently studied in a prospective multicenter observational study using patient-reported outcome measurements (PROMs). The design of the study is outlined in **Chapter 5.**

Economic evaluation of treatments can not only inform policy decision-making, but also physicians and patients in medical shared decision-making, taking into account health-related quality of life (HRQoL) and survival of patients, and costs of the intervention. In advanced laryngeal cancer, surgical and non-surgical treatments are both an option. Surgery and organ preservation have equal survival outcomes, but different impact on patients' HRQoL and have different implications for healthcare costs. **Chapter 6** evaluates the cost-effectiveness of a laryngectomy versus organ preservation (chemo/bio)-radiotherapy) in advanced stage laryngeal cancer from a healthcare perspective.

After laryngectomy, the voice prosthesis and HME are proven to be the best voice restoration and pulmonary rehabilitation respectively. In the United States, patients are not always provided with the HME. Economic evaluation of the HME in **Chapter 7** evaluates the cost-effectiveness of this device in the United States from a healthcare and societal perspective in order to support reimbursement decisions.

In HNC, ample evidence is available in literature on HRQoL, and in current practice, PROMS are often used to capture quality of care. In cost-effectiveness analysis, HRQoL data cannot be used directly, because preference-based measures are necessary instead. To enable use of HRQoL results in a cost-effectiveness analysis, HRQoL outcomes can be converted into utilities (preference-based) by means of a mapping model. In **Chapter 8**, we developed a mapping model which translates the often used EORTC QLQ-C30 outcomes into an EQ-5D utility by means of regression modeling. In addition, the value of adding EORTC QLQ-H&N35 scales to the mapping model was explored.

Together, these chapters provide comprehensive information to optimize access to innovation and rehabilitation for HNC patients at an international level.

References

1. Pathology of head and neck neoplasms. Last accessed: 12-2-2020.; https://www.uptodate.com/contents/pathology-of-head-and-neck-neoplasms?search=pathology-of-head-and-neck&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians.* 2018;68(6):394-424.
3. Netherlands Comprehensive Cancer Organisation. Incidence of head and neck cancer in the Netherlands. [in Dutch]. Last accessed: 3-12-2019.; https://www.cijfersoverkanker.nl/selecties/Dataset_1/img5d19afb60a6fe.
4. Epidemiology and risk factors for head and neck cancer. Last accessed: 11-2-2020.; https://www.uptodate.com/contents/epidemiology-and-risk-factors-for-head-and-neck-cancer.
5. Mourad M, Jetmore T, Jategaonkar AA, Moubayed S, Moshier E, Urken ML. Epidemiological trends of head and neck cancer in the United States: a SEER population study. *Journal of Oral Maxillofacial Surgery.* 2017;75(12):2562-2572.
6. Mehanna H, Paleri V, West C, Nutting C. Head and neck cancer—part 1: epidemiology, presentation, and prevention. *BMJ (Clinical research ed).* 2010;341:c4684.
7. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Paper presented at: Mayo Clinic Proceedings2008.
8. Cooper JS, Pajak TF, Rubin P, et al. Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. *International Journal of Radiation Oncology* Biology* Physics.* 1989;17(3):449-456.
9. Overview of approach to long-term survivors of head and neck cancer. Last accessed: 26-2-2020.; https://www.uptodate.com/contents/overview-of-approach-to-long-term-survivors-of-head-and-neck-cancer.
10. Petersen JF, Berlanga A, Stuiver MM, et al. Improving decision making in larynx cancer by developing a decision aid: A mixed methods approach. *The Laryngoscope.* 2019.
11. Gotay C, Moore T. Assessing quality of life in head and neck cancer. *Quality of Life Research.* 1992;1(1):5-17.
12. Rogers S, Ahad S, Murphy A. A structured review and theme analysis of papers published on 'quality of life'in head and neck cancer: 2000–2005. *Oral oncology.* 2007;43(9):843-868.
13. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Archives of Otolaryngology - Head and Neck Surgery.* 2004;130(7):875-879.
14. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. *European Archives of Oto-Rhino-Laryngology.* 2016;273(6):1577-1587.
15. Verdonck-de Leeuw IM, van Bleek W-J, Leemans CR, de Bree R. Employment and return to work in head and neck cancer survivors. *Oral oncology.* 2010;46(1):56-60.

16. Hammerlid E, Taft C. Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. *British journal of cancer.* 2001;84(2):149-156.

17. Giuliani M, McQuestion M, Jones J, et al. Prevalence and nature of survivorship needs in patients with head and neck cancer. *Head & neck.* 2016;38(7):1097-1103.

18. Clarke P, Radford K, Coffey M, Stewart M. Speech and swallow rehabilitation in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal of Laryngology & Otology.* 2016;130(S2):S176-S180.

19. van Weert E, Hoekstra-Weebers J, Grol B, et al. A multidimensional cancer rehabilitation program for cancer survivors: effectiveness on health-related quality of life. *Journal of Psychosomatic Research.* 2005;58(6):485-496.

20. Barrowman R, Wilson P, Wiesenfeld DJ. Oral rehabilitation with dental implants after cancer treatment. *Australian dental journal.* 2011;56(2):160-165.

21. Roman BR, Goldenberg D, Givi B, Head ECoA, Society N. AHNS Series—Do you know your guidelines? Guideline recommended follow-up and surveillance of head and neck cancer survivors. *Head neck.* 2016;38(2):168-174.

22. Sullivan P, Fisher PJCp. Challenges in a multidisciplinary head and neck oncology program. *Cancer practice.* 1995;3(4):258-260.

23. King G, Lemon J, Martin J. Multidisciplinary teamwork in the treatment and rehabilitation of the head and neck cancer patient. *Texas dental journal.* 1992;109(6):9-12.

24. Netherlands Comprehensive Cancer Organisation. Cancer Guideline (2011). [in Dutch]. Last accessed: 3-12-2019.; https://www.oncoline.nl/medisch-specialistische-revalidatie-bij-oncologie. .

25. Netherlands Cancer Institute. HNR 2.0 (version 2006). . Last accessed: 12-2-2020.; https://www.avl.nl/flipbooks/HHR-HNR%202.0/index.html#p=1. .

26. van der Molen L, Kornman AF, Latenstein MN, van den Brekel MW, Hilgers FJ. Practice of laryngectomy rehabilitation interventions: a perspective from Europe/the Netherlands. *Current opinion in otolaryngology & head and neck surgery.* 2013;21(3):230-238.

27. Before and after laryngectomy. . Last accessed: 16-3-2020.; https://www.uhn.ca/PatientsFamilies/Health_Information/Health_Topics/Documents/Laryngectomy.pdf.

28. Petersen JF, Lansaat L, Timmermans AJ, van der Noort V, Hilgers FJ, van den Brekel MW. Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period. *Head neck.* 2019;41(3):623-631.

29. Lansaat L, de Kleijn B, Hilgers F, van der Laan B, van den Brekel M. A prospective multicenter clinical feasibility study of a new automatic speaking valve for postlaryngectomy voice rehabilitation. *European Archives of Oto-Rhino-Laryngology.* 2017;274(2):1005-1013.

30. Lewis WB. Clinical Intervention for Airway Improvement: Establishing a New Nose. In: *Clinical Care and Rehabilitation in Head and Neck Cancer.* Springer; 2019:119-128.

31. van Sluis KE, van der Molen L, van Son RJ, Hilgers FJ, Bhairosing PA, van den Brekel MW. Objective and subjective voice outcomes after total laryngectomy: a systematic review. *European Archives of Oto-Rhino-Laryngology.* 2018:1-16.

32. Betlejewski S, Ossowski R, Sinkiewicz A. [Rehabilitation after total laryngectomy--vision and realization]. *Otolaryngologia polska = The Polish otolaryngology.* 2007;61(3):344-348.

33. Wierzchowska M, Burduk PK. [Early and late complications after implantation of the Provox 2 voice prosthesis in patients after total laryngectomy]. *Otolaryngologia polska = The Polish otolaryngology.* 2011;65(3):184-187.

34. Hilgers FJ, Ackerstaff AH, Aaronson NK, Schouwenburg PF, Zandwijk N. Physical and psychosocial consequences of total laryngectomy. *Clinical Otolaryngology.* 1990;15(5):421-425.

35. Ackerstaff A, Hilgers F, Aaronson N, Schouwenburg P. Physical and psychosocial sequelae of total larynx extirpation and the use of a heat and moisture exchanger. *Nederlands tijdschrift voor geneeskunde.* 1990;134(50):2438-2442.

36. Jones AS, Young PE, Hanafi ZB, Makura ZGG, 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):361-367.

37. Hilgers FJ, Aaronson NK, Schouwenburg PF, Zandwijk N. The influence of a heat and moisture exchanger (HME) on the respiratory symptoms after total laryngectomy. *Clinical Otolaryngology.* 1991;16(2):152-156.

38. Icuspit P, Yarlagadda B, Garg S, Johnson T, Deschler D. Heat and moisture exchange devices for patients undergoing total laryngectomy. *ORL-Head and Neck Nursing.* 2014;32(1):20-23.

39. van den Boer C, van Harten MC, Hilgers FJ, van den Brekel MW, Retèl VP. Incidence of severe tracheobronchitis and pneumonia in laryngectomized patients: a retrospective clinical study and a European-wide survey among head and neck surgeons. *European Archives of Oto-Rhino-Laryngology.* 2014;271(12):3297-3303.

40. Foreman A, De Santis R, Sultanov F, Enepekides D, Higgins K. Heat and moisture exchanger use reduces in-hospital complications following total laryngectomy: a case–control study. *Journal of Otolaryngology - Head & Neck Surgery Le Journal d'Oto-Rhino-Laryngologie et de Chirurgie Cervico-Faciale.* 2016;45(1):40.

41. Brook I, Bogaardt H, van As-Brooks C. Long-term use of heat and moisture exchangers among laryngectomees: medical, social, and psychological patterns. *Annals of Otology, Rhinology & Laryngology.* 2013;122(6):358-363.

42. Ackerstaff AH, Hilgers FJ, Balm AJ, Aaronson NK, van Zandwuk N. Improvements in respiratory and psychosocial functioning following total laryngectomy by the use of a heat and moisture exchanger. *Annals of Otology, Rhinology & Laryngology.* 1993;102(11):878-883.

43. Ackerstaff A, Hilgers F, Aaronson N, Balm A. Communication, functional disorders and lifestyle changes after total laryngectomy. *Clinical Otolaryngology.* 1994;19(4):295-300.

44. 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. *Otolaryngology and Head and Neck Surgery.* 2003;129(6):705-712.

45. Van Den Boer C, Muller SH, Vincent AD, Züchner 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. *European Archives of Oto-Rhino-Laryngology.* 2014;271(2):359-366.

46. Ratnayake CB, Fles R, Tan IB, et al. Multicenter randomized crossover trial evaluating the provox luna in laryngectomized subjects. 2019;129(10):2354-2360.

47. Lansaat L, van den Boer C, Muller SH, van der Noort V, van den Brekel MW, Hilgers FJ. Ex vivo humidifying capacity and patient acceptability of stoma cloths in laryngectomized individuals. *Head & neck.* 2017;39(5):921-931.
48. WHO definition health innovation. Last accessed: 11-2-2020.; https://www.who.int/topics/innovation/en/.
49. Schreyogg J, Baumler M, Busse R. Balancing adoption and affordability of medical devices in Europe. *Health Policy.* 2009;92(2-3):218-224.
50. Parvizi N, Woods K. Regulation of medicines and medical devices: Contrasts and similarities. *Clinical Medicine, Journal of the Royal College of Physicians of London.* 2014;14(1):6-12.
51. Basu S, Hassenplug JC. Patient access to medical devices--a comparison of U.S. and European review processes. *The New England journal of medicine.* 2012;367(6):485-488.
52. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. *MIS quarterly.* 1989:319-340.
53. Venkatesh V, Bala H. Technology acceptance model 3 and a research agenda on interventions. *Decision sciences.* 2008;39(2):273-315.
54. Rogers EM. *Diffusion of innovations.* Simon and Schuster; 2010.
55. WHO definition Health Technology Assessment (HTA). Last accessed: 11-2-2020.; https://www.who.int/medical_devices/assessment/en/.
56. Philips Z, Bojke L, Sculpher M, Claxton K, Golder SJP. Good practice guidelines for decision-analytic modelling in health technology assessment. 2006;24(4):355-371.
57. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value in health.* 2005;8(5):521-533.
58. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation.* OUP Oxford; 2006.
59. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force–2. *Medical Decision Making.* 2012;32(5):678-689.
60. Garrison LP, Mansley EC, Abbott TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report—part II. *Value in Health.* 2010;13(1):8-13.
61. Akehurst R, Anderson P, Brazier J, et al. Decision analytic modelling in the economic evaluation of health technologies. *Pharmacoeconomics.* 2000;5:443-444.
62. Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment. *Pharmacoeconomics.* 2008;26(2):131-148.
63. Caulley L, Hunink MG, Kilty S, et al. Evidence-based medicine in otolaryngology part 9: valuing health outcomes. *Otolaryngology–Head Neck Surgery.* 2019;160(1):11-21.
64. Szende A, Oppe M, Devlin N. *EQ-5D value sets: inventory, comparative review and user guide.* Vol 2: Springer Science & Business Media; 2007.
65. EQ-5D user guides. Last accessed: 12-2-2020.; https://euroqol.org/publications/user-guides/.
66. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute.* 1993;85(5):365-376.

67. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck module (QLQ-H&N35). *Archives of otolaryngology--head & neck surgery.* 2000;126(4):459-467.

68. Wailoo AJ, Hernandez-Alava M, Manca A, et al. Mapping to Estimate Health-State Utility from Non–Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. *Value in Health.* 2017;20(1):18-27.

69. Smulders Y, Thijs A. Kostprijs per gewonnen levensjaar: Trends en tegenstrijdigheden. *Nederlands tijdschrift voor geneeskunde.* 2006;150(45):2467-2470.

70. Versteegh MM, Ramos IC, Buyukkaramikli NC, Ansaripour A, Reckers-Droog VT, Brouwer WBJP. Severity-Adjusted Probability of Being Cost Effective. 2019;37(9):1155-1163.

71. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.

72. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold. *Pharmacoeconomics.* 2008;26(9):733-744.

73. Black WC. The CE plane: a graphic representation of cost-effectiveness. *Medical decision making.* 1990;10(3):212-214.

74. Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value in health.* 2008;11(5):886-897.

75. Taylor M. What is sensitivity analysis. *Consortium YHE: University of York.* 2009:1-8.

76. Weintraub WS, Cohen DJ. The limits of cost-effectiveness analysis. *Circulation: Cardiovascular Quality Outcomes.* 2009;2(1):55-58.

77. Retèl VP, van den Boer C, Steuten LM, Okła 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. *European archives of oto-rhino-laryngology.* 2015;272(9):2381-2388.

78. Retèl VP, van der Molen L, Hilgers FJ, et al. A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy. *BMC cancer.* 2011;11(1):475.

79. van der Molen L, Kornman AF, Latenstein MN, van den Brekel MW, Hilgers FJ. Practice of laryngectomy rehabilitation interventions: a perspective from Europe/the Netherlands. *Current opinion in otolaryngology & head and neck surgery.* 2013;21(3):230-238.

80. Massa ST, Osazuwa-Peters N, Boakye EA, Walker RJ, Ward G. Comparison of the financial burden of survivors of head and neck cancer with other cancer survivors. *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):239-249.

81. Costa JM, López M, García J, León X, Quer M. Impact of total laryngectomy on return to work. *Acta Otorrinolaringologica Espanola.* 2018;69(2):74-79.

Part II

Assessment of innovative technologies

Chapter 2

Barriers and facilitators of patient access to medical devices in Europe: A systematic literature review

Ann-Jean C.C. Beck
Valesca P. Retèl
Patrick A. Bhairosing
Michiel W.M. van den Brekel
Wim H. van Harten

Health Policy. 2019 Dec;123(12):1185-1198.
doi: 10.1016/j.healthpol.2019.10.002.

Abstract

A large number of medical devices (MDs) is available in Europe. Procedures for market approval and reimbursement have been adopted over recent years to promote accelerating patient access to innovative MDs. However, there remains uncertainty and non-transparency regarding these procedures. We provide a structured overview of market approval and reimbursement procedures and practices regarding access to MDs in the EU.

Market approval procedures were found to be uniformly described. Data on reimbursement procedures and practices was both heterogeneous and incomplete. Time to MD access was mainly determined by reimbursement procedures. The influence of the patient on time to access was not reported. Prescription practices varied among device types.

Barriers to and facilitators of early patient access that set the agenda for policy implications were also analyzed. Barriers were caused by unclear European legislation, complex market approval procedures, lack of data collection, inconsistency in evidence requirements between countries, regional reimbursement and provision, and factors influencing physicians' prescription including the device costs, waiting times and hospital-physician relationships. Facilitators were: available evidence that meets country-specific requirements for reimbursement, diagnosis-related groups, additional payments and research programs.

Further research needs to focus on creating a complete overview of reimbursement procedures and practices by extracting further information from sources such as grey literature and interviews with professionals, and defining clear criteria to objectify time to access.

Introduction

Medical devices (MDs) play a crucial role in healthcare provision for patients in the European Union (EU). Approximately 500,000 different MDs are available on the EU market, covering abroad range of technologies, from wound bandages to implantable devices, serving multiple purposes, including the diagnosis of disease, prevention, treatment, rehabilitation, and increasing the quality of life of patients [1,2].

A summary of what the World Health Organization (WHO) defined as medical device is: any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or similar or article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of: including monitoring, alleviation of disease, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, control of conception, disinfection of medical devices, providing information by means of in vitro examination of specimens derived from the human body; and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means [3].

Although MDs are essential in delivering healthcare, it may take up to six years for a MD to go from bench to the patient's bedside, termed 'effective patient access' [4]. Effective patient access is defined in this study as: the realization of access to MDs for patients. The pathway towards effective patient access is a stepwise process comprising market approval and reimbursement procedures, both consisting of multiple components (e.g. evidence generation and pricing), and prescription practices (Fig. 1) [5,6].

In the EU, market access to MDs has been governed by EU Directive 2007/47/EC (as amended) relating to MDs and active implantable medical devices (AIMDs), and Directive 98/79/EC concerning in vitro diagnostics [7]. These directives were implemented into national legislation and specified requirements at an EU level for the pre- and post-market approval of MDs with the aim of securing patients' safety [8–10]. In April 2017, new MD regulations (Regulation (EU) 2017/745 and Regulation (EU) 2017/746) were adopted [11]. Subsequently, implementation in the EU member states will be achieved in the coming years. Until now, requirements concerning reimbursement procedures have been left to decide at the national level [9].

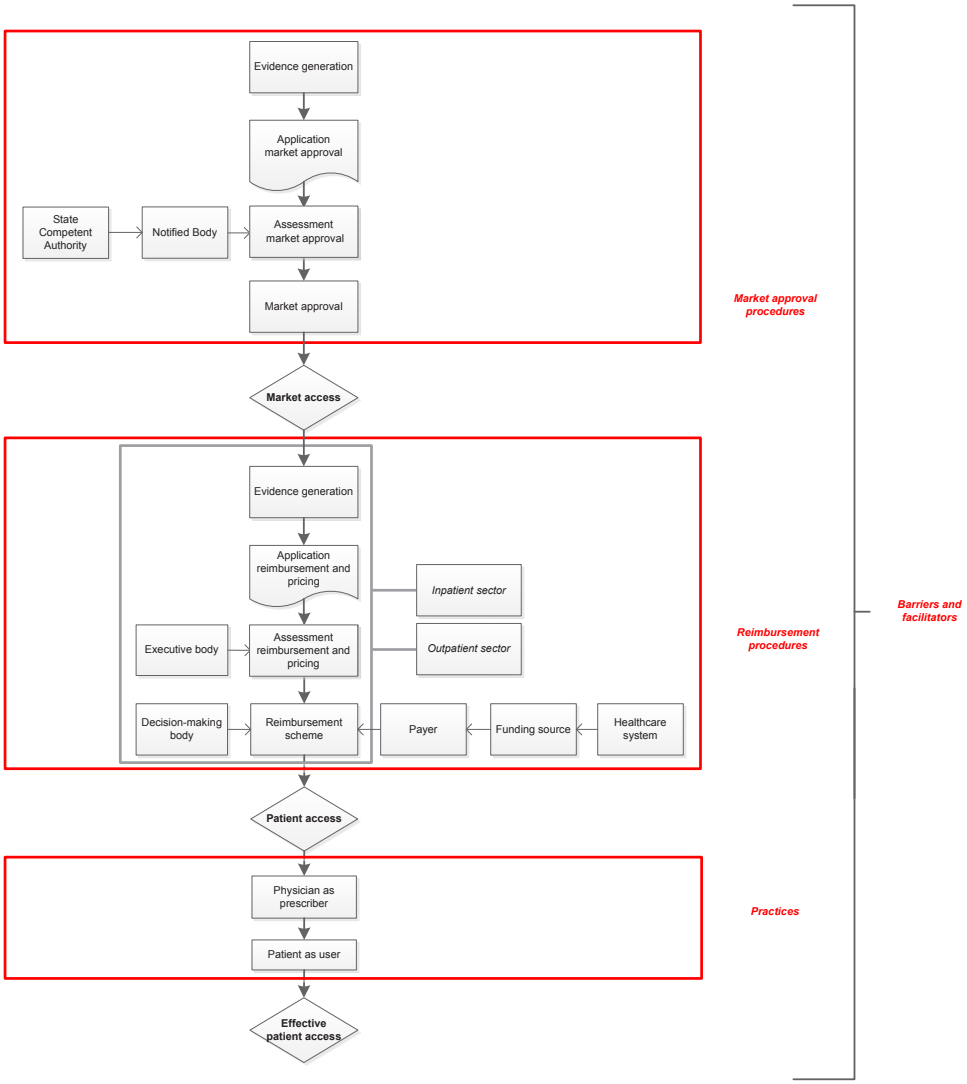

Figure 1. Generalized model concerning procedures and practices towards effective patient access to medical devices. Applications are displayed with document shapes (curved), procedures and authorities with rectangles, and access types that are products resulting from different procedures with rhombuses. The arrows in bold indicate the different steps of the process. Other arrows point from the components that have an influential role to the components that are influenced. The red contours capture the different market approval and reimbursement procedures and practices, and the grey contours the inpatient and outpatient sector.

MDs require a Conformité Européenne (CE) mark, indicating a successful conformity assessment of the device, before it may be placed on the EU market. As the process to obtain market access, starting after completion of CE mark application and involves assessment of device's safety and performance, is estimated to take a maximum of three months, subsequent procedures and practices regarding reimbursement (including evidence generation) and prescription of MDs respectively are considered to play a dominant role in effective and timely patient access [4,12]. Little information is currently available on reimbursement procedures and practices, due to language barriers, incomplete information, non-transparency, and both unclear and rapidly changing regulations [13–15]. Furthermore, manufacturers often have difficulty understanding and applying such regulations, during the process of diffusion of devices [16].

To our knowledge, there is no systematic overview in the literature on market approval and reimbursement procedures, that includes evidence requirements, and prescription practices leading to effective patient access [17]. Providing a comprehensive overview of current procedures regarding market approval and reimbursement of MDs in the EU member states will result in more transparency and could lead to a better understanding of such procedures for medical device companies, health policy makers and healthcare provider introducing MDs in practice in the EU [15].

Therefore, we framed the research question as: 'What are the country-specific procedures involved in obtaining effective patient access to MDs in various EU member states, and what are the barriers and facilitators related to these procedures?'. The aim of this study is to get an overview — through a systematic literature review — of current market approval and reimbursement procedures and practices involved in obtaining effective patient access to MDs in several EU member states. This includes all MDs irrespective of the risk class and use (inpatient or outpatient care) with the exception of drug delivery devices, in vitro diagnostics and implantable powered electronic devices). Secondly, we will identify barriers to and facilitators of early effective patient access. From the results, we will come up with policy recommendations.

Materials and methods

Search strategy

To identify the most relevant publications that reliably reflect current practice, we performed a systematic literature search in MEDLINE/PubMed, Embase (Ovid) and Scopus from January 2000to December 2015. The following keywords were applied in various forms during the search strategy: ('medical devices' AND 'regulation' AND ('costs' OR 'reimbursement') AND 'Europe' (including individual country names)) OR ('device' [title] AND ('regulat*'[title] OR 'reimbursement'

[title]) AND 'Europe' (including individual country names)). The full detailed list of keywords form Table 1 in Appendix A (Supplementary Material).

Box 1. Inclusion and exclusion criteria for the systematic review on effective patient access to medical devices in European countries.

Inclusion criteria	
1.	The objective of the publication concerns: i) market approval procedures of medical devices and/or ii) reimbursement procedures of medical devices and/or iii) prescription of medical devices by the physician or utilization by the patient
2.	The information is country-specific for one or more European countries
3.	The information reliably reflects current practice*
Exclusion criteria	
1.	The objective of the publication concerns: i) drug delivery devices, in vitro diagnostics or implantable powered electronic devices ii) specific examples of medical devices
2.	The information concerns Europe (in general) without country-specific information
3.	The information does not reliably reflect current practice*

* Publications were considered to reliably reflect current practice when the content corresponded to included publications from 2013 until 2015 or up-to-date information on websites published by health authorities.

Publication selection

The inclusion and exclusion criteria (Box 1) were determined and agreed a priori. Publications were included if the main objective was to inform or discuss market approval and/or reimbursement procedures, and practices of MDs in EU member states, and/or barriers to and facilitators of early effective patient access. All languages were considered. There was no limitation on the type of publication, which included editorials, book chapters, and conference abstracts that led to posters and presentations. Authors of conference papers or unavailable publications were contacted for full text publications. Conference papers of which the full text of the article was also included in the search were considered as duplicate publications and were therefore excluded. Furthermore, publications that did not reliably reflect current practice were considered not relevant and thus excluded from this study. Publications were considered to reliably reflect current practice when the content corresponded to included publications from 2013 until 2015. In case of doubt, the author was contacted to verify if the information that he or she reported reliably reflected current practice, and the content of the publication was compared to up-to-date information on websites published by health authorities. In addition, publications focusing only on devices that originally fell under a separate directive, such as in vitro diagnostics (Directive 98/79/EC),implantable powered electronic devices (Directive 90/385/EEC),and drug-delivery devices (assigned as medicinal products: Directive 2004/27/EC), were excluded because procedures and practices may differ from those of the MDs governed by the EU Directive2007/47/EC which

we focus on in our review [10,11,18,19]. Also, publications concerning the EU in general (without mentioning country-specific information) were excluded. Quality assessment was not relevant to this study as identifying forms of bias was not indicated.

Screening on title and abstract was carried out by the first author. The second author screened a random sample of 10% of all publications. The content of full texts was assessed on eligibility by the first author and a random sample of 10% by the second author [20]. In addition, publications of which the suitability was questioned by the first author were assessed and discussed with the second author. If there was an agreement rate of ≥95%, it had been decided that optimal agreement had been established in the screening process. In both screening processes, both authors discussed their choices with the last author in case of disagreement. The judgment of the last author was decisive in determining inclusion or exclusion.

Data extraction and analysis

Data extraction was performed by the first author. Publications reported in other languages than English or Dutch were translated by native speakers experienced in the specific field of research. Based on country-specific healthcare systems roadmaps, we created a generalized access model conceptualizing the MD pathway towards effective patient access and verified the components of the model in this study during the full text assessment (Fig. 1) [21].This model was used to extract key data on [1]: current market approval procedures [2]; reimbursement procedures [3]; and practices of MDs in achieving market access, patient access and effective patient access respectively. In addition [4], barriers to and facilitators of early effective patient access, defined as factors that hinder or promote time to effective patient access respectively, were identified and listed in the Results section. Barriers and facilitators were described in the literature whether or not those specific terms were used. Data on these four aspects were extracted from the included publications. The data was extracted in three phases by the first author during the process of developing the article: 1) extracting data to a database with use of the generalized access model (Fig. 1); 2) developing country-specific flow charts which included all extracted data and 3) processing the data in the manuscript. During these phases, the first author checked the data by comparing the extracted data to the sourced publications during the various phases. The data was checked similarly by the second author during each phase. Moreover, the process was checked by four involved authors. Data included in the selected publications was sorted and categorized according to market access, patient access and/or effective patient access, and subsequently ordered by EU country. The full (country-specific) forms of the abbreviations mentioned in Results section are listed in Appendix B (Supplementary Material). The selection of EU countries, included and compared in the results of this study, was based on the availability of the data in the literature.

Validation and update

An update of the search was conducted from December 2015 until January 2018 to check for those publications within this time period that could be relevant for the study results.

The data was validated in August-September 2018. The validation took place with representatives involved in the reimbursement assessment (e.g. executive bodies) and/or reimbursement procedures (e.g. decision-making bodies) from each country (through telephone contact or e-mailing) with the aim to correlate and confirm our literature findings with current practice. For this purpose, we have contacted health technology assessment (HTA) agencies and governmental institutions through the network of the European Network for Health Technology Assessment (EUnetHTA) and the Dutch Ministry of Health, Welfare and Sport's; the EU Working Group on Medical Devices (via the Dutch National Health Care Institute (ZIN) and health policy advisor in Brussels) and authors of key publications included in this study.

Results

Publication selection

In total, 3806 citations were retrieved from MEDLINE/PubMed, Embase (Ovid) and Scopus covering the time period of January 2000 to December 2015. A total of 844 duplicate citations were identified and excluded. The 2962 unique publications then were screened on title and abstract. In total, 2722 publications were excluded based on title and abstract. The texts of the remaining 240 publications were assessed for eligibility. In total, this led to the exclusion of 200 publications. The rate of agreement between first and second author in both processes was 99%, which was considered as sufficient. Among the excluded publications were publications that did not meet inclusion criteria, mostly because the publications focused on the EU (without country-specific information; n = 60); the main objective was different from that of this study (n = 44) and the publications contained information on a specific device without addressing the main objective of this study (n = 41) (Fig. 2).

A total of 40 eligible publications were included in this study, consisting of: descriptive papers (n = 22), editorials (n = 2), posters (n = 2), correspondence papers (n = 1), literature reviews (n = 5), retrospective studies (n = 3), directories (n = 2), books, comments and specials reports (n = 1 each). Three articles were the result of meetings. Data from publications was organized on: market access (n = 9) [6,8,10,22–27], patient access (n = 17) [12,13,28–42], effective patient access (n = 0) or a combination (n = 14) [9,16,43–54]. Depending on the type of access, the included publications provided data about France, Germany, Italy, Spain, the United Kingdom (UK), the Netherlands, Sweden and/or Poland (see 3.2.1., 3.2.2. and 3.2.3. for the specification of reported countries by access type). Most of the publications were in English. However, publications in German

(n = 5) [27,29,35,47,49] and Italian (n = 1) [33] were also included. Fig. 2 depicts the process of inclusion and exclusion of publications in this study using a PRISMA flow diagram [55].

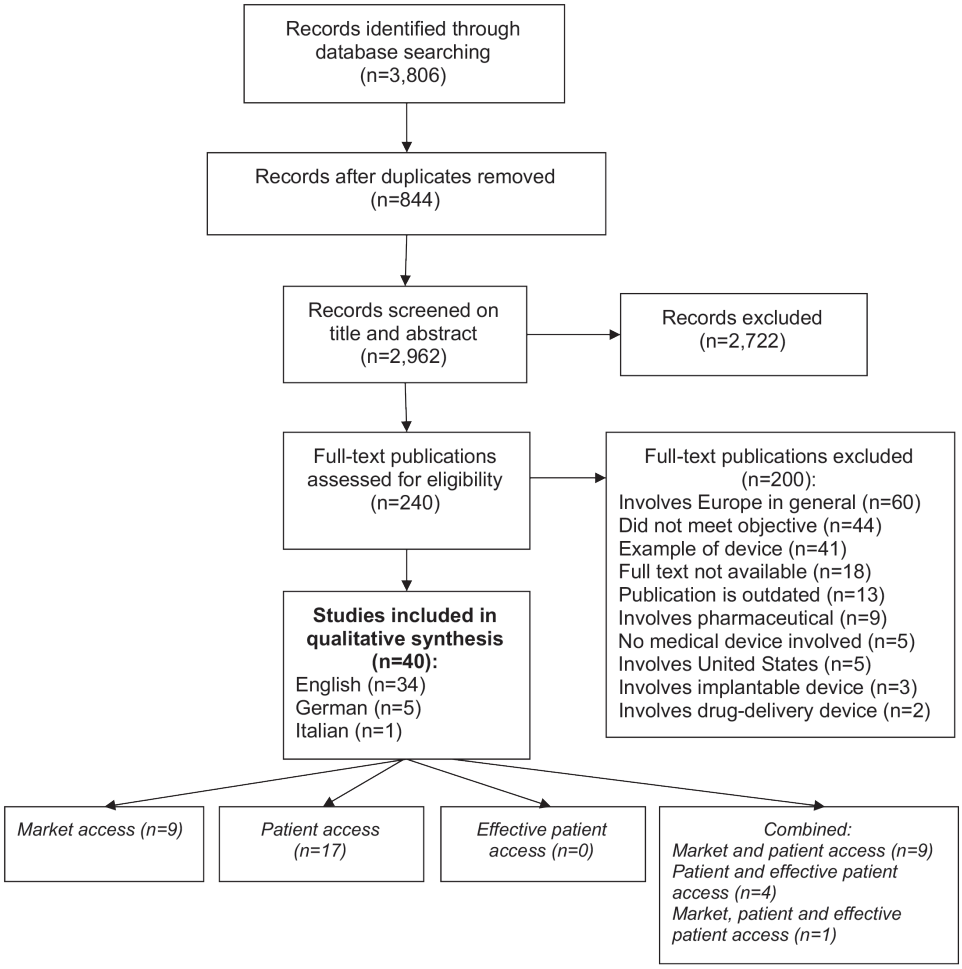

Figure 2. Flow diagram of publication selection process.

Prior to the data extraction, the access model was developed (Fig. 1). This is a generalized model, of which key components we focused on in this study are displayed. The components were based on the online EU healthcare systems roadmaps [21], and verified during full text assessment. In this model, the pathway towards effective patient access is reflected comprising several procedures and practices. Market and patient access are two subsequent intermediary access levels included to display the finalization of the two main procedures: market approval

procedures and reimbursement procedures respectively. After these procedures, realization of patient access (effective patient access) is achieved through certain practices defined as prescription by the physician and utilization by the patient.

Both market approval and reimbursement procedures consist of multiple (corresponding) components that are crucial in the process to access (e.g. evidence generation, application and assessment) leading to market approval or inclusion in a reimbursement scheme. Reimbursement procedures are separately described for the in- and outpatient sector. As a reimbursement scheme is subject to the type of healthcare system, the source of funding and the paying body, we also included these components in the study. Authorities that play a role in the assessment and decision-making procedures are incorporated in the model.

The content of this section comprises information on procedures and practices for effective patient access, structured in accordance with the three access processes shown in Fig. 1. For each of the eight EU member states, the available information is described in this Results section. The unavailability of information in included publications regarding the steps shown in Fig. 1 was not specifically mentioned for each country.

Data on market access, patient access and effective patient access

Market access

Market approval procedures.

Market access to MDs was the main objective in nineteen publications, and concerned five countries: France (n = 3) [16,50,51], Germany (n = 4) [27,43,47,49], the UK (n = 11) [6,8,10,22–24,26,43,52–54], Sweden (n = 2) [48,53], and/or Poland (n = 1) [25].

Uniform market approval procedures were described for these EU member states. A device has to be certified by means of a CE mark before it can be placed on the market [6,8,52]. The assessment of MDs depends on the risk classification: class I (low risk), class IIa (low-moderate risk), class IIb (medium risk) and class III (high risk) [16, 23, 51, 52]. Low-risk devices (class I) can be self-certified by the manufacturer on the basis of safety and performance. Class II and III devices' applications are supported by a literature review or clinical data that can either originate from the device itself or equivalent devices [8,22,23,27,47,49,52]. For class III devices, effectiveness data is required [51]. The assessment is carried out by independent organizations that are chosen and paid by the manufacturer, known as 'notified bodies'. There are approximately 80 notified bodies across the EU [6,16,26,43]. Notified bodies assess compliance with safety and performance requirements in the EU directives and, in the case of high risk devices, the effectiveness of the device [16,50,51]. The device is CE marked when considered eligible, which also implies market approval for all other EU member states [6,8,52]. In each EU member state, notified bodies are assigned and audited by a national competent authority. In addition, the competent authority regulates MDs by evaluation

of vigilance data in the (post-)market approval phase, providing guidance for certain MDs and checking that manufacturers comply with regulations [8,16]. The national competent authorities of France, Germany, the UK and Sweden are the National Agency of Drug Safety and Health Products (ANSM) [50], the Federal Institute of Medicinal Products and Medical Devices (BfArM) [43], the Medicines and Healthcare products Regulatory Agency (MHRA) [10,52–54] and the Medical Products Agency (MPA), respectively [48].

In practice, some differences concerning market approval procedures can be observed due to decentralized implementation of the notified bodies, thereby leading to inconsistencies in applying the assessment procedure [8,26,52]. Whether differences in the implementation approaches of the competent authorities occurred was not described in the literature. Therefore, a statement on the generalizability could not be made. Also, in Poland, manufacturers may only use Polish during submission and labeling of devices [25].

Patient access

Twenty-seven publications specified reimbursement procedures in the EU member states. Extracted data from the included publications were related to seven countries. Most of the publications concerned France (n = 13) [9,13,16,31,34,38,39,41–43,46,50,51] and Germany (n = 17) [9,12,13,29,31,32,35–38,40–42,44,46,47,49]. In addition, some information was available for the UK (n = 11) [9,13,31,38,41–43,46,52–54], Italy (n = 9) [9,13,28,30,33,41,42,45,46], Spain (n = 5) [13,28,41,42,45], Sweden (n = 2) [41,48] and/or the Netherlands (n = 2) [38,41] either on reimbursement procedures related to the inpatient and outpatient sectors and/or related to research programs. The most important findings that addressed the components included in Fig. 1 that were available in the literature for these countries are summarized in this section (see Appendix C (Supplementary Material) for an extended version). However, often detailed descriptions of application and assessment were not mentioned in the included publications, as can be seen in Table 2a. That table is an overview of results according to the reimbursement procedures defined in the generalized access model (Fig. 1), subdivided into inpatient sector and outpatient sectors (Tables 2a and b), payment system and healthcare system (Table 2c in Appendix D, Supplementary Material).

Table 2a. Extracted data from literature on reimbursement procedures in the inpatient sector in seven EU countries.

Country	Reimbursement scheme (described in literature)	Application criteria (reimbursement and pricing)	Assessment criteria (reimbursement and pricing)	Executive body	Decision-making body
France	1. DRG 2. Additional payments (APM) 3. CED (RP) 4. PHRC, PRME (RP)[b]	1. - 2. LPPR registration 3. LPPR registration[a] 4. -	1. - 2. - 3. - 4. -	1. - 2. - 3. - 4. CNEDiMTS	1. - 2. - 3. - 4. Ministry of Health
Germany	1. DRG 2a. DRG: New DRG group 2b. DRG: New OPS code 3. Supplementary payments (APM) 4. NUB (APM) 5. CED (RP)	1. - 2a. Information on: inappropriateness of existing DRG, new DRG, OPS and ICD coding and change on cost weight 2b. Information on: procedure, patients treated yearly, device distribution and change on cost weight 3. - 4. Information on: procedure, patients treated yearly, device distribution and change on cost weight, innovative aspects of device and overview available evidence 5. Available evidence, proposal for clinical evaluation, information on potential device and costs	1. - 2. - 3. - 4. - 5. -	1. - 2a. InEK 2b. DIMDI 3. - 4. InEK 5. IQWiG	1. - 2a. InEK 2b. DIMDI 3.- 4. InEK. Pricing: negotiations hospital and SHI 5. G-BA
UK	1. HRG 2. Additional payments (APM) 3. CED (RP)	1. - 2. - 3. -	1. - 2. - 3. -	1. - 2. - 3. NICE	1. - 2. Negotiations hospital and central or regional authorities 3. NICE
Italy	1. Per-case tariffs 2. Additional payments (APM)	1. - 2. -	1. - 2. -	1. - 2. -	1. Pricing: Reference pricing 2. Negotiations hospital and central or regional authorities

Spain	1. Global hospital budget 2. Additional payments (APM)	1. - 2. -	1. - 2. -	1. - 2. -	1. Negotiations hospital and regional authority or third-party 2. –
Netherlands	CED (RP)	-	-	-	Ministry of Health

This table is structured according to the reimbursement procedures in the inpatient sector of the generalized model (Figure 1). Available reimbursement schemes are numbered per country.

Sources: Summary of available data derived from the publications in the reference list.

A dash (-) means not available in the literature.

Abbreviations: APM, additional payment method; CED, coverage with evidence development; CNEDiMTS, National Committee for the Evaluation of Medical Devices and Health Technologies; DIMDI, German Institute for Medical Documentation and Information; DRG, diagnosis-related group; G-BA, Federal Joint Committee; HRG, Healthcare Resource Group; ICD, International Classification of Diseases; InEK, Institute for the Hospital Remuneration System; IQWiG, Institute for Quality and Efficiency in Healthcare; LPPR, list of products and services; NA, not applicable; NHI, National Health Insurance; NHS, National Health Service; NICE, National Institute for Health and Care; NUB, new examination and treatment methods; OPS, German procedure classification; PHRC, Program for Hospital Clinical Research; PRME, Program for Medical Economic Research; SHI, Statutory Health Insurance; TLV, Dental and Pharmaceutical Benefits agency; RP, research program; UK, United Kingdom.

[a]Applicable to non-implantable devices.

[b]PHRC and PRME do not provide national reimbursement; they are local in-hospital research programs.

Table 2b. Extracted data from literature on reimbursement procedures in the outpatient sector in seven EU countries.

Country	Reimbursement scheme (described in literature)	Application criteria (reimbursement and pricing)	Assessment criteria (reimbursement and pricing)	Executive body	Decision-making body
France	1a. LPPR: brand name 1b. LPPR: generic line	1a. Systematic literature search and clinical data 1b. -	1a. EB and EACV 1b. NA	1a. CNEDiMTS 1b. NA	1a. Ministry of Health, Pricing: Negotiation CEPS and manufacturer 1b. NA
Germany	1. EBM 2. IGeL 3. TAS 4. GOÄ 5. CED (RP)	1. RCT or intervention study, and CEA or BIA 2. Overview of available evidence and costs 3. See EBM application. No benefit: technical report 4. Overview of available evidence, device usage and costs 5. Overview of available evidence, proposal for clinical evaluation, information on potential device and costs	1. (Cost-)effectiveness 2. Inclusion in GOÄ fee schedule 3. (Cost-)effectiveness[a] 4. - 5. –	1. IQWiG 2. - 3. IQWIG. No benefit: 4. GMA 5. IQWiG	1. G-BA 2. - 3. G-BA. No benefit: GKV Spitzenband 4. GMA 5. G-BA
UK	1. Drug tariff list 2. CED (RP)	1. Clinical data 2. -	1. (Cost-)effectiveness 2. -	1. NICE and NHBSA 2. NICE	1. NICE and NHBSA 2. NICE
Italy	-	International and local data	-	-	-
Spain	-	International and local data	-	-	-
Netherlands	CED (RP)	-	-	-	Ministry of Health

This table is structured according to the reimbursement procedures in the outpatient sector of the generalized model (Figure 1). Available reimbursement schemes are numbered per country.

Sources: Summary of available data derived from the publications in the reference list.

A dash (-) means not available in the literature.

Abbreviations: APM, additional payment method; BIA, budget impact analysis; CED, coverage with evidence development; EACV, expected added clinical value; EB, expected benefit; EBM, the Statutory Health Insurance Physician Fee Schedule; CEA, cost-effectiveness analysis; CEPS, Economic Committee for Health Products; CNEDiMTS, National Committee for the Evaluation of Medical Devices and Health Technologies; GKV-Spitzenband, National Association of Statutory Health Insurance Funds; GMA, German Medical Association; GOÄ, Private Health Insurance Physician Schedule; IGeL, Individual Health Services; IQWiG, Institute for Quality and Efficiency in Healthcare; LPPR, list of products and services; NA, not applicable; NHS, National Health Service; NHSBSA, National Health Service Business Service Authority; NICE, National Institute for Health and Care; TAS, Therapeutic Appliance Schedule; TLV, Dental and Pharmaceutical Benefits agency; RP, research program; UK, United Kingdom.

[a]In case of therapeutic effect.

Reimbursement procedures: inpatient and outpatient sectors.

In France, devices used in the inpatient sector are reimbursed through diagnosis-related groups (DRGs) [9,16]. Additional payments apply to innovative and costly devices in the form of conditional reimbursement if the DRG system has not yet been updated [16,31,34,41]. In the outpatient sector, MD reimbursement occurs as a result of registration on the list of products and services qualifying for reimbursement (LPPR) under the 'generic line' (under existing categories) or 'brand name' (in case of innovative MDs). No assessment is necessary under the generic line. Registration under a brand name requires a literature search and clinical data in the French regime, what may originate from similar devices [16,31,34,39]. The application is assessed by the National Committee for the Evaluation of Medical Devices and Health Technologies (CNEDiMTS) in terms of expected benefit (EB), including benefit/risk ratio, role of the MD during treatment and public health impact. When the EB is found to be positive, the device is assessed on the expected added clinical value (EACV), comparing the device to the current gold standard for treatment [16,31,39,50,51]. The Economic Committee for Health Products (CEPS) negotiates the price with the manufacturer, and that is subject to reference pricing. In case of a positive decision by the Ministry of Health, this results in LPPR registration and publication [9,13,34,39,42,46,50]. MDs are reimbursed by the National Health Insurance (NHI) that is funded mainly through employers' contributions and payroll deductions [9,16,34,39].

In the inpatient sector in Germany, adoption of a MD is permitted without proving benefit unless the MD is rejected based on available evidence [38]. Devices enter a DRG if there is a suitable DRG and German procedure classification (OPS). The Institute for the Hospital Remuneration System (InEK) and the German Institute for Medical Documentation and Information (DIMDI) decide on new DRG groupings and OPS coding respectively [12,32,37,47]. Reimbursement of devices used in inpatient care can also occur through supplementary payments from a hospital's budget [37,41]. Innovative and costly MDs can be reimbursed through the new examination and treatment methods (NUB), an extra-budgetary local payment, until the DRG system has been updated. Pricing of an NUB is negotiated between the hospital and the Statutory Health Insurance (SHI) [29,32,37,38,42]. Devices used in the outpatient clinic and ambulatory care are incorporated into Statutory Health Insurance Physician Fee Schedule (EBM) and Therapeutic Appliance Schedule (TAS) respectively. The MD is assessed on (cost-)effectiveness (for devices in TAS only in case of a therapeutic effect) and evaluated by the Institute for Quality and Efficiency in Healthcare (IQWiG), following which inclusion is decided by the Federal Joint Committee (G-BA) [12,13,29,32,38,40,47]. In addition, devices that are not eligible for EBM can be applied to an Individual Health Services (IGeL) scheme for self-paying patients [32]. TAS and EBM are reimbursed by the SHI through fee schedules funded by the contributions of employers and employees [9]. For patients who are insured by Private Health Insurance (PHI), other schemes exist. Devices used in the outpatient sector are included in the Private Health Insurance Physician Schedule (GOÄ) once agreed by the German Medical Association (GMA) [32]. Pricing of devices in the outpatient sector occurs

through reference pricing or competition by means of public tendering [9]. MDs that are bought at a pharmacy are priced based on negotiations between the National Association of Statutory Health Insurance Funds and Federal Association of Pharmacists [35]. Additional payments must be made by patients if the costs of the preferred device are higher than the reference price [41,44].

The UK maintains the Healthcare Resource Group (HRG) system for the inpatient sector, and that is similar to the DRG system. Additional payments may be provided at a national level [9,41,42]. In the outpatient sector, MDs have to apply for inclusion on the drug tariff list [9,13]. The adoption of innovative or costly devices and devices with a high risk profile requires (cost-)effectiveness data [41]. The National Institute for Health and Care Excellence (NICE) assesses the application on indication and makes recommendations on reimbursement [43,52–54]. Pricing is set using mainly reference prices [41]. Devices are reimbursed by the National Health Service (NHS) through central taxes, and organized by decentralized Clinical Commissioning Groups (CCGs) [13,46].

In Italy, reimbursement of MDs is stipulated at a national level by the Ministry of Health and the Medical Device Committee (CUD) [13,33,42]. However, actual access to MDs is arranged separately in 20 Italian regions [9,42,45]. The inpatient sector is regionally funded by per-case tariffs [9,30,42,45]. Additional local payments may be accessible in negotiation with central or regional authorities. Pricing of certain devices (e.g. knee prosthesis and coronary stents) is decided nationally using reference prices [41,42,45]. Devices used in the outpatient sector are assessed per region and require both international data and data collection in the respective region. Funding is provided by the NHS derived from central and regional taxes. MDs are covered in the 'essential levels of care' (LEA). However, the LEA does not explicitly define the care that is reimbursed, leading to heterogeneous provision of care regionally [28,30,33,45,46].

Spain also has a decentralized system at the level of the autonomous communities (ACs). The inpatient sector is paid out of a hospital's budget [13,41,45]. Reimbursement of MDs depends on the contract program that is agreed between the hospital and regional authorities or other payers [45]. Additional payments have been reported in Spain [41]. Pricing is determined by a fixed profit margin [42]. The procedure concerning the outpatient sector was described as being similar to that in Italy [13]. Taxes and national budgets are the main funding sources [45].

Sweden consists of 21 regions with 290 municipalities. Dahlberg et al. [48] describes a decentralized system for assistive devices. Regions and municipalities organize device provision. Decisions on reimbursement are made by an independent governmental organization: the Dental and Pharmaceutical Benefits agency (TLV). Reimbursement is assured through tax income [48,53].

Reimbursement procedures related to research programs.
Various research programs are mentioned for France (see below). The coverage with evidence development (CED) program was described in two articles and has been implemented in France, Germany, the UK and the Netherlands. CED provides conditional reimbursement to innovative devices and simultaneously fosters evidence collection to prove the (cost-)effectiveness of the device [31,38].

CED in France provides reimbursement over at least two years. The CNEDiMTS selects suitable candidates for the program and assesses the application. The Ministry of Health decides which MD will enter the CED program funded by the NHI. Apart from CED, two local research programs are available: the Program for Hospital Clinical Research (PHRC) and the Program for Medical Economic Research (PRME). PHRC and PRME programs are in-hospital programs for which the research departments of hospitals can tender. An independent expert team assesses each application dossier and decides with regard to the PHRC, used for fundamental research, and PRME, used for economic evaluation [31,34,38].

The dossier for applying to CED in Germany can be filed by manufacturers, impartial members or patient representatives of the G-BA, the regional and federal associations of SHI physicians and the federal association of SHI funds. The IQWiG is responsible for evaluating that the application conforms to the criteria mentioned in Olberg et al. [38]: validity, plausibility and applicability. Subsequently, the G-BA makes the final decision on incorporation in the CED. Such a program is funded jointly by the SHI and manufacturer [31,32,38].

In the UK, application for CED is assessed by NICE. The CED program is offered in different forms: use of the MD in clinical practice with additional evidence collection ('Approval With Research' (AWR)) or only for research purposes ('Only In Research' (OIR)). CED is reimbursed by various stakeholders, including the NHS and manufacturers [31,38].

In the Netherlands, the Ministry of Health selects MDs that are eligible for CED. Data on (cost-) effectiveness of the MD is gathered throughout the program. Each clinical study is funded by the Netherlands Organization for Health Research and Development and other payers (e.g. manufacturers) [38,41].

Effective patient access
Following reimbursement, both the physician (as the prescriber) and the patient (as the user) play a role in the final step of gaining effective access to MDs. Five publications described such practices in six countries: France (n = 1) [46], Germany (n = 2) [44,46], the UK (n = 1) [46], Italy (n = 3) [9,45,46], Spain (n = 1) [45] and/or Sweden (n = 1) [48]. Information given about the practices in the

included publications varied among device types. Therefore, various device types are explicitly described in this section.

Practices: physician as the prescriber.
Stoma devices (used after ileostomy, colostomy or urostomy) in France and Germany are provided after prescription of the device by the specialist or the general practitioner (GP). The physicians can choose which brand they want to prescribe.

In Germany, the patient is provided with the stoma device after leaving the hospital. Additional supplementation is prescribed by the GP [46]. Some assistive MDs that are not registered in the TAS are allowed to be prescribed by the physician once the need has been established [44].

Stoma devices are initially prescribed by the specialist in the UK and continued by the GP. To avoid brand selection by specialists, the NHS motivates hospitals to collaborate with suppliers of stoma devices in return for covering the costs at the unit [46].

In Italy, after reimbursement, provision of knee prostheses and coronary stents can be dependent on the costs of such devices. When various types of knee prostheses are reimbursed in the same DRG, the physicians from private institutions tend to offer patients the less costly devices [9,45]. However, this does not apply to various types of implantable cardioverter defibrillators. Decision-making regarding effective patient access to coronary stents is also reported to be dependent on the relationship between hospital managers and physicians [45].

Long waiting times for surgical treatment were described for Spain when that involves the provision of knee prostheses. The educational level and medical cultures of physicians have been associated with variation between the implantable cardioverter defibrillators provided in various regions [45].

In Sweden, access to assistive devices is usually enabled through prescription by healthcare providers. However, in some regions, provision of assistive devices is achieved by applying a voucher system. In the process of the voucher system, the patient receives a voucher from the prescriber. With the voucher, patients can choose the device that is preferred. The assistive device is fully paid for by the patient if the device is not funded publically [48].

Practices: patient as the user.
Patients can fulfill a prominent role in the brand selection of a device in case a voucher system is used. In Sweden, this system enables patients to participate in choosing the most suitable assistive device, and spend the voucher on a brand and type of device that is preferred [48].

There is a trend of direct sponsorship of oncology units in the UK by MD suppliers, giving them preferred supplier status. This limits the physicians' ability to prescribe brands other than those from the sponsoring suppliers [46].

In Germany, the patient can select an assistive device that is preferred, but then has to pay additional costs if they exceed the costs of the device recommended by the health insurer [44].

Barriers and facilitators related to early effective patient access

An overview of the barriers to and facilitators of early effective patient access is presented in this section. The factors were extracted from 23 publications and covered Poland (n = 1) [25], France (n = 6) [16,31,34,38,39,41], Germany (n = 8) [12,28,29,36–38,41,49], Italy (n = 6) [9,13,28,30,41,45], Spain (n = 5) [13,28,30,41,45], the UK (n = 5) [28,38,41,52,54], Sweden (n = 2) [41,48], the Netherlands (n = 1) [38] and/or EU in general (n = 8) [6,16,28,31,43,51,52]. Factors were analyzed as barriers and/or facilitators, and enumerated in Table 3.

Barriers and facilitators: market access

In Poland, manufacturers must document and communicate in Polish, which was the only country-specific factor at the level of market access [25]. In the current analysis, we considered this as a barrier for international manufacturers to obtain early effective patient access.

Barriers that apply to EU member states in general were: unclear EU legislation regarding the requirements for pre-marketing study designs, difficulty in understanding the market approval procedures and demotivation of manufacturers in performing long-term studies due to complex study designs, the tendency to require a higher level of evidence under the new regulations compared to the MD directives, difficulty of keeping track of MD use by physicians and the typically short lifecycles of innovative MDs [6,16,31,51].

Data on effectiveness of the device is not always required for market approval in the EU, thereby facilitating time to market access up to three years earlier in comparison to the US [6]. Also, the application for market approval may be supported by data from similar existing devices [52].

Table 3. Barriers and facilitators to early effective patient access

Country	Study	Access	Barriers	Facilitators
Poland	Bondaryk 2008 (25)	MA	• Documentation and communication in Polish language	
France	Gilard et al. 2013 (34)	PA	• Data for application PA is specific to French setting*	• Data for application PA is specific to French setting*
	Guillou 2011 (16)	PA	• Difficult access to funding	• Available evidence early in device development
	Loge et al. 2015 (39)	PA	• Lack of focus on public health benefit • Lack of high quality studies	• Device measures up with technical standards • Device is accompanied by information on preceding devices • Device is supported by recommendations and guidelines • Application PA is supported by existing evidence from similar devices
	Martelli et al. 2014 (31)	PA		• PHRC and PRME
	Olberg et al. 2014 (38)	PA		• CED
	Sorenson et al. 2013 (41)	PA		• Additional payment systems
Germany	Heinemann 2014 (36)	PA	• Evaluation on cost-effectiveness by IQWiG and G-BA	
	Henschke et al. 2010 (37)	PA	• NUB only available locally	• NUB
	Hertz et al. 2012 (28)	PA		• DRG-based system
	Hessel 2005 (12)	PA	• Difficult access to funding • Decentralization of bodies involved in HTA assessment	
	Olberg et al. 2014 (38)	PA		• CED
	Seidel et al. 2014 (49)	PA	Evidence collection is not well implemented in practice Conduction of trials is costly and time-consuming for small manufacturers	Networks between manufacturers
	Sorenson et al. 2013 (41)	PA		Additional payment systems
	Zens et al. 2015 (29)	PA	Blinding in trials is not feasible and placebo-controlled studies are seen as unethical	

Italy	Cappellaro et al. 2009 (45)	PA/ EPA	• Regional organization of device provision • Relational in-hospital affairs*	• Relational in-hospital affairs*
	Cappellaro et al. 2009 (45), Schreyogg et al. 2009 (9)	EPA	• Amount of costs of device type	
	Finocchiaro Castro et al. 2014 (30)	PA		• DRG-based system
	Hertz et al. 2012 (28)	PA	• Less provision of healthcare, austerity, decrease in healthcare spending and reduction measures	
	Schafer et al. 2013 (13)	PA	• Data for application PA is specific to Italian setting* • Diverse requirements for application PA among regions	• Data for application PA is specific to Italian setting* • Reimbursement approval in prominent regions
	Sorenson et al. 2013 (41)	PA		• Additional payment systems
Spain	Cappellaro et al. 2009 (45)	PA/ EPA	• Regional organization of device provision • Waiting times for surgical treatment	
	Hertz et al. 2012 (28)	PA	• Less provision of healthcare, austerity, decrease in healthcare spending and reduction measures	
	Finocchiaro Castro et al. 2014 (25), Hertz et al. 2012 (30)	PA	• Global hospital budget	
	Schafer et al. 2013 (13)	PA	• Diverse requirements for application PA among regions	• Reimbursement approval in prominent regions
	Sorenson et al. 2013 (41)	PA		• Additional payment systems
UK	Campbell 2013 (52), Dobbs 2007 (54)	PA		• Guidance programs by NICE
	Hertz et al. 2012 (28)	PA		• DRG-based system
	Olberg et al. 2014 (38)	PA		• CED
	Sorenson et al. 2013 (41)	PA		• Additional payment systems

Table 3. Continued

Sweden	Dahlberg et al. 2014 (48)	PA	• Regional organization of device provision	
	Sorenson et al. 2013 (41)	PA		• Additional payment systems
Netherlands	Olberg et al. 2014 (38)	PA		• CED
EU	Guillou 2011 (16)	MA	• Complex MA procedures	
	Boudard et al. 2013 (51), Cohen 2013 (6)	MA	• Requirement of higher level of evidence	
	Cohen 2013 (6)	MA		• Application MA requires less clinical evidence in EU compared to US
	Campbell 2013 (52)	MA		• Application MA is supported by existing evidence from similar devices
	Martelli et al. 2014 (31)	MA	• Unclear EU legislation • Demotivation of manufacturers to perform long-term studies	
	Altenstetter 2003 (43)	PA	• Non-transparency in reimbursement procedures	
	Boudard et al. 2013 (51)	PA	• Inapplicability to perform RCTs	
	Hertz et al. 2012 (28)	PA	• Country-specific data for application PA	

Abbreviations: CED, Coverage with Evidence Development; EPA, Effective Patient Access; EU, European Union; IQWiG, German Institute for Quality and Efficiency in Healthcare; G-BA, Federal Joint Committee; HTA, Health Technology Assessment; MA, Market Access; NICE, National Institute for Health and Care Excellence; NUB, new examination and treatment methods; PA; Patient access; PHRC, Program for Hospital Clinical Research; PRME, Program for Medical Economic Research; RCT, Randomized Controlled Trial; UK, United Kingdom; US, United States.
*Factor is both a barrier and facilitator.

Barriers and facilitators: patient access

Barriers to and facilitators of evidence requirements during reimbursement procedures concerned France, Italy and Germany. In France, a lack of focus on public health benefit and high quality studies are factors that are considered to influence the EB negatively [39]. Devices that meet the technical standards are supported with recommendations and guidelines, and if accompanied by information on similar preceding MDs are more likely to obtain a positive vote on the EB by CNEDiMTS and therefore facilitate early effective patient access. Evidence comprising nonspecific clinical data and is available early in the development prevents that patient access to (innovative) MDs with short lifecycles being impeded [16,39]. For evidence collection in France and Italy, data specific to their country facilitates the reimbursement assessment. However, this can also be a barrier to early effective patient access because, instead of using existing data derived

from other countries, the data has to be gathered explicitly in the respective country which can be time-consuming [13,34]. In Germany, the barriers mentioned in the literature constituted of the need for blinding and randomization in clinical trials, a lack of evidence collection during clinical trials due to cost pressures and lack of personnel in the clinic, and the evaluation of cost-effectiveness by IQWiG and G-BA [29,36,49]. In addition, conducting clinical trials is both costly and time-consuming for small German companies, which may prevent innovative MDs from entering clinical practice. Therefore, networks between manufacturers — that have been initiated to provide an infrastructure to support multicenter trials – facilitate early effective patient access [49].

Organizational barriers and facilitators were reported to be related to the healthcare system and reimbursement procedures in Germany, the UK, Italy and Spain. In Italy and Spain, reducing public healthcare provision, austerity, a decrease in healthcare spending and budgetary cuts have a negative influence on early effective patient access [28]. Also, the regional arrangement of MD provision in Italy, Spain and Sweden can be difficult for the manufacturers when wanting to disseminate their MD at the national level [13,45,48]. Unlike the global hospital's budget in Spain, DRG-based systems implemented, for example, in Italy, the UK and Germany, help serve adoption of innovative MDs in hospitals [28,30]. Concerning the reimbursement procedures, it was stated that the application of the German HTA is delayed by the decentralization of bodies involved in the HTA assessment, and therefore impede progress towards patient access [12]. Guidance programs for MDs provided by NICE in the UK have a positive influence on the reimbursement by the NHS [52,54].

Financially driven barriers were found to be difficulties with funding of MDs in France and Germany. In the case of Germany, the NUB is only provided when hospitals negotiate with SHI [12,16,37]. Additional payments systems (in France, Germany, Italy, the UK, Spain and Sweden) and funded research programs (in France, Germany, the UK and the Netherlands) facilitate early adoption of MDs in the inpatient clinic [38,41].

No facilitators were mentioned at an EU level. Non-transparency with regard to the reimbursement procedures, requirements for country-specific data and inapplicability of performing randomized controlled trials (RCTs) during MD evaluation constitute general barriers in EU member states [28,43,51].

Barriers and facilitators: effective patient access

The physician is exposed to various device-specific barriers and facilitators that determine how and if the MD is prescribed to the patient. Costs of the device types, waiting times and hospital-physician relationships have been analyzed as factors influencing early effective patient access [9,45]. The patient as a user of MDs was not reported to affect early effective patient access.

Results of validation and update

The update search revealed 656 further publications, and screened on title and abstract. The remaining publications were screened on full text and checked for eligibility (n = 31). No conclusion-changing publications were found. Publications that were found to be relevant, e.g. regarding the implementation and content of the MDR throughout the EU, are discussed in the Discussion section. In addition, barriers to and facilitators of early effective patient access related to the MDR can only be evaluated in literature after the MDR has been implemented for a longer period of time.

To ensure the accuracy of the data included in this study, we recruited representatives from each country for validation. In total, six out of eight countries responded. In addition, in this study, little evidence regarding the practices related to MD use in Denmark was reported to be inconsistent with current practice by the Danish representative from the National Board of Social Services. This information was therefore excluded from this study. For the included countries, we were able to validate core findings with representatives of Germany, the Netherlands, France, Poland, Sweden and the UK. The representatives are employed at the National Association of Statutory Health Insurance Funds (GKV-Spitzenband), ZIN, French National Authority for Health (HAS), Agency for Health Technology Assessment and Tariff System (AOTMiT) and TLV. The UK was represented by an author of one of the key publications included in the review. All representatives confirmed key findings to reflect current practice. The German representative noted additionally that in practice, the G-BA does not decide about the costs of MDs. The G-BA may assess cost-effectiveness, but usually focusses on patient-relevant medical benefits and damage potential of the device. This is due to the fact that usually there is too little evidence on the effectiveness between two methods, whereby cost-effectiveness is difficult to assess. The Dutch representative noted that the consequences of the current MDR implementation will not be fully detectable in literature yet but will have an effect on market approval procedures in the coming years. The representative of the French HAS commented that in France, PHRC and PRME are not national reimbursement schemes, but rather local (in-hospital) research programs. The MDs used in the programs are not always funded publically; costly MDs are paid by the manufacturer. In Sweden, the regulation of reimbursement by TLV is limited to the devices needed to administer or monitor pharmaceuticals and stoma products [56]. In some cases, TLV assists with conduction of HTA of MDs [57]. Concluding, the validation confirmed our findings reported in the Results section 3.2.

Discussion

To our knowledge, this is the first systematic review to provide a comprehensive literature overview that takes into account country-specific market approval and reimbursement procedures and practices related to effective patient access to MDs in eight EU member states.

Information on the pathway towards market access mentioned for France, Germany, the UK, Sweden and Poland was uniformly described at an EU level [6,8,10,16,22–27,43,47–54]. Differences in implementation of the notified bodies were observed; however, differences could not be retrieved from the literature about the competent authorities [8,16,50,51]. Reimbursement procedures varied among the EU member states that were included in the current study. Our results suggest that reimbursement procedures are not only heterogeneous but also more complex and extensive when compared to market approval procedures [9,12,13,16,31,32,34,37,39,41,42,46,47,50,51]. Also, obtaining reimbursement in one country will not apply to other EU member states, as is the case with the CE mark [6,8,52]. Although we did not measure this aspect quantitatively, this reveals a negative influence over time to effective patient access throughout the EU, often resulting in a longer time needed for reimbursement than for market approval. Our findings are in line with previously published publications showing wide variations in reimbursement procedures across EU member states and a much longer time to obtain patient access compared to obtaining market access [4,17,58]. Basu et al. [4] measured the time differences between market and patient access, and described a one to three month duration for market approval procedures, whereas the time for reimbursement procedures ranged from 16.4 to 71.3 months.

One important aspect of MD approval that emerged from our study concerns the collection and assessment of evidence accompanying the MD. We observed notable differences in the evidence required for each phase. For market approval, safety and performance measures are assessed. In addition to these requirements, evidence for reimbursement approval often requires effectiveness data, data on post-market surveillance and a (cost-)effectiveness analysis [4,16,34,41,51]. The available evidence in the literature describes the disintegration of the market approval and reimbursement procedures. Consequently, evidence collection for e.g. cost-effectiveness analysis for reimbursement purposes can be hindered due to absence of evidence generation during the market approval phase [17,59,60]. Implementation of the new Medical Device Regulation (MDR 2017/745) will lead to stricter clinical evidence requirements and pre- and post-market control. The new MDR also contains changes to improve regulation, including stricter criteria that apply to notified bodies, improved transparency by developing an EU-wide MD database and providing traceability of MDs using a Unique Device Identification system [11,38,61].

The information on the prescription and utilization practices was scarce, especially when utilization of MDs by the patient is considered [44,46,48]. Available information concerning the patient's role in MD access showed no correlation with early effective patient access but focused mainly on brand selection by patients. Practices and factors affecting the time to patient access (e.g. costs of device types, waiting times and hospital-physician relationships) varied among specific device types [9,45]. According to Davis et al. [62], decisions regarding prescription of MDs by physicians are affected by the physician's perceived ease of use and usefulness of the device. Determinants that influence the ease of use and usefulness are: individual differences

among physicians, device characteristics, social influence and facilitating conditions [63]. In this study, multiple factors, such as financial interests, organizational factors related to the work capacity and hospital managements, as studied by Cappellaro et al., were identified [45]. Our study indicates that these are important examples of facilitating conditions. In addition, a further examination of the other determinants may also be valuable.

Barriers to and facilitators of effective patient access identified in this literature study correspond to the recently published study by Fuchs et al. [64], which explored the MD assessment by HTA institutions including challenges and future perspectives through semi-structured interviews with representatives of EUHTA institutions. Findings mentioned in this study related to the insufficient level of evidence collection and weak market access regulation were challenges reported in their study. In addition, adoption of CED, sufficient evidence collection and solving disintegration between the licensing and reimbursement process are key aspects in our study that were highlighted and concluded accordingly in their study.

Strengths and limitations

The main strength of this study is the systematic approach applied to obtain the data on patient access to medical devices in eight EU member states. Presenting the market approval and reimbursement procedures (inpatient and outpatient sectors) and practices according to the generalized access model shown in Fig. 1 strengthened the structure of this review. However, we acknowledge that country-specific aspects or details can differ among EU countries, so that this is rather a generalizable model on MD access. The results were described in a transparent manner, especially the section on reimbursement procedures, which is unique when compared to the findings reported in the available literature. In addition, all types of publications – including domestic publications – were taken into account to provide insight into the available evidence and access to the data written in languages other than English. The broad search strategy conducted in the three databases aimed to retrieve most important available evidence in the literature on the processes towards effective patient access and on barriers and facilitators. The update of the search and data validation provided reliable results in accordance with practice.

Several limitations to the study need to be taken into account. First, information on reimbursement procedures was only available for France and Germany due to the limited number of valuable health policy publications that had detailed descriptions of the processes towards effective patient access [16,31,32,39]. For the UK, Spain, Italy, Netherlands and Sweden, available information was scarce. Second, we are aware that by confining ourselves to the literature as the main source in this study, possibly valuable information regarding the eight countries discussed in this study was overlooked, but also regarding other EU member states. Third, although contacting authors of the eligible publications to confirm whether the data reflected current practice was a strength in this study, it was only effective in a small part, due to the low response rate. Fourth, an important

limitation was the absence of information on quantifying time to access. Such information on time to access (data not shown) that was available was scarce and showed inexplicable discrepancies between publications regarding the length of reimbursement procedures, making it difficult to compare [13,16,34,40,42]. Fifth, changes may have occurred in the respective countries since the final update of the search and validation of the data. A restriction of the study is that we focused on all MDs irrespective of the risk class and use (inpatient or outpatient care) but excluded drug delivery devices, in vitro diagnostics and implantable powered electronic devices. Finally, a formal quality assessment was not performed in view of the nature of the publications, most of which contained level 4 evidence according to the hierarchy by Cochrane Collaboration; almost all was descriptive or policy oriented [65]. Therefore, we limited the data extraction to factual information.

Policy and research implications

From the findings of the current study, health policy suggestions were formulated. Time dependence on heterogeneous and extensive reimbursement procedures could be improved by simplifying and harmonizing these procedures across EU member states. This could also lower the costs of such procedures [66].

Collecting robust evidence prior to market approval that is obligatory for reimbursement of MDs could be established by better aligning the market approval and reimbursement procedures [59]. This recommendation also came out of a recent study that interviewed representatives from 16 EU HTA institutions [64]. The MDR may potentially help in solving this dilemma by its stricter evidence requirements [11].

Barriers created by unclear EU legislation [51] and complex market approval procedures [16] could be minimized by providing more feasible guidelines, in terms of uniformity, clarity and complexity, and that are more accessible to manufacturers by involved parties, such as the national competent authorities, incorporated in guidelines of EUnetHTA or the Global Harmonization Task Force worldwide [67]. Most countries have implemented a DRG-based system in the inpatient sector, thereby facilitating more effective patient access. By applying this system, costs and incomes are controlled within hospital departments, making healthcare providers more conscious of the healthcare spending and promoting the national provision of MDs. In countries such as Italy and Spain, costs are managed using tariffs and global budgets respectively, and provision is arranged at a regional level [13,45]. In these countries, effective implementation of DRG-systems (in Spain) and centralization of procedures would encourage reimbursement and provision of MDs nationally. But for now, it is both desirable and feasible for manufacturers to obtain approval in the more prominent, large scaled and influential regions in these countries, such that other regions will follow positive advice by means of the 'domino effect' [13].

Securing financing nationally for innovative and costly devices is crucial for MD adoption, especially in an early stage of device development. National implementation of funded research programs such as CED and additional payment systems as part of the reimbursement procedures should be prioritized by health policymakers across the EU to encourage the adoption of innovative MDs [31,37,38,41,66].

This current study provides an incentive to fill in the gap in the literature by consulting other sources, such as governmental reports, websites of health authorities and white papers. In addition, methodological alternatives such as time series analysis, review of case notes, surveys and interviews with health policymakers, members of relevant institutes and manufacturers could validate and generate in-depth information on barriers and facilitators [68]. In addition, involving researchers in the field in a survey study could have led to a broader perspective on this topic.

Further research should focus more on exploring the utilization of MDs by patients and prescription practices, taking into account both physician's individual and device characteristics of different device types [63]. This could be achieved by means of studies on specific devices involving conduction of surveys and interviews with healthcare professionals. We will further examine this in a future qualitative study focusing particularly on devices used in head and neck cancer rehabilitation.

More objective information should be provided on the taken time to achieve effective patient access. It should be taken into account that currently there are only four notified bodies (instead of 80) [69,70] due to the MDR which aims at a more centralized system with stricter requirements including the accreditation of notified bodies. Quantitative information on the time to access could be improved in the future by clearly describing the procedures involved in measuring the time to access and defining criteria on (standard) measurement points in future studies [71]. In this way, time to access could be compared objectively among EU member states objectively. Furthermore, attention should be paid to differences in time to market access following the implementation of a new MDR, involving the provision of adequate evidence to protect the safety of patients without extending the time taken to make potentially beneficial devices available to patients [11].

Conclusions

In the literature, market approval procedures were uniformly described for the EU member states. Information on reimbursement procedures, with exception of France and Germany, and prescription practices was incomplete. Reimbursement procedures were heterogeneous across the EU, which had a significant impact on accessibility of MDs for patients. Little information was

available about patients as users of MDs, and prescriptions by physicians varied among device types.

Important barriers to early effective patient access were found unclear EU legislation, complex market approval procedures, requirements for a particular level of evidence and evidence collection during reimbursement procedures, and reimbursement and provision of MDs at the regional level. Procedures concerning market and patient access are facilitated by sufficient evidence collection, implementation of a DRG-based system, additional payment methods and research programs. The physician's prescription was influenced by the waiting times, costs of device types and hospital-physician relationships, whereas none of the publications described the patient's role in early effective patient access.

Policy recommendations arising from this study include those for feasible guidelines on market access, alignment between market approval and reimbursement procedures, centralization of reimbursement procedures, additional payment methods and funded research programs. Furthermore, sourcing other information about reimbursement procedures and practices – including clearly defined measurement points regarding time to MD access – is highly recommended.

References

1. Hancher L, Eva Földes M. Revision of the regulatory framework for medical devices in the European union: the legal challenges. Eur. J. Risk Regul. (EJRR)2013;4(4):429–35, http://dx.doi.org/10.1017/S1867299X0000307X.
2. WHO. Core Medical Equipment. Last accessed: 16-02-2018. [Available from: http://www.who.int/medical devices/publications/med dev core equipt/en/].
3. WHO. Medical Device – Full Definition. Last accessed: 16-02-2018. [Available from: http://www.who.int/medical devices/fulldeffinition/en/].
4. Basu S, Hassenplug JC. Patient access to medical devices — a comparison of U.S. And European review processes. N Engl J Med 2012;367(6):485–8.
5. Smith SR. Patient access to medical devices. N Engl J Med 2012;367(20):1963–4,author reply 4-5.
6. Cohen D. Devices and desires: Industry fights toughening of medical device regulation in Europe. BMJ (Online) 2013;347(f6204), http://dx.doi.org/10.1136/bmj.f6204.
7. European Parliament. DIRECTIVE 2007/47/EC OF THE EUROPEAN PARLIAMENTAND OF THE COUNCIL of 5 September 2007. Last accessed: 16-02-2018. [Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L. 2007.247.01.0021.01.ENG].
8. Parvizi N, Woods K. Regulation of medicines and medical devices: contrasts and similarities. Clin Med J Royal College Phys London 2014;14(1):6–12.
9. Schreyogg J, Baumler M, Busse R. Balancing adoption and affordability of medical devices in Europe. Health Policy (New York) 2009;92(2-3):218–24.
10. Hodges CJS. European regulation of medical devices; 2009. p. 507–21.
11. European Commission. Regulatory framework. Last accessed: 16-02-2018.[updated daily. Available from: https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en#new_regulations].
12. Hessel F. Reimbursement for high-priced innovative medical devices in a DRG-based hospital care system: the German situation. Expert Rev Pharmacoecon Outcomes Res 2005;5(4):377–81.
13. Schafer E, Schnell G, Bobakova T. Diabetes device reimbursement in the EU-5.J Diabetes Sci Technol 2013;7(4):1084–92.
14. Simoens S. Health economics of medical devices: opportunities and challenges. J Med Econ 2008;11(4):713–7.
15. Eldessouki R, Smith MD. Health care system information sharing: a step toward better health globally. Value Health Reg Issues 2012;(1.1):118–20.
16. Guillou J. Medical device reimbursement in France process of decision. [French, English] Remboursement des dispositifs medicaux en France processus de decision. STP. Pharma Pratiques 2011;21(5):425–32.
17. Kruger LJ, Evers SMAA, Hiligsmann M, Wild C. Divergent evidence requirements for authorization and reimbursement of high-risk medical devices – the European situation. Health Policy Technol 2014;3(4):253–63.
18. MHRA. Borderlines between medical devices and medicinal products. Last accessed: 16-02-2018. [updated June 2013. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment data/file/284493/Borderlines between medical devices and medicinal products.pdf].

19. Donawa M. New European guidance on borderline products. Med Device Technol 2009;20(5):22, 4-5.

20. McDonagh M, Peterson K, Raina P, Chang S, Shekelle P. Avoiding bias in selecting studies. Methods guide for effectiveness and comparative effectiveness reviews[internet]. Agency for Healthcare Research and Quality (US); 2013.

21. ISPOR. The ISPOR Global Health Care Systems Road Map. Last accessed: 15-8-2018. [updated 2018. Available from: https://tools.ispor.org/htaroadmaps/.

22. How medical devices are regulated in the UK. Drug Ther Bull 2010;48(7):82–4.

23. Abrams P, Chapple CR, Drake M, El-Neil S, Ludgate S, Smith ARB. Synthetic vaginal tapes for stress incontinence: proposals for improved regulation of new devices in Europe. Eur Urol 2011;60(6):1207–11.

24. Williams N. The scandal of device regulation in the UK. Lancet2012;379(9828):1789–90.

25. Bondaryk K. Medical device legislation — a Polish view: Poland brings medical device law into line with European regulation, NOV; 2008. p. 12.

26 . Horton R. Offline: the scandal of device regulation in the UK. Lancet 2012;379(9812):204.

27. Lauer W, Stosslein E, Brinker A, Broich K. Medical devices. Regulatory framework and contribution of the German Federal Institute for Drugs and Medical Devices (BfArM) to the safe application. [German] Medizinprodukte. Regulatorischer Rahmen und Beitrag des BfArM zur sicheren Anwendung. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2014;57(12):1355–61.

28. Hertz D, Marcarelli AD, Patel L, Garfield S. Adoption of new technologies in twenty established and emerging markets. Value Health 2012;15(7).A323-A4.

29. Zens Y, Fujita-Rohwerder N, Windeler J. [Benefit assessment of medical devices]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2015;58(3):240–7.

30. Finocchiaro Castro M, Guccio C, Pignataro G, Rizzo I. The effects of reimbursement mechanisms on medical technology diffusion in the hospital sector in the Italian NHS. Health Policy 2014;115(2-3):215–29.

31. Martelli N, van den Brink H. Special funding schemes for innovative medical devices in French hospitals: the pros and cons of two different approaches. Health Policy (New York) 2014;117(1):1–5.

32. Schwander B, Krone FA, Walzer S. Clinical and health economic evidence requirements for obtaining health insurance coverage for innovative medical devices in Germany. Value Health 2013;16(7):A474.

33. Scroccaro G, Steffenino G, Marini P, Trippoli S, Santarlasci B. Costs and benefits of medical devices. The case of drug-eluting stents. [Italian] La valutazione deibenefici e dei costi dei dispositivi medici. Il caso degli stent medicati. Pharmaco Economics - Italian Res Articles 2005;7(3):195–206.

34. Gilard M, Debroucker F, Dubray C, Allioux Y, Aper E, Barat-Leonhardt V, et al. Scientific evaluation and pricing of medical devices and associated procedures in France. Therapie 2013;68(4):201–8.

35. Graf Von Der Schulenburg JM, Mittendorf T, Kulp W, Greiner W. Health Technology Assessment (HTA) for medical devices - Do the same rules apply? Gesundheitsökonomie & Qualitätsmanagement 2009;14(3):144–55.

36. Heinemann L. EASD diabetes technology meeting: medical associations are on track. J Diabetes Sci Technol 2014;8(4):900–3.

37. Henschke C, Baeumler M, Gaskins M, Busse R. Coronary stents and the uptake of new medical devices in the German system of inpatient reimbursement. J Interv Cardiol 2010;23(6):546–53.

38. Olberg B, Perleth M, Busse R. The new regulation to investigate potentially beneficial diagnostic and therapeutic methods in Germany: Up to international standard? Health Policy (New York) 2014;117(2):135–45.

39. Loge P, Delalande F, Reymond MC, Germain S. Factors influencing reimbursement of medical devices in France. Int J Technol Assess Health Care2015;31(6):399–406.

40. Schaefer E, Karch A. Reimbursement for diabetes medical devices in Germany.J Diabetes Sci Technol 2014;8(1):186–7.

41. Sorenson C, Drummond M, Burns LR. Evolving reimbursement and pricing policies for devices in Europe and the United States should encourage greater value. Health Aff (Millwood) 2013;32(4):788–96.

42. Wilkinson G, Drummond M. Impact of reimbursement policies on the adoption of medical devices in an outpatient setting. Health Policy Technol2014;3(4):281–6.

43. Altenstetter C. EU and member state medical devices regulation. Int J Technol Assess Health Care 2003;19(1):228–48.

44. Winkelmann P. REHADAT: the German information system on assistive devices; 2011. p. 163–9.

45. Cappellaro G, Fattore G, Torbica A. Funding health technologies in decentralized systems: a comparison between Italy and Spain. Health Policy (New York)2009;92(2-3):313–21.

46. Cornago D, Garattini L. The stoma appliances market in five European countries: a comparative analysis. Appl Health Econ Health Policy 2002;1(1):43–50.

47. Moller B, Stockheim M, Kraus T, Weber A. [Medical innovations in the area of conflict between certification and allowance]. Dtsch Med Wochenschr 2010;135(42):2088–92.

48. Dahlberg R, Blomquist UB, Richter A, Lampel A. The service delivery system for assistive technology in Sweden: current situation and trends. Technol Disabil 2014;26(4):191–7.

49. Seidel D, Brass P, Sehnke N, Jakob V, Eglmeier W, Neugebauer EA. [Assessment of the benefit of medical devices in surgical practice. Problems and possible solutions]. Chirurg 2014;85(5):407–15.

50. Parquin F, Audry A. Clinical evaluation of medical devices: main constraints and specificities. Therapie 2012;67(4):311–8.

51. Boudard A, Martelli N, Prognon P, Pineau J. Clinical studies of innovative medical devices: What level of evidence for hospital-based health technology assessment? J Eval Clin Pract 2013;19(4):697–702.

52. Campbell B. Regulation and safe adoption of new medical devices and procedures. Br Med Bull 2013;107(1):5–18.

53. Frønsdal K, Pichler F, Mardhani-Bayne L, Henshall C, Røttingen JA, MørlandB, et al. Interaction initiatives between regulatory, health technology assessment and coverage bodies, and industry. Int. J. Technol. Assess. Health Care2012;28(4):374–81.

54. Dobbs H. Current developments and the medical device directive — A regulator's perspective. IDrugs 2007;10(4):253–5.

55. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

56. Pricing and reimbursement of medical device consumables. Last accessed:13-9-2018. [updated 10-11-2017. Available from: https://www.tlv.se/in-english/medical-devices/pricing-and-reimbursement-of-medical-device-consumables.html].

57. Economic evaluations of medical devices. Last accessed: 13-9-2018. [updated8-11-2017. Available from: https://www.tlv.se/in-english/medical-devices/economic-evaluations-of-medical-devices.html].
58. Mason N, Schurer M, Chapman A-M, Akehurst R. European HTA, pricing and reimbursement roadmaps: revisited 2016. Value Health 2016;19(3):A288.
59. Ciani O, Wilcher B, Giessen A, Taylor RS. Linking the regulatory and reimbursement processes for medical Devices: the need for integrated assessments. Health Econ 2017;26(S1):13–29.
60. Storz-Pfennig P, Schmedders M, Dettloff M. Trials are needed before new devices are used in routine practice in Europe. BMJ: Br Med J (Online) 2013;346.
61. Migliore A. On the new regulation of medical devices in Europe. Taylor & Francis; 2017.
62. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. Mis Q 1989:319–40.
63. Venkatesh V, Bala H. Technology acceptance model 3 and a research agenda on interventions. Decis Sci 2008;39(2):273–315.
64. Fuchs S, Olberg B, Panteli D, Perleth M, Busse R. HTA of medical devices: challenges and ideas for the future from a European perspective. Health Policy (New York) 2017;121(3):215–29.
65. Clarke M, Oxman A. Cochrane reviewers' handbook: update software; 2000.
66. OECD. New health technologies: managing access, value and sustainability;2017.
67. Gupta SK. Medical device regulations: a current perspective. J Young Pharm 2016;8(1):6.
68. Sheldon TA, Cullum N, Dawson D, Lankshear A, Lowson K, Watt I, et al. What's the evidence that NICE guidance has been implemented? Results from a national evaluation using time series analysis, audit of patients' notes, and interviews. Br Med J Publ Group 2004;329(Oct. (7473)):999.
69. Italy's IMQ fourth notified body designated in EU. Last accessed: 6-11-2019. [Available from: https://www.medtechdive.com/news/italys-imq-fourth-notified-body-designated-in-eu/561284/.
70. Nando (New Approach Notified and Designated Organisations) Information System. Last accessed: 6-11-2019. [Available from: https://ec.europa.eu/growth/tools-databases/nando/index.cfm.
71. Hassenplug J. Patient access to medical devices. N Engl J Med2012;367(20):1963–5.

Acknowledgements

We would like to thank R.J.J.H van Son and J.C. Mewes for translating publications reported in other languages in this study. This work was supported by a non-restricted research grant from ATOS Medical AB contributing to the existing infrastructure for health-related quality of life research of the department of Head and Neck Oncology and Surgery.

Conflict of interest

ATOS Medical AB had no involvement in the conduction of the study.

Appendix A

Table 1. Full set of keywords of the search strategy. All keywords were searched as MeSH term (or equivalent in Embase and Scopus), and in title and abstract unless stated otherwise.

Medical Devices	**Costs/ Reimbursement**	**Europe**	
Apparatus	Insurance, Health, Reimbursement	Europe*	Malta
Device Approval*	Budget*	European Union	Moldova
Device Recall*	Case Mix*	Albania	Monaco
Device* [title] or [tiab]	Cost Of Illness	Andorra	Montenegro
Equipment And Supplies	Cost-Benefit Analysis	Armenia	Netherlands
Equipment*	Cost-Benefit*	Austria	Norway
Instrument*	Cost-Control	Azerbaijan	Poland
Inventor*	Cost-Effect*	Belarus	Portugal
Medical Device Legislation	Costs And Cost Analysis	Belgium	Romania
Medical Device Recalls	Cost-Utilit*	Bosnia	Russia
Medical Device*	Diagnosis-Related Groups	Herzegovina	San Marino
Supplies	Drug Cost*	Bulgaria	Serbia
	Economic Burden	Croatia	Slovakia
Regulation	Economic Evaluat*	Cyprus	Slovenia
Government Regulation	Economics, Medical	Czech Republic	Spain
Regulat* [title] or [tiab]	Government	Denmark	Sweden
	Health Economics	Estonia	Ukraine
	Health Expenditures	Finland	United Kingdom
	Health Insurance For Aged	France	Vatican City
	Illness Burden	Georgia	
	Insurance Claim Review	Germany	
	Insurance Coverage	Greece	
	Insurance*	Hungary	
	Insurance, Health	Iceland	
	Marginal Analys*	Ireland	
	Medical Financ*	Italy	
	Medicare	Kazakhstan	
	Out-Of-Pocket	Kosovo	
	Pricing	Latvia	
	Reimbursement Mechanisms	Liechtenstein	
	Reimbursement*	Lithuania	
	Socioeconomic Factors	Luxembourg	
	Third Part* And Pay*	Macedonia	

Appendix B

List of abbreviations. Full (country-specific) forms of the abbreviations are given in this appendix. Country-specific forms are provided in italic.

AC	Autonomous community
AIMD	Active implantable medical device
ANSM	*Agence Nationale de Sécurité du Médicament et des Produits de Santé;* National Agency of Drug Safety and Health Products
AOTMiT	*Agencja Oceny Technologii Medycznych i Taryfikacji*; Agency for Health Technology Assessment and Tariff System
AWR	Approval With Research
BfArM	*Bundesinstitut für Arzneimittel und Medizinprodukte*; Federal Institute of Medicinal Products and MDs
BIA	Budget impact analysis
CCG	Clinical Commissioning Group
CE	*Conformité Européenne*; European Conformity
CEA	Cost-effectiveness analysis
CED	Coverage with evidence development
CEPS	*Comité Economique des Produits de Santé*; Economic Committee for Health Products
CNEDiMTS	*Comission Nationale d'Évaluation des Dispositifs Médicaux et des Technologies de Santé*; National Committee for the Evaluation of Medical Devices and Health Technologies
CUD	*Commissione Unica sui Dispositivi Medici*; Medical Device Committee
DIMDI	*Deutsche Institut für Medizinische Dokumentation und Information*; German Institute for Medical Documentation and Information
DRG	Diagnosis-related group
EACV	Expected added clinical value
EB	Expected benefit
EBM	*Einheitlicher Bewertungsmaßstab*; Statutory Health Insurance Physician Fee Schedule
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
G-BA	*Gemeinsame Bundesausschuss*; Federal Joint Committee
GOÄ	*Gebührenordnung für Arzte*; Private Health Insurance Physician Schedule
GMA	*Bundesärtekammer*; German Medical Association
GP*	General practitioner
HAS	*Haute Autorité de Santé*; French National Authority for Health
HTA	Health technology assessment
HRG	Healthcare resource group
ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio

IGeL	*Individuelle GesundheitsLeistungen*; Individual Health Services
InEK	*Institut für das Entgeltsystem im Krankenhaus*; Institute for the Hospital Remuneration System
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*; Institute for Quality and Efficiency in Healthcare
LEA	*Livelli Essenziali di Assistenza*; Essential levels of care
LPPR	*Liste des Produits et Prestations Remboursable;* List of products and services qualifying for reimbursement
MD*	Medical device
MDC	Major diagnostic categories
MDR	Medical Device Regulation
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	*Läkemedelsverket*; Medical Products Agency
NHI	National Health Insurance
NHS	National Health Service
NHSBSA	National Health Service Business Service Authority
NICE	National Institute for Health and Care Excellence
NUB	*Neue Untersuchungs- und Behandlungsmethoden*; New examination and treatment methods
OIR	Only In Research
OPS	*Operationen- und Prozedurenschlüssel;* German procedure classification
PHI	Private Health Insurance
PHRC	*Programme Hospitalier de Recherche Clinique;* Program for Hospital Clinical Research
PRME	*Programme de Recherche Médico-Economique*; Program for Medical Economic Research
RCT	Randomized controlled trial
SHI	Statutory Health Insurance
TAS	*Heil- und Hilfsmittelverzeichnis*; Therapeutic Appliance Schedule
TLV	*Tandvårds- och läkemedelsförmånsverket*; Dental and Pharmaceutical Benefits agency
UK	United Kingdom
US	United States
WHO	World Health Organization
ZIN	*Zorginstituut Nederland;* National Health Care Institute

*Non-official abbreviations used in the paper.

Appendix C

Extended version of Results section 3.2.2. Patient access.

Reimbursement procedures: inpatient and outpatient sectors

In France, medical devices (MDs) used in the inpatient sector are included in diagnosis-related groups (DRGs) [1,2]. Additional payments are used for innovative and costly devices, which are qualified when they are an implantable MD or the device is assigned to the list of products and services qualifying for reimbursement (*Liste des Produits et Prestations Remboursables* - LPPR). The LPPR is a list with reimbursable technologies used in the outpatient sector. The additional payment method can be requested by manufacturers and function as a conditional reimbursement scheme if the DRG system has not yet been updated, and therefore, uptake of the MD in the inpatient sector is avoided [3-5]. Devices that lead to a variety in costs when implemented, can apply for the supplementary list after registration on the LPPR [1]. From the literature, it is not clear whether the additional payment method and supplementary list define the same reimbursement process. In the outpatient sector, reimbursement of MDs occurs as a result of registration on the LPPR. Application to the LPPR has dichotomous pathways: application for registration under the 'generic line' or 'brand name'. Devices that apply for registration by the manufacturer under a generic line are placed under existing categories on the LPPR list. These MDs do not have to be accompanied with evidence data, whereby immediate registration on the LPPR is made possible. In case of an innovative MD or certain aspects of the MD need to be altered or revised, application under a brand name is necessary. The manufacturer is obligated to provide an application dossier containing a systematic search in the literature and clinical data, which has to be in accordance with the French regime, and can derive from similar devices [1,3,4,6]. The application dossier is assessed initially in terms of expected benefit (EB) and, when the EB is found to be positive, on the expected added clinical value (EACV). Assessment of EB comprises of three components: the benefit/risk ratio, the role of the MD during treatment and the public health impact. The EACV implies that the MD is compared to the current gold standard for treatment. The assessment is executed by the National Committee for the Evaluation of Medical Devices and Health Technologies (*Comission Nationale d'Évaluation des Dispositifs Médicaux et des Technologies de Santé* - CNEDiMTS), which is a subdivision of the French National Authority for Health (*Haute Autorité de Santé* - HAS). The CNEDiMTS gives either a positive or negative advice on the EB. In case of a positive advice, EACV is assessed. After EACV assessment, a number ranging from level 1 to 5 is assigned to the MD, whereupon MDs with the highest improvement level are ranked the highest (level 1) and no improvement is ranked as level 5 [1,3,6-8]. The Economic Committee for Health Products (*Comité Économique des Produits de Santé* - CEPS) determines the price of MDs in negotiation with the manufacturer, and is subject to reference pricing. Pricing of MDs relies on the advice of the CNEDiMTS (EACV assessment). The final decision on reimbursement is made by the Ministry of Health, that results in registration and

publication in the LPPR in case of a positive decision [2,4,6,7,9-11]. The LPPR is subdivided into four categories as stated by Loge et al. [6]. materials and treatments in the ambulatory care, dietary products and dressings (1), orthotics and prosthesis (2), implantable MDs (3) and assistive MDs (4). Once the MD is listed on the LPPR, registration is valid for five years. Devices on the LPPR are reimbursed by the National Health Insurance (NHI), that is funded mainly through employers' contributions and payroll deductions [1,2,4,6].

Germany maintains two general contrastive pathways for MDs regarding the inpatient and outpatient sectors when evaluating level of evidence requirements. In the inpatient sector in Germany, adoption of a MD is permitted without proving benefit unless the MD is rejected based on available evidence [12]. Devices enter the DRG if there is a suitable DRG and German procedure classification (*Operationen- und Prozedurenschlüssel* - OPS) available. The DRG system is a prospective payment system that is built up from major diagnostic categories (MDCs), which are further divided into (adjacent) DRGs depending on patient characteristics. If no suitable DRG exists, then the manufacturer has to file an application dossier for a new DRG group or OPS code. To establish a new DRG group, the hospital has to provide a dossier that informs on: the inappropriateness of the existing DRG groups, the related International Classification of Diseases (ICD) coding and OPS codes, and the proposal for a new DRG. When a new DRG grouping is proposed due to increasing costs caused by the MD, then the application should provide insight in costs and incremental cost-effectiveness ratio (ICER). The Institute for the Hospital Remuneration System (*Institut für das Entgeltsystem im Krankenhaus* - InEK) decides on new DRG grouping. The introduced MD can be applied for a new OPS code in case it is associated with a new procedure. The hospital has to deliver information on: the procedure, number of patients treated per year with the procedure, distribution of the MD across the country and details on costs and ICER. The German Institute for Medical Documentation and Information (*Deutsches Institut für Medizinische Dokumentation und Information* - DIMDI) organizes the OPS coding and assesses and decides on new procedures [13-16]. Reimbursement of inpatient care can also occur through supplementary payments from the hospital's budget, whereby a distinction is made in fixed and negotiated amounts that are deliberated at a central and hospital level respectively [5,14]. Among these aforementioned reimbursement manners that are included in the hospital's budget, innovative and costly MDs can also apply for local payments outside of this budget, known as new examination and treatment methods (*Neue Untersuchungs- und Behandelungsmethoden* - NUB). The application dossier contains similar information as the OPS code application, supplemented with information about innovative aspects of the device and an overview of available evidence for pricing purposes. The dossier is assessed by InEK. The price of the MD is negotiated between the hospital and the Statutory Health Insurance (SHI). Reimbursement by NUB is valid for one year and can bridge time until the DRG system has been updated [9,12-14,17]. Unlike the inpatient sector, MD uptake in the outpatient sector only occurs

when sufficient evidence is provided, including cost-effectiveness analysis [5,18]. Devices are either reimbursed by the SHI, roughly 90% of the population, or by the Private Health Insurance (PHI) (for employees that earn more than 50.000 per year) [19]. Devices that are used in the outpatient sector are included under the Statutory Health Insurance Physician Fee Schedule (*Einheitlichter Bewertungsmaßstab* - EBM). The device is assessed on effectiveness by means of a clinical study (randomized controlled trial (RCT) or intervention study) and on cost-effectiveness by means of a cost-effectiveness analysis (CEA) or budget impact analysis (BIA). The data is evaluated by the Institute for Quality and Efficiency in Healthcare (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* - IQWiG), which brings out an advice on the inclusion in the EBM. The final decision on EBM inclusion is made by the Federal Joint Committee (*Gemeinsame Bundesausschuss* - G-BA), a body that constitutes of key stakeholders, including hospitals, physicians, patients and health insurers [12,13,15-17]. MDs that are declined for the EBM, can be applied to an Individual Health Services (*Individuelle GesundheitsLeistungen* - IGeL) scheme. Application for the IGeL scheme consists of an overview of available evidence and costs. Uptake in the IGeL scheme means that the device is included in the service for self-paying patients [13]. MDs that are used in the ambulatory care are incorporated into the Therapeutic Appliance Schedule (*Heil und Hilfsmittelverzeihn*is - TAS. If the MD has a therapeutic effect, then the same procedure is applicable as for the EBM. MDs with no therapeutic effect are assessed based on their technical report and decided whether or to include in the TAS. Reimbursement of MDs included in the physicians' services in the outpatient sector occurs through the SHI through fee schedules [10,12,13,18]. For patients who are insured by the PHI, other schemes exist. Devices used in the outpatient sector have to be included in the Private Health Insurance Physician Schedule (*Gebührenordung für Ärtze* - GOÄ) to be reimbursed by PHI through fee schedules. An overview of available evidence is needed to apply for the GOÄ. In addition, information on the MD usage and costs has to be added for the purpose of pricing of the device. The decision regarding inclusion in the GOÄ is made by the German Medical Association (*Bundesärtekammer* - GMA) [13]. Pricing of the MD in the outpatient sector is formed through reference pricing or competition by means of public tendering [2]. MDs that are bought in the pharmacy are priced through negotiations with the National Association of Statutory Health Insurance Funds and the Federal Association of Pharmacists [20]. Additional payments are made by the patient if costs are higher than the reference price or if the patient chooses a more expensive device than recommended by health insurances. For the TAS, initial costs are provided by the patient when it concerns more costly assistive devices. Funding from the SHI derives from payments of employers and payroll deductions [2,5,19].

The United Kingdom (UK) has a grouping system for the inpatient sector, and that is similar to the DRG system: Healthcare Resource Group (HRG) system. Additional payments may be provided at a national level [2,5,9]. In the outpatient sector, MDs have to apply for inclusion on the

drug tariff list that is published on a monthly basis [2,10]. The application dossier requires data on (cost-)effectiveness if this involves innovative devices, devices accompanied by high costs or a high risk profile [5]. The National Institute for Health and Care Excellence (NICE) and the National Health Service Business Service Authority (NHSBSA) assess each application dossier on indication and makes recommendations on reimbursement in a process that is described as the 'Technology appraisal guidance' [21-24]. High budget impact MDs, when approved by NICE, are provided to the target population within three months of the guidance publication. For innovative devices that are potentially more effective than standard care, a 'Medical technology guidance' is available. After evaluation, NICE brings out an advice but it is not obligatory for National Health Service (NHS) to follow the advice. In case a new procedure or an innovative diagnostic MD is involved, the MD is applied to the 'Interventional procedure guidance' or 'Diagnostics guidance' respectively [21]. Pricing is set using mainly reference prices [5]. Central taxes fund the healthcare through the NHS. The funding of services is organized by decentralized Clinical Commissioning Groups (CCGs) [10,11].

In Italy, reimbursement of MDs is stipulated at a national level by the Ministry of Health and the MD Committee (*Commissione Unica sui Dispositivi Medici* – CUD). The Ministry of Health is advised by the CUD that manages a list of reimbursable MDs that were included based on (cost-)effectiveness analysis [9,10,25]. However, the actual access to MDs is arranged separately in the 20 Italian regions [2,9,26]. The inpatient sector is funded by regional per-case tariffs based on the DRG system of the US [2,9,26,27]. Pricing of some devices (e.g. knee prosthesis, coronary stents) is decided at a national level using reference prices. Additional payments may be accessible when approved in negotiation with central or regional authorities at a hospital level [5,9,26]. MDs used in the outpatient sector are assessed per region and require international both data and data collection in the respective region. The funding is provided by the NHS derived from central and regional taxes. MDs are covered in the 'essential levels of care' (*Livelli Essenziali di Assistenza* - LEA). However, the LEA does not explicitly define care that is reimbursed, which leaves room for interpretation leading to heterogeneous provision of care in the different regions [11,25-28].

Spain has also has a decentralized system, which is provided at the level of the autonomous communities (ACs) and is paid out of a global hospital's budget in the inpatient sector [5,10,26]. Reimbursement of MDs depend on the contract program that is agreed between the hospital and regional authorities and other payers [26]. Additional payments have been reported in Spain [5]. Pricing is determined by a fixed profit margin [9]. The procedure concerning the outpatient sector was described similar to that of Italy [10]. Central and regional taxes are the main funding sources [26].

Sweden consists of 21 regions with 290 municipalities. Dahlberg et al. [29] describes a decentralized system for assistive devices. Regions and municipalities organize provision of these devices.

Decisions on reimbursement are made by an independent governmental organization, the Dental and Pharmaceutical Benefits agency (*Tandvårds- och läkemedelsförmånsverket* - TLV). Reimbursement is assured through tax income [23,29].

Temporary reimbursement procedures

Throughout the EU, certain programs are available to provide (early) patient access to innovative MDs by arranging conditional reimbursement and simultaneously fostering evidence collection that is necessary to prove the device's (cost-)effectiveness. Among others, the coverage with evidence development (CED) program is a known program that is implemented in France, Germany, the UK and the Netherlands [3,12].

CED in France provides reimbursement over at least a two year period. Application is not possible, but instead the CNEDiMTS selects suitable candidates for the program and assesses the application. The Ministry of Health selects MDs that will enter the CED program, which is completely funded by the NHI. In addition, two local research programs are available: the Program for Hospital Clinical Research (*Programme Hospitalier de Recherche Clinique* - PHRC) and the Program for Medical Economic Research (*Programme de Recherche Médico-Economique* - PRME). PHRC and PRME programs are in-hospital programs for which researchers of hospital departments can apply in response to a tender. An independent expert team assesses each application dossier and decides on the PHRC, used for fundamental research, and PRME, used for economic evaluation [3,4,12].

The dossier for applying to CED in Germany can be filed by manufacturers, impartial members or patient representatives of the G-BA, the regional and federal associations of SHI physicians and the federal association of SHI funds. The application dossier includes data on available evidence, information on the potential of the device, a proposal for clinical evaluation and the estimated costs [13]. IQWiG is responsible for evaluating that the application conforms to criteria mentioned in Olberg et al. [12]: validity, plausibility and applicability. Subsequently, the G-BA makes the final decision on incorporation in the CED. Such a program is partially funded by the SHI, whereas the remainder is funded by the manufacturer, including repayment after reimbursement [3,12,13].

In the UK, application for CED is assessed by NICE. The CED program is offered in different forms: the MD is applied in clinical practice with additional evidence collection ('Approval With Research' (AWR)) or is only used for research purposes ('Only In Research' (OIR)). CED is reimbursed by various stakeholders, including the NHS and the manufacturer [3,12].

In the Netherlands, the Ministry of Health selects MDs that are eligible for CED. Data on (cost-) effectiveness of the MD is gathered throughout the program. Each clinical study is funded by the Netherlands Organization for Health Research and Development and other payers (e.g. manufacturers) [5,12].

References Appendix C

1. Guillou J. Medical device reimbursement in France process of decision. [French, English] Remboursement des dispositifs medicaux en France processus de decision. *STP.* 2011;Pharma Pratiques. 21(5):425-432.
2. Schreyogg J, Baumler M, Busse R. Balancing adoption and affordability of medical devices in Europe. *Health Policy.* 2009;92(2-3):218-224.
3. Martelli N, van den Brink H. Special funding schemes for innovative medical devices in French hospitals: The pros and cons of two different approaches. *Health Policy.* 2014;117(1):1-5.
4. Gilard M, Debroucker F, Dubray C, et al. Scientific evaluation and pricing of medical devices and associated procedures in France. *Therapie.* 2013;68(4):201-208.
5. Sorenson C, Drummond M, Burns LR. Evolving reimbursement and pricing policies for devices in Europe and the United States should encourage greater value. *Health affairs (Project Hope).* 2013;32(4):788-796.
6. Loge P, Delalande F, Reymond MC, Germain S. FACTORS INFLUENCING REIMBURSEMENT OF MEDICAL DEVICES IN FRANCE. *Int J Technol Assess Health Care.* 2015;31(6):399-406.
7. Parquin F, Audry A. Clinical evaluation of medical devices: Main constraints and specificities. *Therapie.* 2012;67(4):311-318.
8. Boudard A, Martelli N, Prognon P, Pineau J. Clinical studies of innovative medical devices: What level of evidence for hospital-based health technology assessment? *Journal of Evaluation in Clinical Practice.* 2013;19(4):697-702.
9. Wilkinson G, Drummond M. Impact of reimbursement policies on the adoption of medical devices in an outpatient setting. *Health Policy and Technology.* 2014;3(4):281-286.
10. Schafer E, Schnell G, Bobakova T. Diabetes device reimbursement in the EU-5. *J Diabetes Sci Technol.* 2013;7(4):1084-1092.
11. Cornago D, Garattini L. The stoma appliances market in five European countries: a comparative analysis. *Applied health economics and health policy.* 2002;1(1):43-50.
12. Olberg B, Perleth M, Busse R. The new regulation to investigate potentially beneficial diagnostic and therapeutic methods in Germany: Up to international standard? *Health Policy.* 2014;117(2):135-145.
13. Schwander B, Krone FA, Walzer S. Clinical and health economic evidence requirements for obtaining health insurance coverage for innovative medical devices in Germany. *Value in Health.* 2013;16 (7):A474.
14. Henschke C, Baeumler M, Gaskins M, Busse R. Coronary stents and the uptake of new medical devices in the German system of inpatient reimbursement. *Journal of Interventional Cardiology.* 2010;23(6):546-553.
15. Hessel F. Reimbursement for high-priced innovative medical devices in a DRG-based hospital care system: the German situation. *Expert review of pharmacoeconomics & outcomes research.* 2005;5(4):377-381.
16. Moller B, Stockheim M, Kraus T, Weber A. [Medical innovations in the area of conflict between certification and allowance]. *Deutsche medizinische Wochenschrift (1946).* 2010;135(42):2088-2092.

17. Zens Y, Fujita-Rohwerder N, Windeler J. [Benefit assessment of medical devices]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz.* 2015;58(3):240-247.

18. Schaefer E, Karch A. Reimbursement for Diabetes Medical Devices in Germany. *J Diabetes Sci Technol.* 2014;8(1):186-187.

19. Winkelmann P. REHADAT: The German information system on assistive devices. In. Vol 292011:163-169.

20. Graf Von Der Schulenburg JM, Mittendorf T, Kulp W, Greiner W. Health Technology Assessment (HTA) for medical devices - Do the same rules apply? 2009;14(3):144-155.

21. Campbell B. Regulation and safe adoption of new medical devices and procedures. *British Medical Bulletin.* 2013;107(1):5-18.

22. Dobbs H. Current developments and the medical device directive - A regulator's perspective. *IDrugs.* 2007;10(4):253-255.

23. Frønsdal K, Pichler F, Mardhani-Bayne L, et al. Interaction initiatives between regulatory, health technology assessment and coverage bodies, and industry. 2012;28(4):374-381.

24. Altenstetter C. EU and member state medical devices regulation. *International Journal of Technology Assessment in Health Care.* 2003;19(1):228-248.

25. Scroccaro G, Steffenino G, Marini P, Trippoli S, Santarlasci B. Costs and benefits of medical devices. The case of drug-eluting stents. [Italian] La valutazione dei benefici e dei costi dei dispositivi medici. Il caso degli stent medicati. *PharmacoEconomics - Italian Research Articles.* 2005;7(3):195-206.

26. Cappellaro G, Fattore G, Torbica A. Funding health technologies in decentralized systems: A comparison between Italy and Spain. *Health Policy.* 2009;92(2-3):313-321.

27. Finocchiaro Castro M, Guccio C, Pignataro G, Rizzo I. The effects of reimbursement mechanisms on medical technology diffusion in the hospital sector in the Italian NHS. *Health policy (Amsterdam, Netherlands).* 2014;115(2-3):215-229.

28. Hertz D, Marcarelli AD, Patel L, Garfield S. Adoption of new technologies in twenty established and emerging markets. *Value in Health.* 2012;15 (7):A323-A324.

29. Dahlberg R, Blomquist UB, Richter A, Lampel A. The service delivery system for assistive technology in Sweden: Current situation and trends. *Technology and Disability.* 2014;26(4):191-197.

Appendix D

Table 2c. Extracted data from literature on the payer, funding source and healthcare system in seven EU countries.

Country	Payer	Funding source	Healthcare system
France	NHI	Employers' payments and payroll deductions	Bismarck
Germany	SHI (90%), PHI (10%)	Employers' payments and payroll deductions	Bismarck
UK	NHS	Central taxes	Beveridge
Italy	NHS	Central and regional taxes	Beveridge
Spain	NHS	Regional taxes and national budgets	Beveridge
Netherlands	-	-	-
Sweden	-	Taxes	Beveridge

Sources: Summary of available data derived from the publications in the reference list.

Abbreviations: NHI, National Health Insurance; NHS, National Health Service; PHI, Private Health Insurance; SHI, Statutory Health Insurance; UK, United Kingdom.

Chapter 3

Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries

Ann-Jean C.C. Beck
Valesca P. Retèl
Michiel W.M. van den Brekel
Wim H. van Harten

Oral Oncol. 2019 Apr;91:56-64.
doi: 10.1016/j.oraloncology.2019.02.017.

Abstract

Objectives

Patient access to the voice prosthesis and heat and moisture exchanger (HME) is not always guaranteed in Europe. Therefore, the aim of this qualitative study is to evaluate factors influencing physician's prescription and reimbursement of these devices in eight European countries, and to identify barriers of and facilitators to effective patient access.

Materials and methods

In this mixed methods study, we conducted a survey among stakeholders evaluating prescription (Part 1 of the survey), reimbursement (Part 2), and barriers of and facilitators to effective patient access (Part 3). Part 1 was completed by head and neck surgeons employed in France, Germany, the United Kingdom, Italy, Spain, Belgium, the Netherlands and Poland. Part 2 and 3 were completed by medical device company representatives in respective countries, followed by semi-structured interviews.

Results

Based on the survey, filled in by 36 surgeons, all prescribed the voice prosthesis. Four surgeons didn't prescribe the HME in Italy and Poland due to lack of both reimbursement and experience/training, and feeling uncomfortable with device use. Most restrictive factors (e.g. increased workload, insufficient staff) occurred in countries with decentralized healthcare systems including Spain and Italy.

Conclusion

Non-HME-usage was influenced by economical and physician-related factors. Restrictive factors were related to limited regional device reimbursement and provision. Nationwide reimbursement, guideline implementation, support for physicians by training/education and providing a rehabilitation team will increase device use.

Introduction

As the survival rate of patients with head and neck cancer (HNC) continues to improve over the past years, attention has been growing towards survivorship and rehabilitation care [1]. After total laryngectomy, rehabilitation of HNC survivors focuses on restoration of functions such as the ability to phonate and the improvement of pulmonary function. Placement of a voice prosthesis, an internal valve which is implanted in the tracheoesophageal wall, gives optimal voice rehabilitation [2,3]. The heat and moisture exchanger (HME) minimizes pulmonary problems by providing stoma occlusion and ensuring humidification, heating and filtering of inhaled air [4–7]. In addition, the utilization of voice prostheses and HMEs has contributed to the improvement of patients' quality of life (QoL) [3,5–8].

Yet, in spite of the valuable role of the voice prosthesis and HME, device access for laryngectomy patients, defined in this study as 'effective patient access', is not always provided in the European Union (EU) [9]. Effective patient access is enabled by reimbursement and prescription practices, which may be driven by the physician's knowledge as well as perceived ease of use and usefulness of the device [10–12].

Factors influencing device's ease of use and usefulness can be evaluated by the Technology Acceptance Model (TAM) described by Davis et al. [12]. TAM is commonly used to understand how the behavioral intention and actual usage of a device are influenced. This framework consists of the key elements that can properly facilitate the exploration of factors that affect physicians' decisions to prescribe the voice prosthesis and HME.

Evidence on the prescription of medical devices (in general) is scarce and dependent on the device type. Furthermore, information regarding reimbursement in different EU countries remains incomplete [11,13]. Publications specifically related to prescription and reimbursement of the voice prosthesis and HME mostly describe reimbursement issues (e.g. lack of reimbursement, restrictions to reimbursement dependent on a maximum amount or number of devices provided) in EU countries (see details in Appendix A) [9,14–18]. A comprehensive overview of prescription practices and reimbursement systems of the voice prosthesis and HME could bring forth insights to improve effective access.

Therefore, the aim of this mixed methods study is to evaluate factors influencing prescription and reimbursement of voice prostheses and HMEs, and to identify barriers to and facilitators of effective patient
access in the EU.

Materials and methods

We performed a survey among head and neck surgeons and medical device representatives to study patient access in eight EU countries. Sequentially, we conducted interviews with the representatives to gather into-depth insights from the supplier perspective into the barriers and facilitators identified in the survey.

Online survey

An online survey was developed focusing on: physician's prescription (Part 1) and reimbursement (Part 2) of voice prostheses and HMEs, and barriers to and facilitators of effective patient access (Part 3). Part 1 was completed by head and neck surgeons who treated laryngectomy patients in Belgium, France, Germany, Italy, the Netherlands, Poland, Spain and the UK. As head and neck surgeons play a key role in the provision of both devices in the EU, we selected them to complete the first survey of the study. The contact details of the surgeons were obtained through the networks of some healthcare professionals employed at the Netherlands Cancer institute (NKI-AVL). All surgeons were sent an e-mail with information regarding the study including a survey link for participation. A minimum of three to four respondents per country was decided upon a priori. Part 2 and 3 were completed by representatives (managers) (n=8) employed at a medical device company in the respective countries. Because the representatives are wellversed with policy- and practice-related matters regarding device use, it was assumed that they could provide a representative overview on device reimbursement and access at a national level.

In Part 1 of the online survey, various factors influencing prescription of both devices were questioned by applying the TAM (Fig. 1) [12]. TAM is considered to be a robust model and is often used in Information Technology (IT). According to TAM, two beliefs – the perceived usefulness and perceived ease of use – determine the attitude towards using the technology, thereby also affecting behavioral intention and use. These beliefs are influenced by multiple external factors [19]. Based on the available literature and input from a multidisciplinary panel, we identified important possible factors to consider and defined the questions [19]. The panel consisted of clinicians, experts in the field of health technology assessment and the head of clinical affairs of a device company. Also, the innovativeness was characterized by the diffusion theory of Rogers [20]. Five categories were distinguished within the external factors: organizational, economical, clinical, physician- and patient-related. Each category contains several factors, shown in Fig. 1, which were covered with at least one item in the survey. In addition, two items reflected the behavioral intention and actual use of the devices.

Multiple choice items regarding the reimbursement of voice prostheses and HMEs (Part 2) were developed based on publications included in a previous systematic literature review [11,21–26]. The items reflected key aspects of reimbursement described in the review.

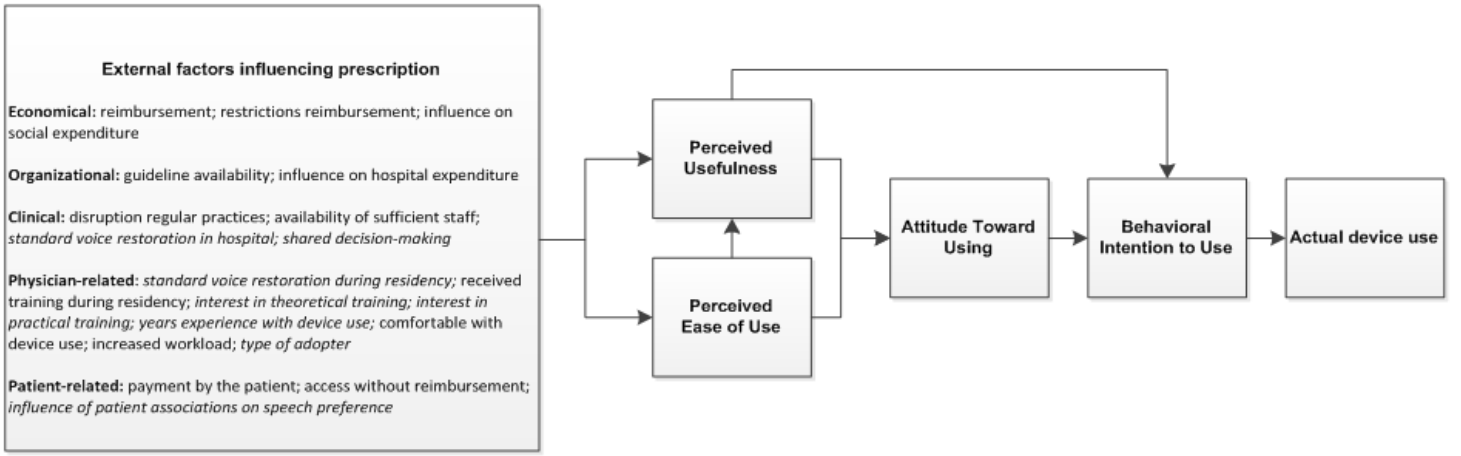

Figure 1. Technology Acceptance Model (TAM) of voice prosthesis and HME utilization. Most external factors are outlined in Table 2. The remaining factors are stated in italic in the figure.

These aspects included: reimbursement scheme (e.g. hospital budget), level of reimbursement (e.g. national, regional), restrictions to reimbursement and type of payer (e.g. health insurer, out of pocket payment). Questions were addressed for both devices separately.

Part 3 of the survey comprised of open items concerning barriers to and facilitators of effective patient access to the voice prosthesis and HME, and asked at the reimbursement, physician's and patient's level.

Before dissemination, the survey was reviewed by a team of experts consisting of researchers specialized in the field of health technology assessment, speech-language pathologists (SLPs) and head and neck surgeons involved in laryngectomy rehabilitation prior to the start of the study. To prevent the occurrence of missing data, the online tool required completion of all questions in the survey.

Semi-structured interviews

Semi-structured telephone interviews were carried out with each representative of the medical device industry by both the first author and a research assistant. Part 2 and 3 of the survey, including a combination of multiple choice and open items, were used to perform a more in-depth exploration of the barriers to and facilitators of effective patient access reported in the survey. If necessary, data from the survey was confirmed and clarified with the respondents.

Analysis

Available data in the literature was compared across EU countries. In Part 1, the external factors were interpreted as either having a facilitating or restrictive effect on the actual device use, in case the majority (>50%) of the respondents indicated the factors to be favorable or unfavorable of device prescription respectively. The results of the survey were analyzed by utilization (users versus non-users) and country.

The semi-structured interviews were recorded and transcribed verbatim by two trained typists. Subsequently, the first author coded text fragments according to: type of factor (barrier/facilitator), type of device (voice prosthesis/HME) and level of access (reimbursement/physician/patient). Coding of the fragments, performed by the first author, was checked by the second author. Next, the coding was confirmed by the representatives. Results were compared among EU countries.

Results

Survey and semi-structured interviews

Part 1: Physician's prescription of the voice prosthesis and HME

In total, 36 out of 110 head and neck surgeons employed in 30 different hospitals in Belgium (n=4), France (n=6), Germany (n=5), Italy (n=4), the Netherlands (n=6), Poland (n=5), Spain (n=3) and the UK (n=3) completed the survey. Table 1 provides an overview of their demographics. Most respondents were male (83%) and employed in an academic center (89%). Of the surgeons, 81% performed >10 total laryngectomies annually.

Table 1. Demographics of respondents (head and neck surgeons).

Characteristics	Total no. (%)
Sex	
Male	30 (83)
Female	6 (17)
Country	
France	6 (17)
Netherlands	6 (17)
Germany	5 (14)
Poland	5 (14)
Belgium	4 (11)
Italy	4 (11)
Spain	3 (8)
UK	3 (8)
Hospitals	
No. of hospitals	30
Academic	32 (89)
Non-academic	3 (8)
Cancer center	1 (3)
No. of total laryngectomies per year	
5-10	7 (19)
>10	29 (81)
Years experience (average (range))	
Voice prosthesis	17 (3-33)
HME	11 (0-30)

Abbreviations: HME, heat and moisture exchanger; UK, United Kingdom.

First, we analyzed the data focusing on the group of non-users compared to the users. All 36 surgeons were experienced in fitting voice prostheses. Four (11%) surgeons in Poland (n=3) and Italy (n=1) did not use HMEs in practice. Three of these surgeons had the intention to use HMEs, and one surgeon did not report his intention. Absence of reimbursement was reported by all non-users. Lack of training/experience and feeling uncomfortable with HME use were reported by Polish non-users. The non-users confirmed that these factors were restrictive on the actual use.

Second, we evaluated the effect of the factors across EU countries. In Table 2, the effect (restrictive or facilitating) of the factors on access to the voice prosthesis are displayed per country (complete overview including the HME is provided in Appendix B). Most notable results are outlined in this section. In the Netherlands and the UK, no restrictive factors were identified. The UK was the only country where responses regarding reimbursement were inconclusive, meaning answers varied (answered by respondents: 'yes', 'sometimes', 'no', or 'I don't know') and no majority was identified. In Belgium, reimbursement was available but restricted to five voice prostheses and 200 HMEs per patient yearly. Here, hospital guidelines for both devices were available for two of the four surgeons. Poor guideline implementation was the only restrictive factor mentioned by the majority of respondents in France (n=5) and Germany (n=3). Decrease of the social expenditure by HME implementation was expected in Germany (n=3) [27]. In Italy, the reimbursement of voice prostheses was restricted to the number provided per year, and surgeons experienced increased workload through use of voice prostheses (n=3) and HMEs (n=2). In addition, the majority reported absence of guidelines. In Poland, the HME was not reimbursed but paid by the patient (n=3). Furthermore, the HME was not available in their hospital. Increase in hospital and social expenditure by the HME was reported by 4 surgeons. With regard to Spain, no device guidelines were available. In addition, device implementation was thought to reduce societal costs, but increase hospital expenditure (n=2). Insufficient staff, lack of HME training, and increased physician workload by device implementation were reported (n=2).

Third, the remaining factors (in italic in Fig. 1) were analyzed. Most hospitals used tracheoesophageal speech as the standard care for voice restoration, whereas two hospitals in France and Italy applied standard esophageal speech. Standard care as taught during residency consisted of tracheoesophageal speech (n=22) and esophageal speech (n=14). Surgeons in Italy, Spain and Poland were interested in practical and theoretical device training. Innovativeness was questioned in the survey according to Rogers' diffusion theory. Most surgeons (n=20) reported to be early adopters, 10 surgeons were late majorities, including the Polish non-HME-users, and six were innovators [20]. Thirty surgeons reported shared decision-making. In addition, most respondents in Germany, France, Italy and Poland indicated that patient associations (promoting either tracheoesophageal, esophageal speech or electrolarynx) have an impact on speech preference of patients.

Table 2. Survey results: Factors influencing physician's prescription of the voice prosthesis (n=36).

		Voice prosthesis							
		B (n=4)	G (n=5)	N† (n=6)	UK (n=3)	F (n=6)	S (n=3)	I (n=4)	P (n=5)
ECONOMICAL	Reimbursement	Y*	Y*	Y*	IC	Y*	Y*	Y*	Y*
	Restrictions reimbursement	Y*	N*	N	N	N*	N*	IC	N
	Influence on social expenditure	IC	N	IC	IC	IC	N	NK	Y
ORGANIZATIONAL	Guideline availability	IC	N	Y*	Y	N	N*	N*	Y*
	Influence on hospital expenditure	IC	N	NK	IC	N	Y	IC	N
CLINICAL	Disruption of regular practices	N	N	N	N	N	N	N	N
	Availability of sufficient staff	Y*	Y*	Y*	Y*	Y	N	Y*	Y
PHYSICIAN-RELATED	Residency: Received training	Y*	Y*	Y*	Y*	Y	Y	Y*	Y*
	Comfortable with device use	Y*	Y*	Y*	Y*	Y*	Y*	Y	Y
	Increased workload	IC	N	IC	N*	N	Y	Y	N
PATIENT-RELATED	Payment by the patient	N*	N*	N*	N*	N*	N*	N*	N
	Access without reimbursement	IC	NA	NA	NA	NA	NA	NA	NA

Legend:
The abbreviations used in the table are explained below the table. The overview is based on answers that were given by the majority (>50%) of respondents. When the respondents' answers were uniform (e.g. all respondents answered 'yes'), this is indicated with an asterisk ('Y*'). In case respondents' answers to the question varied within a country and no majority could be identified, this was stated as inconclusive (IC).

Responses that are interpreted as facilitating to effective patient access are marked in green; responses that are interpreted as restrictive to effective patient access are marked in red. No influence is indicated without markings. Grey markings were given when answers were inconclusive, or in case the majority answered 'I don't know' or 'not applicable'.

'Influence on social expenditure' was defined as the impact of device implementation in practice on the societal costs (e.g. positive influence of device use on return to work reduces cash benefits for unemployed patients) derived from the definition stated by the Organisation for Economic Co-operation and Development (OECD) [27].
'Influence on hospital and social expenditure': 'Y' indicates that the device use results in an increase in the expenditure; 'N' indicates that the device use has no influence (not marked) or results in a decrease in expenditure (marked in green).

Abbreviations: B. Belgium; F, France; G, Germany; I, Italy; IC, inconclusive; N†, Netherlands; N, no; NA, not applicable; NK, not known; P, Poland; S, Spain; UK, United Kingdom; Y, yes.

Part 2: Reimbursement systems

Table 3 provides an overview of the reimbursement systems applied to the voice prosthesis and HME in the EU.

Belgium applies a lump sum in the inpatient sector. The lump sum is dependent on the maximum price per voice prosthesis and a fixed number of HMEs (regardless of the unit price). The sum is mainly funded by the Belgian National Health Insurance (NHI). In addition, a small contribution is made by the patient quarterly. Excess costs are paid by the hospital or the patient.

In France, the voice prosthesis and HME are funded by the NHI in the outpatient sector through a list of products and services qualifying for reimbursement (*Liste des Produits et Prestations Remboursable* – LPPR) under the generic line (existing categories) and brand name (innovative devices) respectively.

Table 3. Survey and interview results: Reimbursement of the voice prosthesis and HME (n=8).

Country	Device	Reimbursement method	Funding by IP or OP	Payer
Belgium	VP	Lump sum	IP	NHI + contribution patient
	HME	Lump sum	IP	NHI + contribution patient
France	VP	Itemized billing[b]	OP	NHI
	HME	Itemized billing[b]	OP	NHI
Germany	VP	1. DRG + flat rate 2. DRG + itemized billing	1. IP + OP 2. IP + OP	1. SHI 2. PHI
	HME	1. DRG + flat rate 2. DRG + itemized billing	1. IP + OP 2. IP + OP	1. SHI 2. PHI
Italy	VP	Per case tariffs	IP	NHS (Regions)
	HME	None	NA	NHS (HD) or patient
Netherlands	VP	DRG-based	IP	PHI + contribution patient
	HME	Itemized billing[b]	OP	PHI + contribution patient
Poland	VP	Hospital budget[a]	IP	NHS
	HME	None	NA	Patient
Spain	VP	Hospital budget[a]	IP	MOH
	HME	Itemized billing[b]	OP	NHS
UK	VP	Hospital budget[a]	IP	NHS
	HME	Itemized billing[b]	OP	NHS

Abbreviations: DRG, diagnosis-related group; HD, health histrict; HME, heat and moisture exchanger; IP, inpatient; MOH, Ministry of Health; NA, not applicable; NHI, National Health Insurance; NHS, National Health Service; OP, outpatient; PHI, Private Health Insurance; UK, United Kingdom; SHI, Statutory Health Insurance; VP, voice prosthesis.

[a]No direct reimbursement but indirectly funded by the NHS/MOH.

[b]Reimbursement list.

Reimbursement in Germany is dependent on the type of insurance: the Statutory (SHI) or Private Health Insurance (PHI). The (first) devices applied postoperatively are included in the diagnosis-related group (DRG) of the laryngectomy. During follow-up, devices are reimbursed under the flat rate system. The system provides a monthly fixed amount covering (unlimited) rehabilitation care including nurses. The PHI insures through 'itemized billing': patients order at the medical device company and receive an invoice for the insurer.

In Italy, the voice prosthesis is paid through per-case tariffs (DRG-based) funded regionally through the Italian National Health Service (NHS). The HME is paid by the health districts or the patient.

In the Netherlands, the voice prosthesis is provided nationally using a DRG-based DBC (*Diagnose Behandel Combinatie)* system. The HME is incorporated in a reimbursement list and funded through itemized billing. Patients pay an annual fixed amount, 'the own risk excess', after which the device costs are covered by the PHI.

The hospital budget pays for the voice prosthesis in Poland. The budget is funded by the NHS post factum. The HME is paid by the patients.

Spain and the UK also fund the voice prosthesis out of the hospital budget, which is provided by the Ministry of Health (MOH) and NHS respectively. The HME is incorporated in a reimbursement list funded through itemized billing.

Part 3: Barriers to and facilitators of effective patient access to voice prosthesis and HME
Barriers and facilitators are outlined in Table 4 per level of access.

Lack of reimbursement is a barrier to access the HME in Poland and Italy, resulting in out of pocket payment by the patient. Restrictions on budget and device provision were mentioned in Belgium (e.g. fixed lump sum) and Poland (e.g. hospital budget and incentives of health policy makers). In Germany, an unrestricted flat rate system is applied, whereas provision may be constrained when distributors are not profitable. The presence of reimbursement or access to a reimbursement list was mentioned as a facilitator in the Netherlands and the UK.

Positive opinions on the device as well as device support from hospitals (e.g. political lobby), patient associations, healthcare professionals (e.g. informing patients) and manufacturers were reported among Belgium, Italy and Spain. In Germany and France, absence of support by the physician and patient associations negatively affected prescription and utilization respectively.

Table 4. Survey and interview results: Barriers of and facilitators to effective access to voice prosthesis and HME according to the different levels (reimbursement/physician/patient). Further explanation on the barriers and facilitators is provided in Part 3 of the Results section (n=8).

	BARRIERS	FACILITATORS
	REIMBURSEMENT LEVEL *What are barriers of and facilitators to reimbursement of the voice prosthesis and HME?*	
Belgium	• No reimbursement beyond the fixed amount of the lump sum • Provision by hospital pharmacies is dependent on the lump sum	• Support from patient associations and academic hospitals
Germany	• Healthcare provision is sometimes restricted under the flat-rate system when it becomes non-profitable for distributors	
Italy		• Development of a national guideline • Collaborations of manufacturers with the Health Ministry
Netherlands		• Availability of clinical evidence
Poland	• Incentives of health policy makers: decision-making regarding reimbursement • Budget restrictions by the hospital[a]	
Spain		• Positive opinion of physicians[a]
UK		• Listing on the Drug Tariff[b]
	PHYSICIAN'S LEVEL *What are barriers of and facilitators to physician's prescription of the voice prosthesis and HME?*	
France	• Physicians are not convinced[a] • Lack of education of physicians[a] • Workload of physicians: providing rehabilitation care[a] • Lack of collaboration between physicians and SLPs after treatment[b]	• Availability of clinical evidence[a]
Italy	• Voice teachersprefer esophageal speech[a] • Workload of physicians: providing rehabilitation care[a] • Lack of rehabilitation personnel[a] • No reimbursement[b]	
Netherlands		• Reimbursement of the device
Poland	• No national guideline available[a] • Complications in the past[a] • Incentives of hospital directories: maintaining traditional treatment regime[a] • Workload: administration/documentation during replacements[a] • No reimbursement[b]	• Education of physicians[a]

Spain	• Workload of physicians: providing rehabilitation care[a] • Lack of experience with rehabilitation by physicians[a] • Complications in the past[a]	• Rehabilitation team with SLPs[a] • Positive opinion of physicians[b]
UK	• Complications in the past[a]	• Education of physicians, SLPs and patients[a]
	PATIENT'S LEVEL *What are barriers of and facilitators to patient's utilization of the voice prosthesis and HME?*	
Belgium		• Support from SLPs and physicians[a] • Support from SLPs and patient associations[b]
France	• Social isolation of patients[a] • Utilization is no priority to patients[b]	• Education of patients on the device • Previous experiences of patients with the device
Germany	• No support from patient associations[b]	• Unrestricted healthcare provision provided by flat rate system[b]
Italy	• Patient associations and voice teachers prefer esophageal speech[a] • Tradition of patients not to wear a HME[b] • Payment by patient[b]	
Netherlands		• Perceived quality of the device • Improvement of quality of life of patients by using the device • Ease of use of the device
Poland	• Lack of education of patients[a] • Hospital admission for VP replacement[a] • Payment by patient[b]	
Spain	• Secondary puncture[a]	• Support from manufacturers and healthcare professionals[a] • Education of patients[a]
UK	• Complications in the past[a] • Lack of education of patients[a] • Negative performance of the device[b]	• Ease in speaking and voice quality[a] • Long device lifetime[a] • Improving breathing[b]

Abbreviations: HME, heat and moisture exchanger; SLP, speech language pathologist; UK, United Kingdom; VP, voice prosthesis.
[a]Related to only the voice prosthesis.
[b]Related to only the HME.

Available clinical evidence on the device is a facilitator to access in the Netherlands and France. Guideline implementation has a positive influence on reimbursement in Italy, whereas guideline absence was reported in Poland.

Increased physician workload by device prescription (e.g. providing rehabilitation care, administration) and a lack of rehabilitation personnel was stated in France, Italy, Poland and Spain. In Spain, a rehabilitation team with SLPs is sometimes facilitated to support the physician.

(Lack of) education or experience of patients and healthcare professionals (SLPs and physicians) were mentioned either as a barrier or facilitator (France, Spain, Poland and the UK).

Positive device-specific features mentioned in the Netherlands and the UK included quality of the device, ease of use, performance (e.g. improvement of voice quality and QoL) and device lifetime. Complications or negative experiences related to the device were hindering access in the Poland, Spain and the UK.

Other barriers to physician's prescription or patient's utilization that were mentioned: preferred esophageal speech (Italy), maintenance of traditions related to non-usage (Poland and Italy), isolation of and prioritization by patients (France), secondary puncture for voice prosthesis placement (Spain) and the requirement for hospitalization during voice prosthesis replacement (Poland).

Discussion

To our knowledge, this is one of the first studies in the HNC field presenting drivers to prescription and reimbursement of voice prostheses and HMEs in eight EU countries. In addition, this analysis included identification of barriers to and facilitators of effective patient access. Access to the voice prosthesis was established through (indirect) funding and prescription by all respondents. The HME was not reimbursed in Poland and Italy. At the individual level, four surgeons did not prescribe the HME. Compared to the HME-users, the four non-HME users encountered specific restrictive factors including absence of reimbursement, lack of experience/training of the surgeons and feeling uncomfortable with the HME usage. At a country-based level, most restrictive factors were identified for Poland, Spain and Italy, and included – among the factors related to non-users – increased physician workload and insufficient number of staff. Guideline absence was stated by respondents from Germany, France, Spain and Italy. From the interviews, restrictions to reimbursement (e.g. fixed lump sum), lack of physician's and patient's education, increased workload and complications after device use were the most common barriers. Most common facilitators to effective patient access were providing education to healthcare professionals and patients, and support from healthcare professionals regarding the device.

Our results were in accordance with findings on device access in literature. In our study, absence of reimbursement applied to all nonusers in Italy and Poland, although most of them had the intention to use HMEs. Thus, financial reimbursement is an important barrier in physician's prescription, and the representatives stated this accordingly. This was also found in the study of Van der Houwen et al., describing a large difference in adhesives utilization by laryngectomized patients between reimbursing and non-reimbursing countries [16]. In studies previously published

on cardiac implantable devices and transcatheter aortic valve (TAVR) implants utilization, similar results were observed [28,29]. In addition, the frequency of prosthesis replacements is dependent on the country's reimbursement system, as DRG-based systems enable adequate device access (e.g. regular prosthesis replacements) in contrary to hospital budgets which are being led by restrictions on funding [18]. For instance, the voice prosthesis is replaced six times per year in the Netherlands, whereas in Spain this was reported to be only three times [30,31]. Within the EU, countries with regional autonomy such as Italy and Spain encounter more barriers to effective patient access. As a consequence, device utilization is lower in these countries than those with national reimbursement (data not shown). Decentralized healthcare systems are more susceptible to variations in device reimbursement (e.g. funding at the hospital level) and differences in provision between the regions, of which the latter is strongly dependent on physician-related factors [32]. In this study, physician-related factors for non-usage included lack of training during residency and feeling uncomfortable with using the device. Three of the four non-users tend to start using the device in a late stage of device diffusion, whereas most users were early adopters. At the physician level, Cappellaro et al. also described the cultural background of the physician as to impact device provision [11]. At an organizational level, absence of guidelines was a restrictive factor for device provision reported in four out of eight countries. This barrier was also described by Boriani et al. for cardiac device implementation [33].

Several limitations should be taken into account. To identify factors influencing device prescription, comparing data of users and non-users is inevitable. Although we believe that the responses of the 36 surgeons provided a good representation of current practices, a small bias cannot be excluded. We may not have captured all the possible variation within each country. This may be caused because we either did not identify non-users of the voice prosthesis in the sample of the study, or the non-users did not respond. For instance, we know that in most countries where utilization of the voice prosthesis is not optimal, (e.g. Spain and Italy) many patients still rely on esophageal speech. This selection bias may be caused by the fact that, although we achieved to include 30 hospitals in this study, most responding surgeons were employed in an academic hospital. Also, as the degree of concentration of HNC care differs among EU countries, some variation in the restrictive factors may not have been identified in countries with less concentrated care. A possible limitation of the study is that only representatives employed at one medical device company participated in the study. On the other hand, there are only two leading companies in the EU and no differences exist in device reimbursement and patient access. Some discrepancies were found in responses from surgeons and representatives. Regarding reimbursement-related issues, representatives focused on reimbursement systems, whereas surgeons' responses also included other financial support (e.g. health districts in Italy). Barriers and facilitators were partly obtained from device company representatives, who might be biased as they also represent other interests (e.g. device marketing). Several strengths of the study include applying the TAM framework to evaluate device use, and the involvement of

various stakeholders in the survey. This study is unique because, to our knowledge, this is the first study in the field of HNC to provide insight on reimbursement as well as prescription of HNC-specific devices, and on facilitating and restrictive factors affecting patient device use in eight EU countries. Ultimately, these results can be used in optimizing access to these devices.

For further research, we recommend obtaining more data from nonusers of the voice prostheses and HMEs, especially in (regions of) countries with lower device utilization, e.g. where esophageal speech is still standard of care. A larger sample size would also allow for the performance of statistical analyses of differences in reimbursement and device use across EU countries or intercontinentally (e.g. EU versus North-America). Conducting semi-structured interviews with surgeons, particularly non-users, could be a next step to deepen drivers to device prescription. In addition, device-related factors should be included as external factors in the TAM, as suggested by Venkatesh et al. to identify the impact of the device and its outcomes on prescription practices [19].

Several implications for clinical practice come forth. Providing national reimbursement of HMEs in Poland and Italy is essential to increase utilization. In addition, introducing more flexibility in reimbursement systems such as the hospital budget and lump sum for the voice prosthesis in Poland and Belgium respectively could increase access to patients. Uniformity in device access and use in France, Germany, Italy and Spain could be achieved by national guideline implementation. At the physician level, increased workload during in the follow-up and rehabilitation phase could be alleviated by providing support from health professionals in countries such as Spain, Poland, France and Italy. Finally, physician's and patient's lack of training and experience with the device could be addressed during and after residency by means of continuous education.

Conclusion

In this mixed-methods study, factors associated with non-prescription were, apart from the absence of reimbursement – a key driver to effective patient access –, lack of training/experience and feeling uncomfortable with device use. Restrictive factors to device access were identified often in decentralized healthcare systems in countries such as Spain and Italy leading to lower device utilization. From this study, we recommend nationwide reimbursement and guideline implementation on both devices, and the availability of a rehabilitation team to support the physician in healthcare provision. Furthermore, inexperienced physicians as well as patients should be trained and educated e.g. by competent professionals and supported by manufacturers. For further research, it is recommended to gain more data from non-users, investigate device-related factors, and conduct interviews with physicians to deepen causality between external factors and actual use of the voice prosthesis and HME.

References

1. Gatta G, Botta L, Sanchez MJ, Anderson LA, Pierannunzio D, Licitra L. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study. Eur J Cancer 2015;51(15):2130–43.
2. van Sluis KE, van der Molen L, van Son RJ, Hilgers FJ, Bhairosing PA, van den Brekel MW. Objective and subjective voice outcomes after total laryngectomy: a systematic review. Eur Arch Otorhinolaryngol 2018:1–16.
3. Clements KS, Rassekh CH, Seikaly H, Hokanson JA, Calhoun KH. Communication after laryngectomy: an assessment of patient satisfaction. Arch Otolaryngol-Head Neck Surgery 1997;123(5):493–6.
4. Ackerstaff AH, Hilgers FJ, Balm AJ, Aaronson NK, van Zandwuk N. 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.
5. 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.
6. Hilgers FJ, Aaronson NK, Schouwenburg PF, Zandwijk N. The influence of a heat and moisture exchanger (HME) on the respiratory symptoms after total laryngectomy. Clin Otolaryngol 1991;16(2):152–6.
7. Ackerstaff A, Hilgers F, Aaronson N, Schouwenburg P. Physical and psychosocial sequelae of total larynx extirpation and the use of a heat and moisture exchanger. Ned Tijdschr Geneeskd 1990;134(50):2438–42.
8. Hilgers FJ, Ackerstaff AH, Aaronson NK, Schouwenburg PF, Zandwijk N. Physical and psychosocial consequences of total laryngectomy. Clin Otolaryngol 1990;15(5):421–5.
9. van der Molen L, Kornman AF, Latenstein MN, van den Brekel MW, Hilgers FJ.Practice of laryngectomy rehabilitation interventions: a perspective from Europe/the Netherlands. Curr Opin Otolaryngol Head Neck Surg. 2013;21(3):230–8.
10. Basu S, Hassenplug JC. Patient access to medical devices–a comparison of U.S. and European review processes. N Engl J Med. 2012;367(6):485–8.
11. Cappellaro G, Fattore G, Torbica A. Funding health technologies in decentralized systems: a comparison between Italy and Spain. Health Policy 2009;92(2–3):313–21.
12. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Quarterly 1989:319–40.
13. Schreyogg J, Baumler M, Busse R. Balancing adoption and affordability of medical devices in Europe. Health Policy 2009;92(2–3):218–24.
14. Betlejewski S, Ossowski R, Sinkiewicz A. Rehabilitation after total laryngectomy– vision and realization. Otolaryngol Pol 2007;61(3):344–8.
15. Ten Hallers EJ, Marres HA, Rakhorst G, Hagen R, Staffieri A, Van Der Laan BF, et al. Difficulties in the fixation of prostheses for voice rehabilitation after laryngectomy. Acta Otolaryngol 2005;125(8):804–13.
16. 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.
17. Wierzchowska M, Burduk PK. Early and late complications after implantation of the Provox 2 voice prosthesis in patients after total laryngectomy. Otolaryngol Pol 2011;65(3):184–7.

18. Zimmer-Nowicka J, Morawiec-Sztandera A. Causes and indwelling times of multiple voice prosthesis replacements in patients after total laryngectomy–analysis of 184 replacements in 42 patients. Otolaryngol Pol 2012;66(5):322–7.
19. Venkatesh V, Bala H. Technology acceptance model 3 and a research agenda on interventions. Decision Sci 2008;39(2):273–315.
20. Rogers EM. Diffusion of innovations. Simon and Schuster; 2010.
21. Olberg B, Perleth M, Busse R. The new regulation to investigate potentially beneficial diagnostic and therapeutic methods in Germany: up to international standard? Health Policy 2014;117(2):135–45.
22. Martelli N, van den Brink H. Special funding schemes for innovative medical devices in French hospitals: the pros and cons of two different approaches. Health Policy 2014;117(1):1–5.
23. Parquin F, Audry A. Clinical evaluation of medical devices: main constraints and specificities. Therapie 2012;67(4):311–8.
24. Guillou J. Medical device reimbursement in France process of decision. [French, English] Remboursement des dispositifs medicaux en France processus de decision. STP. Pharma Pratiques 2011;21(5):425–32.
25. Loge P, Delalande F, Reymond MC, Germain S. Factors influencing reimbursement of medical devices in France. Int J Technol Assess Health Care 2015;31(6):399–406.
26. Schwander B, Krone FA, Walzer S. Clinical and health economic evidence requirements for obtaining health insurance coverage for innovative medical devices in Germany. Value Health 2013;16(7):A474.
27. Social Expenditure Last accessed: 28-1-2019. [updated 13-3-2003. Available from: https://stats.oecd.org/glossary/detail.asp?ID=2485.
28. Mylotte D, Osnabrugge RL, Windecker S, Lefevre T, de Jaegere P, Jeger R, et al. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. J Am Coll Cardiol 2013;62(3):210–9.
29. Mairesse GH, Braunschweig F, Klersy K, Cowie MR, Leyva F. Implementation and reimbursement of remote monitoring for cardiac implantable electronic devices in Europe: a survey from the health economics committee of the European Heart Rhythm Association. EP Europace 2015;17(5):814–8.
30. Mayo-Yanez M, Cabo-Varela I, Dovalo-Carballo L, Calvo-Henriquez C, Martinez- Moran A, Gonzalez-Botas JH. Provox 2® and Provox Vega® device life-time: a casecrossover study with multivariate analysis of possible influential factors and duration. Eur Arch Otorhinolaryngol 2018:1–4.
31. Petersen JF, Lansaat L, Timmermans AJ, van der Noort V, Hilgers FJ, van den Brekel MW. Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period. Head Neck 2018.
32. Castro MF, Guccio C, Pignataro G, Rizzo I. The effects of reimbursement mechanisms on medical technology diffusion in the hospital sector in the Italian NHS. Health Policy 2014;115(2–3):215–29.
33. Boriani G, Burri H, Mantovani LG, Maniadakis N, Leyva F, Kautzner J, et al. Device therapy and hospital reimbursement practices across European countries: a heterogeneous scenario. Europace 2011;13(suppl_2):ii59–65.

Acknowledgements

We would like to thank K. Jóźwiak PhD, J.C Mewes and R. Ots, for their practical support in translating articles reported in other languages than English and conducting the study. This work was supported by a non-restricted research grant from Atos Medical AB contributing to the existing infrastructure for health-related quality of life research of the department of Head and Neck Oncology and Surgery.

Conflict of interest statement

This work was supported by a non-restricted research grant from Atos Medical AB contributing to the existing infrastructure for healthrelated quality of life research of the department of Head and Neck Oncology and Surgery. Atos Medical AB had no involvement in the development of the study.

Role of funding source

Atos Medical AB had no involvement in the development of the study.

Appendix A

In the European Union (EU), patient access to the voice prosthesis is hindered by its costs, which is reported to be 1200 euros on a yearly basis per patient in the Netherlands. Frequent replacement of the voice prosthesis is costly, which therefore has an additional financial impact on the healthcare system [1]. Utilization of adhesives is dependent on its funding, as 58% of patients used the adhesive when it was reimbursed compared to 9% of patients in countries where it was not reimbursed [2]. Reimbursement is often provided in EU countries when the added value of the device such as the heat and moisture exchanger (HME) is endorsed. Also, data on cost-effectiveness will increasingly play an important role in decision-making regarding reimbursement of devices [3].

Reimbursement of devices used in laryngectomy rehabilitation was reported in countries such as the Netherlands, the UK, Scandinavia, Switzerland and Croatia [3]. Whereas in Poland, the voice prosthesis is reimbursed but the HME and starter kits including inhalers, products for the tracheostoma and skincare are not provided in spite of negotiations with the Ministry of Health, Sickness Funds and National Health Fund [3,4]. Adhesives are reimbursed in the Netherlands, Belgium and France, but are not funded in Italy, Spain and Portugal. In Belgium and Germany, reimbursement is restricted to a maximum amount [3].

Three Polish articles provided additional information on Poland [4-6]. In Poland, reimbursement of two voice prostheses is provided by the National Health Fund annually. However, the number of voice prostheses reimbursed is restricted by the lack of reimbursement and the timing of replacement is subject to reimbursement rules [5]. Additional reimbursement is needed for tracheoesophageal speech, and healthcare insurances should take into account extra costs in case of more frequent replacements due to complications e.g. leakage of the prosthesis. Financial support for laryngectomy rehabilitation by the National Fund for Disabled people is provided but not guaranteed. Consequently, rehabilitation care is organized based on social initiatives, and it has been proposed to apply esophageal speech as a primary treatment to lower the costs [4,6].

Prescription practices were only reported for Poland, describing that patients do not receive rehabilitation care by public health services after hospital discharge [4]. In addition, apart from the health-related factors of the patient and device reimbursement, the number of voice prosthesis replacements per patient is dependent on the experience of the physician [5].

References Appendix A

1. Ten Hallers EJ, Marres HA, Rakhorst G, et al. Difficulties in the fixation of prostheses for voice rehabilitation after laryngectomy. *Acta Otolaryngol.* 2005;125(8):804-813.
2. 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):235-241.
3. van der Molen L, Kornman AF, Latenstein MN, van den Brekel MW, Hilgers FJ. Practice of laryngectomy rehabilitation interventions: a perspective from Europe/the Netherlands. *Curr Opin Otolaryngol Head Neck Surg.* 2013;21(3):230-238.
4. Betlejewski S, Ossowski R, Sinkiewicz A. [Rehabilitation after total laryngectomy--vision and realization]. *Otolaryngol Pol.* 2007;61(3):344-348.
5. Zimmer-Nowicka J, Morawiec-Sztandera A. [Causes and indwelling times of multiple voice prosthesis replacements in patients after total laryngectomy--analysis of 184 replacements in 42 patients]. *Otolaryngol Pol.* 2012;66(5):322-327.
6. Wierzchowska M, Burduk PK. [Early and late complications after implantation of the Provox 2 voice prosthesis in patients after total laryngectomy]. *Otolaryngol Pol.* 2011;65(3):184-187.

Appendix B

Survey results: Factors influencing physician's prescription of the voice prosthesis and HME (n=36).

		Voice prosthesis								HME							
		B (n=4)	G (n=5)	N† (n=6)	UK (n=3)	F (n=6)	S (n=3)	I (n=4)	P (n=5)	B (n=4)	G (n=5)	N† (n=6)	UK (n=3)	F (n=6)	S (n=3)	I (n=4)	P (n=5)
ECONO-MICAL	Reimbursement	Y*	Y*	Y*	IC	Y*	Y*	Y*	Y*	Y*	Y*	Y*	IC	Y*	Y	Y	N
	Restrictions reimbursement	Y*	N*	N	N	N*	N*	IC	N	Y	N	N*	N	N	N	IC	NA
	Influence on social expenditure	IC	N	IC	IC	IC	N	NK	Y	IC	N	IC	IC	IC	N	NK	Y
ORGANI-ZATIONAL	Guideline availability	IC	N	Y*	Y	N	N*	N*	Y*	IC	N	Y*	Y	N	N*	N	IC
	Influence on hospital expenditure	IC	N	NK	IC	N	Y	IC	N	IC	N	NK	IC	N	Y	IC	Y
CLINICAL	Disruption of regular practices	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	NA
	Availability of sufficient staff	Y*	Y*	Y*	Y*	Y	N	Y*	Y								
PHYSICIAN-RELATED	Residency: Received training	Y*	Y*	Y*	Y*	Y	Y	Y*	Y*	Y	Y*	Y	Y	Y	N	Y*	N
	Comfortable with device use	Y*	Y*	Y*	Y*	Y*	Y*	Y	Y	Y*	Y*	Y*	Y*	Y	Y	Y*	N
	Increased workload	IC	N	IC	N*	N	Y	Y	N	IC	N	IC	N	N	Y	IC	NA
PATIENT-RELATED	Payment by the patient	N*	N*	N*	N*	N*	N*	N*	N	N*	N*	N	N	N*	N	N	Y*
	Access without reimbursement	IC	NA	NA	NA	NA	NA	NA	NA	IC	NA	NA	NA	IC	NA	NA	N

Legend:
The abbreviations used in the table are explained below the table. The overview is based on answers that were given by the majority (>50%) of respondents. When the respondents' answers were uniform (e.g. all respondents answered 'yes'), this is indicated with an asterisk ('Y*'). In case respondents' answers to the question varied within a country and no majority could be identified, this was stated as inconclusive (IC).

Responses that are interpreted as facilitating to effective patient access are marked in green; responses that are interpreted as restrictive to effective patient access are marked in red. No influence is indicated without markings. Grey markings were given when answers were inconclusive, or in case the majority answered 'I don't know' or 'not applicable'.
'Availability of sufficient staff' (written in italics) was not asked separately for both devices. Responses are shown in the table of the voice prosthesis (boxes are hatched in the table for the HME).

'Influence on social expenditure' was defined as the impact of device implementation in practice on the societal costs (e.g. positive influence of device use on return to work reduces cash benefits for unemployed patients) derived from the definition stated by the Organisation for Economic Co-operation and Development (*OECD*) [1].
'Influence on hospital and social expenditure': 'Y' indicates that the device use results in an increase in the expenditure; 'N' indicates that the device use has no influence (not marked) or results in a decrease in expenditure (marked in green).

Abbreviations: B. Belgium; F, France; G, Germany; HME, heat and moisture exchanger; I, Italy; IC, inconclusive; N†, Netherlands; N, no; NA, not applicable; NK, not known; P, Poland; S, Spain; UK, United Kingdom; Y, yes.

References Appendix B

1. SOCIAL EXPENDITURE. Last accessed: 28-1-2019.; https://stats.oecd.org/glossary/detail.asp?ID=2485.

Part III

(Cost-)effectiveness of head and neck rehabilitation and quality of life

Chapter 4

Guideline implementation and adherence in cancer rehabilitation: A nation-wide survey among Dutch head and neck cancer centers

Ann-Jean C.C. Beck*
Ellen Passchier*
Valesca P. Retèl
Martijn M. Stuiver
Lisette van der Molen
Arash Navran
Wim H. van Harten**
Michiel W.M. van den Brekel**
*First author
**Last author

Submitted

Abstract

Purpose

In 2012 a national evidence-based cancer rehabilitation guideline was developed to achieve optimal cancer rehabilitation. Nevertheless, in head and neck cancer (HNC) rehabilitation, considerable practice variation is observed. The aim of this study was to evaluate guideline implementation and adherence in all 14 Dutch HNC centers, and explore associated factors.

Methods

We conducted a national survey covering five themes: 1) organizational structure; 2) rehabilitation modules; 3) financial matters; 4) barriers and facilitators for rehabilitation provision; 5) satisfaction and future improvements. The items were derived from the national cancer rehabilitation guideline and quality domains of the Institute of Medicine. Respondents were healthcare professionals of the dedicated rehabilitation team and employees of financial departments.

Results

Most centers (86%) applied a type of rehabilitation protocol. Four centers (29%) had implemented the national guideline, of which two centers (14%) fully adhered to its recommendations. The most endorsed facilitators were attitude, motivation and expertise of healthcare professionals, and availability of a contact person and informing patients on HNC rehabilitation The most endorsed barriers included patient's comorbidity, transport (time), patients' health literacy, financial capacity, patients' motivation, and reimbursement. No clear associations were found between barriers and facilitators and guideline implementation.

Conclusion

Implementation of and adherence to the national cancer rehabilitation guideline was limited. Most facilitators were clinician-oriented, whereas barriers were patient-related. Directions for guideline implementation, tailored patient interventions, multidisciplinary meetings and rehabilitation-specific reimbursement could optimize national HNC rehabilitation.

Introduction

In the Netherlands, 3200 patients are diagnosed with head and neck cancer (HNC) annually [1]. After treatment, patients are often left with functional problems such as dysphagia, altered speech, shoulder disability, fatigue, severe deconditioning and/or psychosocial problems. These limitations can affect their daily life activity and as such their ability to participate in society, hence reducing health-related quality of life (HRQoL). Due to the variety and complexity of these – often interrelated – problems, HNC patients require specialized and personalized rehabilitation.

In 2012, a national multidisciplinary cancer rehabilitation guideline was published by the Netherlands Comprehensive Cancer Organization (*Integraal Kankercentrum Nederland* - IKNL). The guideline aims to support optimal cancer rehabilitation, in terms of timely and personalized supportive care for adult individuals with any type of cancer, during and after treatment [2,3]. The guideline was updated in 2017 and is based on best-available evidence, which includes level 1 evidence, regarding the positive effect of cancer rehabilitation on restoring HRQoL and improving physical functioning [4-7].

From the guideline, a framework was developed that includes important aspects of cancer rehabilitation: signaling of symptoms; patient referral; diagnosis (intake) and interventions; effect evaluation and patient empowerment [2,3]. The framework focuses on rehabilitation of patients with, or at risk for, late effects throughout the cancer care continuum. This includes recommendations on triaging to either mono-, multi- or interdisciplinary rehabilitation, based on complexity and inter-relatedness of patient's problems. The rehabilitation plan consists of interventions, provided by (a dedicated team of) various healthcare professionals (e.g. physiotherapist, dietitian, psychologist), with a multi- or interdisciplinary approach [3,8]. Before and after rehabilitation, effect evaluation should take place by means of validated instruments to objectify the results [3,9].

Due to the complexity of treatment and rehabilitation, HNC care in the Netherlands is centralized in eight academic/cancer centers and six satellite centers. Medical specialists, as well as researchers, and health care professionals are organized in the Dutch Head and Neck Society (DHNS) for rules and regulations. Nevertheless, in HNC rehabilitation considerable practice variation is observed. Practice variation has also frequently been reported for implementation of and adherence to other guidelines for cancer treatment, with adherence figures ranging from 40 to 99% [10-15].

Internationally, several initiatives have been taken to provide guidelines on multidisciplinary care during HNC treatment and rehabilitation, with the objective to optimize patients' life after treatment [8,16-21]. However, few studies report a personalized and goal-oriented approach such as described in the cancer rehabilitation guideline [22,23]. In addition, little evidence is available yet regarding the extent to which guideline implementation occurs.

Obtaining insight into the organization of rehabilitation provided in clinical practice and related barriers and facilitators is necessary to understand variations in guideline implementation and adherence [10]. Currently, an overview including these aspects and possible factors of influence is lacking.

Therefore, the objectives of this study are to (1) evaluate the implementation of and adherence to the national cancer rehabilitation guideline, in the context of HNC rehabilitation as offered in 14 Dutch HNC centers; and (2) identify factors associated with implementation. The aim of this study is to gain insights that can provide direction in the optimization of multidisciplinary rehabilitation for HNC patients on a national, and possibly international level.

Methods

In this cross sectional study, the term cancer rehabilitation is used as defined by the Dutch National Health Care Institute (*ZorgInstituut Nederland* – ZIN): 'care that focusses on functional, physical, psychological and social problems related to cancer, including supportive and rehabilitation care' [2]. Accordingly, 'rehabilitation' was used as an umbrella term for mono-, multi-, and interdisciplinary care.

Online survey

We constructed an online survey, which consisted of 86 multiple choice and open questions. The first questions (n=5) queried information on characteristics of survey respondents. Next, the survey contained five sections: organizational structure of the respondents institute (Section 1; n=28), locally available rehabilitation modules (Section 2; n=32); financial matters (Section 3; n=10); barriers and facilitators for rehabilitation provision (Section 4; n=8) and health professionals' satisfaction and suggestions for future improvements (Section 5; n=3) Based on function, respondents were referred to discipline specific parts of the questionnaire (Figure 1). Section 1 of the survey was designed according to the framework of the Dutch cancer rehabilitation guideline [3]. Barriers and facilitators in section 3 were based on the six domains of the Institute of Medicine (IOM) [24]. Design and background of the survey can be found in Appendix A.

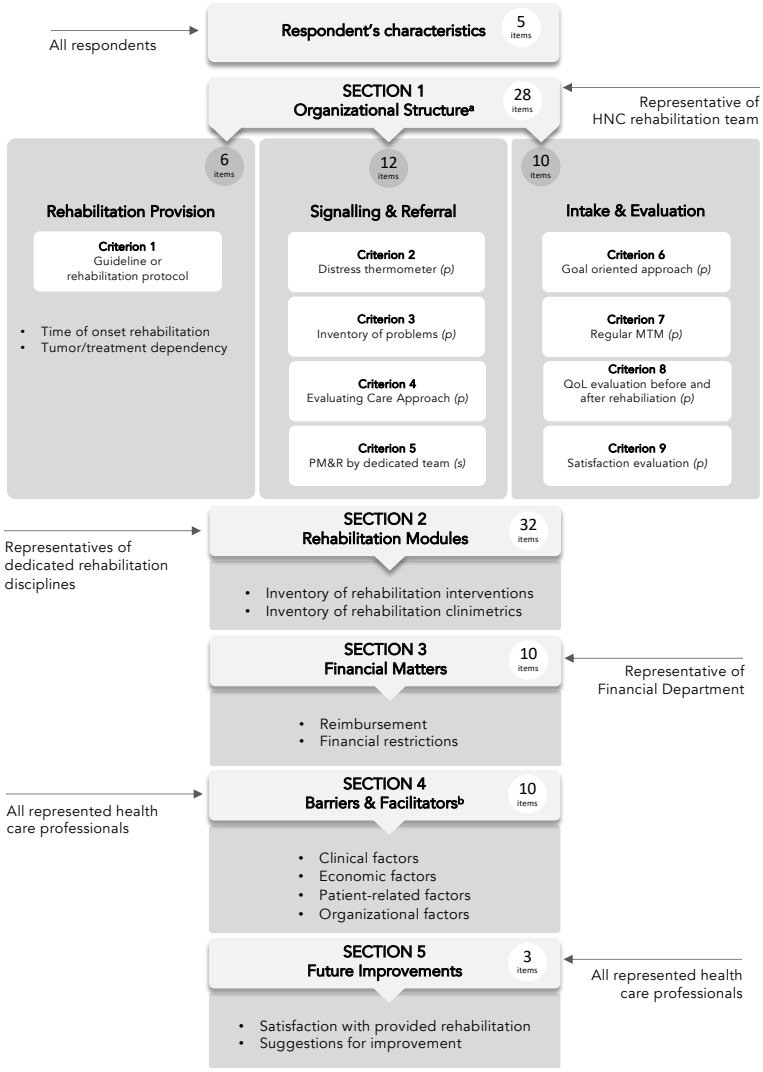

Figure 1. Structure and content of the survey.

Criteria were based on recommendations of the national cancer rehabilitation guideline. The criteria were either structural indicators (s) or process indicators (p). Survey respondents: The representative of the team was a chairman of the DHNS (head and neck surgeon, radiotherapist), nurse specialist or PM&R physician. The representative of the disciplines comprised of healthcare professionals of the dedicated rehabilitation team. If available, each discipline answered items related to the discipline. The representative of the Financial Department comprised of a manager or employee of the department.

Abbreviations: MTM, multidisciplinary team meeting; PM&R, physical medicine and rehabilitation; QoL, quality of life; DHNS, Dutch Head and Neck Society.

[a]Based on recommendations guideline cancer rehabilitation.

[b]Barriers and facilitators were based on the six domains of the Institute of Medicine, in total 43 items 24.

Survey respondents

The survey was sent out in 2017 and completed by professionals involved in the clinical or financial aspects of HNC rehabilitation in the Netherlands. All 14 Dutch HNC centers were approached through the chairman of the DHNS.

Section 1 was completed by (at least) one representative of the HNC rehabilitation team of each center; a medical specialist or oncology nurse specialist. For the second section, each chairman indicated which of the disciplines were involved in their dedicated rehabilitation team. Based on their response, at least one representative (healthcare professional) of each available discipline was asked to fill in their part of the survey. In addition, all items on barriers and facilitators (Section 4) and satisfaction and suggestions for future improvements (Section 5) were completed by all respondents. Managers and/or employees at the Financial Department of each hospital responded to Section 3 and the second part of the economic category of Section 4 (three items).

The survey was disseminated in collaboration with the DHNS by sending a link to the respondents which referred to an online platform [25]. The online platform required completion of all items which resulted in no missing values.

If sections were completed in duplicate (i.e. because two representatives had responded) and showed discrepancies, these were resolved by email contact.

Data analysis

The data was analyzed within and between centers using descriptive analysis. Each of the 9 criteria was scored separately per center to assess whether it was satisfied or not. An inventory of the Top 7 items reported as most frequent reported barriers and facilitators was made.

The results were also observed to assess patterns between subgroups based on type of center (academic versus non-academic), geographic location (rural versus urban) and function (medical specialist versus disciplines). Ultimately, possible associations between barriers and facilitators and the extent to which the guideline was implemented and adhered according to the 9 criteria, was evaluated. Hypothesis tests were not performed due to the small sample sizes per center.

Analysis was conducted in IBM SPSS Statistics 22.

Results

Characteristics of survey respondents

All 14 HNC – eight main HNC academic/cancer centers and six affiliated non-academic centers – were approached and responded in full. We included 113 respondents. Most respondents were female (73%, 82/113 respondents), and their mean age was 45.7 years. Section 1 was completed by head and neck surgeons mostly (48%, 13/27 respondents). Seventy healthcare professionals completed Section 2, of which most respondents were SLP (23%, 16/70 respondents), dietitian (21%, 15/70) and physiotherapist (17%, 12/70), if disciplines were not available, the responses to corresponding these items were consequently also not available. Section 3 was completed by DBC (*diagnose behandel combinatie* – Dutch diagnosis-related group (DRG)) consultants (44%, 7/16 respondents), employees (31%, 5/16) and managers (25%, 4/16) of the Financial Department. Mean years of experience was 12 years on average (Table 1).

Indications of rehabilitation provision

Rehabilitation (mono-, multi, or interdisciplinary) care was mostly provided on a regular basis (according to protocol, 64%, 9/14 centers), on indication (21%, 3/14 centers) or both (14%, 2/14 centers). Rehabilitation was initiated either before treatment (93%, 13/14 centers), during (57%, 8/14 centers) and/or after (57%, 8/14 centers) treatment. In 4 centers (29%, 4/14), the extent of rehabilitation provision was dependent on tumor type (most often late stage laryngeal, oropharyngeal and nasopharyngeal cancer) and in 2 centers (14%, 2/14) dependent on treatment modality (radiotherapy or surgery and chemoradiation). Various national and/or local guidelines and protocols were used for care provision, of which the national guideline on detecting the need for psychosocial care (n=8) and department's protocols (n=6) were the most applied (Figure 2) [26].

Survey results

Section 1: Organizational structure

From the 14 centers, four centers (29%, 4/14 centers) had implemented the national cancer rehabilitation guideline in practice (Table 2). Of these four, two centers (14%, 2/14 centers) met all our criteria. Four other centers (29%, 4/14), which worked according to a local protocol and the national guideline detection need for psycho-social care, did not meet four or more criteria; of which in three centers the criteria were unmet regarding the intake and evaluation phase, and in one center regarding the signaling and referral phase.

The criteria regarding inventory of patient's problems and utilization of the distress thermometer were mostly met (93%; 13/14 centers). The criteria that were least often met were guideline implementation (29%, 4/14 centers) and QoL effect evaluation (21%, 3/14 centers).

Table 1. Characteristics of survey respondents of 14 Dutch head and neck cancer centers.

		Respondents to Section 1: Organizational structure (%)	Respondents to Section 2: Rehabilitation modules (%)	Respondents to Section 3: Financial matters (%)	Total respondents (%)
Number of respondents (n)		27	70	16	113
Mean age, y (range)		50.4 (31-64)	45.1 (24-64)	40.3 (25-63)	45.7 (24-64)
Sex					
	Male	13 (48.1)	12 (17.1)	5 (31.3)	30 (26.5)
	Female	14 (51.9)	58 (82.9)	11 (68.8)	83 (73.5)
Function					
	Head and neck surgeon	13 (48.1)			13 (11.5)
	Nurse specialist	12 (44.4)			12 (10.6)
	Radiotherapist	1 (3.7)			1 (0.9)
	PM&R physician	1 (3.7)			1 (0.9)
	Art therapist		2 (2.9)		2 (1.8)
	Dietitian		15 (21.4)		15 (13.3)
	Medical social worker		9 (12.9)		9 (8.0)
	Occupational therapist		3 (4.3)		3 (2.7)
	Psychiatrist		1 (1.4)		1 (0.9)
	Psychiatric nurse (specialist)		4 (5.7)		4 (3.5)
	Psychologist		7 (10.0)		7 (6.2)
	Physiotherapist		12 (17.1)		13 (11.5)
	Speech-language therapist		16 (22.9)		16 (14.2)
	DBC* consultant			7 (43.8)	7 (6.2)
	Employee Financial Dept.			5 (31.3)	5 (4.4)
	Manager Financial Dept.			4 (25)	4 (3.5)
Institute					
	Academic/cancer center	13 (48.1)	46 (65.7)	10 (62.5)	69 (61.1)
	Non-academic center	14 (51.9)	24 (34.3)	6 (37.5)	44 (38.9)
Mean work experience, y (range)		14.3 (2-32)	12.4 (1-40)	6.3 (1-20)	12.0 (1-40)

Abbreviations: DBC, *diagnose behandel combinatie;* Dept., Department; PM&R physician, physical medicine and rehabilitation physician.

*A DBC is a Dutch diagnosis-related group (DRG).

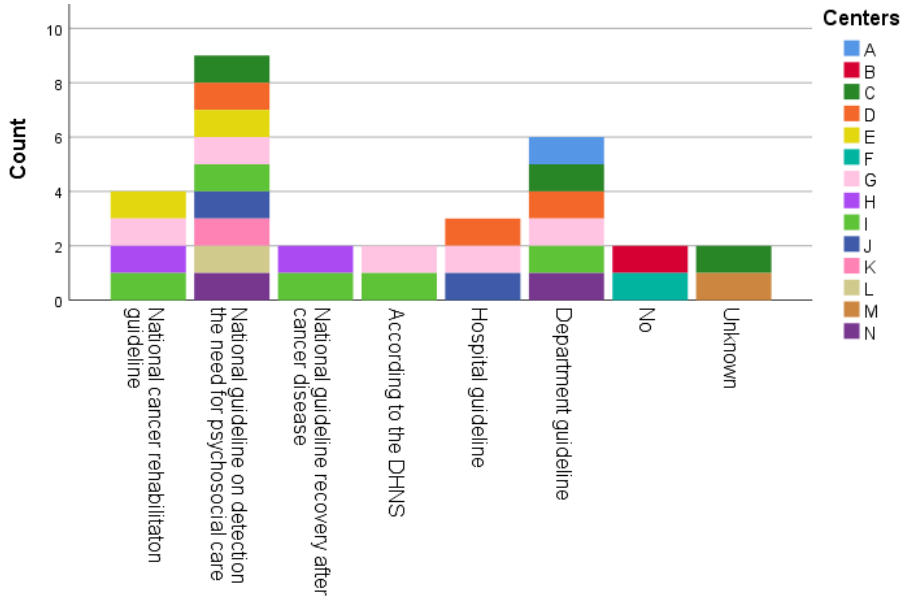

Figure 2. Guideline implementation among 14 Dutch head and neck cancer centers

NB: Center L reported that guideline adherence is not (always) feasible due to staff capacity

Abbreviations: DHNS; Dutch Head and Neck Society

Section 2: Rehabilitation modules

A detailed overview of clinimetrics used and interventions provided per discipline is provided in Appendix B, for each center. A dietitian, physiotherapist and speech-language pathologist were available in all centers, whereas a psychiatric nurse (specialist) (n=4 centers), occupational therapist (n=3), art therapist (n=2) and psychiatrist (n=1) were part of rehabilitation in only 4 centers or less. A medical social worker and a psychologist were involved in the team in eight and seven centers, respectively. Most centers (11/14) in which certain disciplines were not part of the dedicated team reported to refer patients either within the hospital, or to external primary care givers, as indicated. This concerned physiotherapy (n=2), nutritional care (n=1), occupational therapy (n=4), psychology (n=6), and psychiatry/psychiatric nursing (n=7).

Table 2. Evaluation of recommendations for implementation of the national cancer rehabilitation guideline among 14 Dutch head and neck cancer centers according to 9 criteria.

Criteria		Centers													
		A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Guideline implementation	-	-	-	-	+	-	+	+	+	-	-	-	-	-
2	Distress thermometer	+	-	+	+	+	+	+	+	+	+	+	+	+	+
3	Inventory of problems	+	-	++	++	++	++	+	+	++	++	++	+	++	++
4	Evaluating care approach	+/-	+	+	++	++	+	+	U	+	++	+/-	++	+	+
5	PM&R in dedicated team	+/-	+/-	-	+/-	+/-	+/-	++	+/-	++	+/-	+/-	+/-	+/-	-
6	Goal-oriented approach	+	+/-	-	+	++	U	+	U	+	+	+	+/-	+	-
7	Regular MTM	+/-	++	++	+/-	++	+/-	+	++	++	-	-	++	++	-
8	QoL evaluation	-	-	-	++	-	U	++	U	++	-	-	U	U	U
9	Satisfaction evaluation	-	++	+/-	+	++	U	+	+/-	++	+/-	-	+/-	U	-

Criterion: 1) implementation of the national cancer rehabilitation guideline; 2) use of the distress thermometer; 3) systematic inventory of physical and/or psychosocial problems; 4) evaluating the need for mono- or multidisciplinary care; 5) involvement of a PM&R physician in the dedicated team; 6) goal-oriented approach to rehabilitation interventions; 7) regular MTM with the dedicated team; 8) effect evaluation of QoL by means of the EORTC QLQ-C30 questionnaire; 9) patient satisfaction evaluation of rehabilitation care.
Criterion 2 to 5 are part of the signaling and referral phase; criteria 6 to 9 of the intake and evaluation phase.
Criterion scoring system: All items were scored on a 4-point scale ('++', always; '+', often; '+/-', sometimes, '-', never) except for Criterion 1 and 2 which were scored yes ('+') or no ('-').

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MTM, multidisciplinary team meeting; U, unknown; PM&R, physical medicine and rehabilitation, QoL, quality of life; SLP, speech-language pathologist.

Section 3: Financial matters

Only one center covered the majority of rehabilitation costs with a rehabilitation-specific DRG (Appendix C). In three centers, costs were sufficiently covered by other various sources, in five other centers this was not the case, and in six centers this was unknown. For three centers, lack of reimbursement options was the reason for referring patients to primary care. In three centers, reimbursement of care provided was insufficient because of the unavailability of a DRG and use of maximum tariffs. In one center, dental care and provision of rehabilitation during the follow-up period in the outpatient clinic by healthcare professionals (e.g. SLP, physiotherapist) were not refunded.

Section 4: Barriers and facilitators

All invited healthcare professionals in 14 HNC centers, in total 97 respondents completed Section 4 categorized into clinical, economic (first part), organizational and patient-related factors (Appendix D). In addition, 16 respondents of the Financial Department of all 14 HNC centers completed the second part of the economic items.

The 97 health care professionals more often scored items as being a facilitator (average number of respondents per item n=42 of 97, 44%) rather than barriers (n=18 of 97, 19%). Most frequently reported facilitators were on a clinical level, whereas the barriers were mostly patient-related (Table 3). Clinical facilitators included the attitude, motivation and expertise/knowledge of healthcare professionals in the team; informing patients on HNC rehabilitation and the presence of a contact person. Patient-related barriers were medical history (e.g. psychiatric disease), travel(time), health literacy and motivation. Lack of reimbursement for rehabilitation was also reported as a barrier.

In the second part of the economic category, which was completed by the Financial Department only, the financial support/grants from the hospital was mentioned as a facilitating factor in one hospital. In contrast, three other centers reported barriers on negotiated tariffs, hospital's financial support/grants and contractual agreements.

The two centers that implemented and fully adhered to the cancer rehabilitation guideline scored more items as facilitator compared to those two that had only partially adhered. No clear associations between barriers and facilitators and guideline implementation were found (Figure 3); neither were there clear relations of reported barriers and facilitators between centers, or subgrouping into type of center and geographic location.

Table 3. Top 7 barriers and facilitators of providing head and neck cancer rehabilitation care completed by 97 survey respondents in 14 Dutch centers.

Barriers			Facilitators		
No.	**Category**	**Barrier (no. of respondents)**	**No.**	**Category**	**Facilitator (no. of respondents)**
1	Patient-related	• Psychiatric history and/or comorbidity (59)	1	Clinical	• Attitude of HP towards rehabilitation (76)
2	Patient-related	• Travel time to/from the hospital (53)	2	Clinical	• Motivation of HP to provide rehabilitation (76)
3	Patient-related	• Transport to/from the hospital (52)	3	Clinical	• Expertise/knowledge of specialists and HP (73)
4	Patient-related	• Health literacy of patients (45)	4	Organizational	• Availability of a contact person for patients (69)
5	Patient-related	• Financial capacity of patients (43)	5	Clinical	• Attitude of specialists towards rehabilitation (67)
6	Economic	• Reimbursement structure for rehabilitation (36)	6	Clinical	• Knowledge of HP (in general) on rehabilitation (67)
7	Patient-related	• Motivation and therapy compliance of patients (35)	7	Patient-related	• Availability patient information on rehabilitation (67)

Healthcare professionals reflect the persons who provide supportive care.

Abbreviations: HP, healthcare professionals.

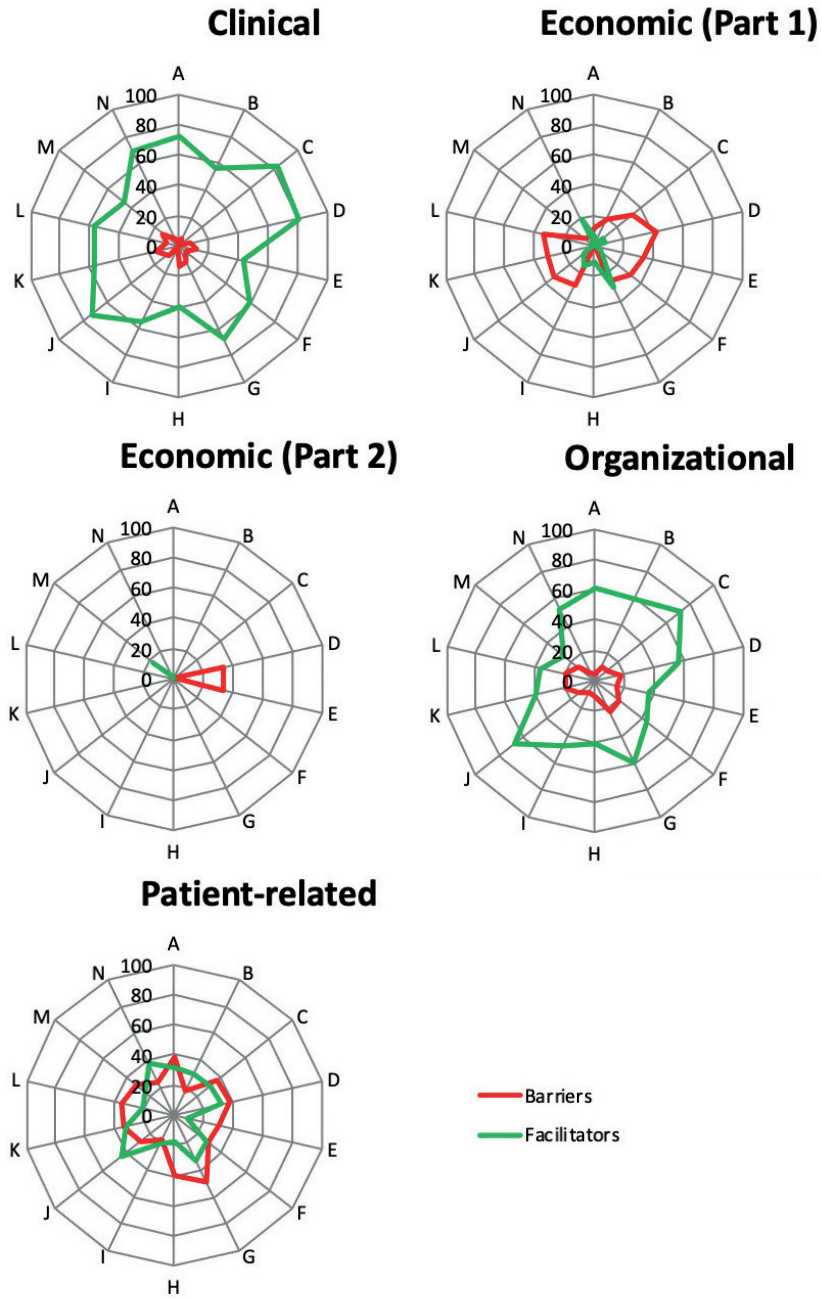

Figure 3. Barriers of and facilitators to rehabilitation care provision plotted per category: Clinical (3a), Economic Part 1 and Part 2 (3b and 3c), Organizational (3d) and Patient-related (3e) Each plot displays the percentage (axis: %) of barriers and facilitators reported per center.

Section 5: Health professionals' satisfaction and suggestions for future improvements

Eighty-four percent of the respondents considered the presence of a multidisciplinary rehabilitation program, in which patient-tailored care is established, to be of added value. Most respondents (n=80, 71%) were (very) satisfied with their rehabilitation provision, regardless of the extent of guideline implementation in their center. Six respondents (5%) were (very) dissatisfied (24% reported neutral opinion).

Five frequently reported suggestions for improvements were related to: 1) improving (availability of) inter/multidisciplinary rehabilitation (n=20; including MTMs and multidisciplinary consultations); 2) patient screening (n=10; including use of a screening tool and patient-reported outcomes measures (PROMS), focus on malnutrition, dental care and psychiatric/psychological problems); 3) standard and early consultation by healthcare professionals (n=9; including SLP, physiotherapist, psychiatrist and psychosocial care); 4) reimbursement of rehabilitation – e.g. by means of improving the DRG structure – and funding for relatives (n=8) and 5) consultation of healthcare professionals during the follow-up period (n=6; including the supportive care after admission).

Discussion

This study investigated the extent to which rehabilitation interventions are offered in the Dutch HNC centers and in particular if and how the national cancer rehabilitation guideline has been implemented and is adhered to, in HNC rehabilitation. We used the guideline's framework for screening, triage and intervention allocation as reference [2,3]. Additionally, factors influencing this process were explored. All Dutch HNC centers were approached and responded in full, and all reported to provide at least some HNC rehabilitation. Most centers (86%) applied a local protocol. Only four centers (29%) had implemented the national guideline to at least some extent, while merely two centers (14%) fully adhered to all guideline recommendations. Thus, provision of tailored multi-/interdisciplinary rehabilitation coordinated by a PM&R in Dutch HNC centers is still scarce and prone to practice variation. The SLP, physiotherapist and dietitian were always part of dedicated rehabilitation, whereas other healthcare professionals took part in less than 60%. Most facilitators to providing HNC rehabilitation were clinician-oriented, whereas most barriers were patient-related and system-related. Only one center had secured sustainable funding through a rehabilitation-specific DRG; others used various less sustainable funding sources. Economic barriers were reported as the second most important factor, and reimbursement of HNC rehabilitation seems not fully available. The two centers that reported to have implemented the national guideline and fully adhered to it, scored more items as being a facilitator compared to the centers that partially implemented the cancer rehabilitation guideline. There was, however, no clear association between the barriers and facilitators experienced and (the extent of) guideline implementation.

Guideline implementation was not optimal in our study. This is in accordance with other reports in literature [11]. We observed that the attitude and expertise of healthcare professionals was facilitating, while in literature this is often found to be a barrier in the context of other diseases [10,12]. This could be explained by the findings of Grol et al., in which is reported that various target groups (e.g. disease types) can be improved by certain strategies and approaches, as demonstrated by cooperation between DHNS and PWHHT [27]. Patient-related barriers have been described earlier in literature e.g. related to the implementation of a physical activity program for cancer patients [12]. It is not surprising that most barriers in our study are patient-related, as this frail patient population is more prone to e.g. excessive smoking and alcohol consumption, and tends to be lower educated which is associated with poor health literacy [28,29]. Also, these patients often suffer from financial toxicity due to their limited financial capacity [30,31]. We found that barriers and facilitators were not related to guideline implementation; this might be explained by the level of unconsciousness about possibilities and positive effects regarding multidisciplinary rehabilitation, in centers without implementation of the guideline.

This study has several strengths. To our knowledge, this is the first study to provide a national overview of the extent to which the rehabilitation guideline is implemented and adhered in HNC rehabilitation in practice, including an overview of attributes that might relate to guideline implementation. We obtained responses from all stakeholder representatives of all HNC centers, and there was no missing data. Yet, several limitations also have to be taken into account in this study. First, by conducting a survey study, results are prone to subjectivity and probably positive exaggeration. Second, because the national guideline is aimed at all individuals with cancer, it does not provide specific directions with regard to e.g. disciplines required in the dedicated team. Also, at the time of conducting the study, no formal indicators for guideline implementation were available; as a consequence, we derived our own set of criteria based on guideline recommendations. This made it challenging to determine and assess adherence to the guideline, and it introduces a certain level of arbitrarity. Third, we did not include dental care professionals (e.g. maxillofacial prosthodontist) in our survey sample, while these professionals also provide dedicated care. Problems in oral intake after HNC treatment are often interrelated with change in teeth or oral mucosa, therefore adding dental care to the HNC rehabilitation team might be relevant. Finally, the sample sizes per center were too small to perform formal statistical hypothesis tests to compare subgroups and study associations.

Implications for clinical practice include, on the level of guideline implementation and adherence, formulating specific directions (e.g. indicators) to stimulate effective dissemination, implementation and adherence of the guideline (e.g. evaluation within an audit) [32]. To overcome patient-related barriers, tailored patient guidance by means of a contact person who can chart individual goals and support patients during the rehabilitation period could enhance patients' motivation and compliance. This should also be supported by written and multimedia resources

e.g. an e-health platform for provision of tailored information [33,34]. Additionally, by reimbursing patient's travel costs, health insurers could facilitate rehabilitation provision. Also, insufficient hospital reimbursement was reported by 36% of centers that combined financial sources. Use of a rehabilitation-specific DRG could provide sustainable reimbursement for multidisciplinary care organization, as evidenced by the one center that had successfully secured such funding. Additional recommendations based on the respondents' future improvements include regular MTMs and timely and personalized screening and consultation by various allied health care disciplines (e.g. SLP, physiotherapist) during the cancer care continuum.

Several research implications have to be considered. Although no clear associations between guideline implementation and the influencing factors were found, the barriers and facilitators reported can provide direction for further implementation of tailored rehabilitation. Preferably future research includes qualitative methods such as individual semi-structured interviews or focus group discussions that lead to more in-depth information on possible solutions for the reported barriers. As this survey was conducted only from a hospital perspective, it would be of interest to involve patients (societies) in order to analyze barriers and facilitators from a patient's perspective [35]. Furthermore, for evaluation of outcome indicators, it would be of value to standardize the use of HRQoL questionnaires in practice. These could also be used to conduct cost-effectiveness analyses, which are needed to support decisions on reimbursement of structured multidisciplinary rehabilitation programs. The latter is addressed in a current ongoing study, which also evaluates important other outcome indicators such return to work, unmet needs, satisfaction and clinical outcomes [9].

Conclusion

All 14 Dutch Head and Neck Center provided some form of rehabilitation (e.g. mono, multi- or interdisciplinary), and most centers applied a protocol to identify, triage and refer patients to rehabilitation interventions. However, only few centers had attempted full implementation of the national rehabilitation guidelines, and very few fully adhered to all our criteria for successful implementation. Thus, comprehensive provision of tailored multi-/interdisciplinary rehabilitation coordinated by a PM&R in Dutch HNC centers is still scarce and subject to practice variation despite the availability of a national guideline. Most facilitators related to rehabilitation provision were clinician-oriented, whereas most barriers were patient-related and economic. Future research should explore possible solutions for barriers by conducting in-depth interviews with professionals and patients, exploring the societal perspective, and assessing outcome indicators. For clinical practice, we recommend specific directions for guideline implementation and adherence, a dedicated and specialized rehabilitation team, tailored patient interventions,

regular MTMs, standard screening and consultation during the cancer care continuum, PROM evaluation, and reimbursement through a rehabilitation-specific DRG.

References

1. Netherlands Comprehensive Cancer Organisation. Incidence of head and neck cancer in the Netherlands. [in Dutch]. Last accessed: 3-12-2019.; https://www.cijfersoverkanker.nl/selecties/Dataset_1/img5d19afb60a6fe.
2. Netherlands Comprehensive Cancer Organisation. National cancer rehabilitation guideline (2011). [in Dutch]. Last accessed: 3-12-2019.; https://www.oncoline.nl/medisch-specialistische-revalidatie-bij-oncologie. .
3. Van den Berg J, Velthuis M, Gijsen B, et al. Guideline" Cancer rehabilitation". *Nederlands tijdschrift voor geneeskunde.* 2011;155(51):A4104.
4. Korstjens I, May AM, van Weert E, et al. Quality of life after self-management cancer rehabilitation: a randomized controlled trial comparing physical and cognitive-behavioral training versus physical training. *Psychosomatic medicine.* 2008;70(4):422-429.
5. May AM, Korstjens I, van Weert E, et al. Long-term effects on cancer survivors' quality of life of physical training versus physical training combined with cognitive-behavioral therapy: results from a randomized trial. *Supportive Care in Cancer.* 2009;17(6):653-663.
6. Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *Journal of clinical oncology.* 2005;23(16):3830-3842.
7. Korstjens I, Mesters I, van der Peet E, Gijsen B, van den Borne B. Quality of life of cancer survivors after physical and psychosocial rehabilitation. *European journal of cancer prevention.* 2006;15(6):541-547.
8. Licitra L, Keilholz U, Tahara M, et al. Evaluation of the benefit and use of multidisciplinary teams in the treatment of head and neck cancer. *Oral oncology.* 2016;59:73-79.
9. Beck A-JC, Passchier E, Retèl VP, et al. Study protocol of a prospective multicenter study comparing (cost-) effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo-or bioradiotherapy. *BMC cancer.* 2019;19(1):655.
10. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation—a scoping review. Paper presented at: Healthcare2016.
11. Heins MJ, de Jong JD, Spronk I, Ho VK, Brink M, Korevaar JC. Adherence to cancer treatment guidelines: influence of general and cancer-specific guideline characteristics. *The European Journal of Public Health.* 2016;27(4):616-620.
12. IJsbrandy C, Hermens RP, Boerboom LW, Gerritsen WR, van Harten WH, Ottevanger PB. Implementing physical activity programs for patients with cancer in current practice: patients' experienced barriers and facilitators. *Journal of cancer survivorship.* 2019;13(5):703-712.
13. Verstijnen J, Damude S, Hoekstra H, et al. Practice variation in Sentinel Lymph Node Biopsy for melanoma patients in different geographical regions in the Netherlands. *Surgical oncology.* 2017;26(4):431-437.
14. Spitaels D, Vankrunkelsven P, Desfosses J, et al. Barriers for guideline adherence in knee osteoarthritis care: a qualitative study from the patients' perspective. *Journal of evaluation in clinical practice.* 2017;23(1):165-172.
15. Keikes L, Koopman M, Stuiver MM, Lemmens VE, van Oijen MG, Punt CJ. Practice variation on hospital level in the systemic treatment of metastatic colorectal cancer in The Netherlands: a population-based study. *Acta Oncologica.* 2020:1-9.

16. Clarke P, Radford K, Coffey M, Stewart M, Otology. Speech and swallow rehabilitation in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal of Laryngology.* 2016;130(S2):S176-S180.
17. van Weert E, Hoekstra-Weebers J, Grol B, et al. A multidimensional cancer rehabilitation program for cancer survivors: effectiveness on health-related quality of life. *Journal of Psychosomatic Research.* 2005;58(6):485-496.
18. Barrowman R, Wilson P, Wiesenfeld DJ. Oral rehabilitation with dental implants after cancer treatment. *Australian dental journal.* 2011;56(2):160-165.
19. Roman BR, Goldenberg D, Givi B, Head ECoA, Society N. AHNS Series—Do you know your guidelines? Guideline recommended follow-up and surveillance of head and neck cancer survivors. *Head neck.* 2016;38(2):168-174.
20. Sullivan P, Fisher PJCp. Challenges in a multidisciplinary head and neck oncology program. *Cancer practice.* 1995;3(4):258-260.
21. King G, Lemon J, Martin J. Multidisciplinary teamwork in the treatment and rehabilitation of the head and neck cancer patient. *Texas dental journal.* 1992;109(6):9-12.
22. Barnhart MK, Ward EC, Cartmill B, et al. Content analysis of rehabilitation goals for patients following non-surgical head and neck cancer treatment. *Supportive Care in Cancer.* 2019;27(2):639-647.
23. Eades M, Murphy J, Carney S, et al. Effect of an interdisciplinary rehabilitation program on quality of life in patients with head and neck cancer: review of clinical experience. *Head neck.* 2013;35(3):343-349.
24. Wolfe A. Institute of Medicine Report: crossing the quality chasm: a new health care system for the 21st century. *Policy, Politics, Nursing Practice.* 2001;2(3):233-235.
25. Exploratio. . Last accessed: 10-12-2019.; https://explora-zorg.nl/.
26. National guideline on detection the need for psychosocial care. Last accessed: 10-12-2019.; https://www.oncoline.nl/detecteren-behoefte-psychosociale-zorg.
27. Grol R, Wensing M. Implementation of change in healthcare: A complex problem. *Improving Patient Care.* 2013:1-17.
28. Goldenberg D, Lee J, Koch WM, et al. Habitual risk factors for head and neck cancer. *Otolaryngology—Head Neck Surgery.* 2004;131(6):986-993.
29. Koay K, Schofield P, Gough K, et al. Suboptimal health literacy in patients with lung cancer or head and neck cancer. *Support Care Cancer.* 2013;21(8):2237-2245.
30. Massa ST, Osazuwa-Peters N, Boakye EA, Walker RJ, Ward G. Comparison of the financial burden of survivors of head and neck cancer with other cancer survivors. *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):239-249.
31. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. *Pharmacoeconomics.* 2014;32(9):865-882.
32. Grol R, Wensing MJIPCTiocihc. Effective implementation of change in healthcare: a systematic approach. 2013:40-63.
33. Jabbour J, Milross C, Sundaresan P, et al. Education and support needs in patients with head and neck cancer: A multi-institutional survey. *Cancer Metastasis Rev.* 2017;123(11):1949-1957.
34. Melissant HC, Verdonck-de Leeuw IM, Lissenberg-Witte BI, Konings IR, Cuijpers P, Van Uden-Kraan CFJAO. 'Oncokompas', a web-based self-management application to support patient activation and optimal supportive care: a feasibility study among breast cancer survivors. 2018;57(7):924-934.
35. Midgley AW, Lowe D, Levy AR, Mepani V, Rogers SN. Exercise program design considerations for head and neck cancer survivors. *Eur Arch Otorhinolaryngol.* 2018;275(1):169-179.

Acknowledgements

We would like to thank the healthcare professionals and managers/employees of the Financial Department of all Dutch Head and Neck Cancer centers for their cooperation and participation in the study. This study was supported by the Dutch Head and Neck Society. We would like to thank C. Algoe for her practical support in conducting the study.

Availability of data and material

The data will be available upon request (contact person: E. Passchier: e.passchier@nki.nl).

Code availability

Not applicable.

Conflicts of interest

The study is funded by the Netherlands Cancer Institute (Plesmanlaan 121, 1066CX, Amsterdam, the Netherlands). AB and MS are supported by a non-restricted research grant from ATOS Medical AB.

Funding

The study is funded by the Netherlands Cancer Institute (Plesmanlaan 121, 1066CX, Amsterdam, the Netherlands). AB and MS are supported by a non-restricted research grant from ATOS Medical AB.

Appendix A

Design and background of the survey in five sections.

In Section 1 of the survey, key elements of (multidisciplinary) rehabilitation - represented in the framework - are covered. We developed 9 criteria based on guideline recommendations that reflect the organizational structure, these include two structural indicators and seven process indicators. The criteria were scored on a four-point scale (always/often/sometimes/never) except for three items (yes/no) (Figure 1).

Section 2 was used to inventory the availability of clinimetrics and interventions. Availability was defined as having healthcare professionals explicitly appointed to the HNC rehabilitation team. The inventory included a physiotherapist, speech-language pathologist (SLP), dietitian, occupational therapist, medical social worker, psychologist, psychiatrist/psychiatric nurse (specialist) and an art therapist. These disciplines were chosen based on guideline recommendations for physical and psychosocial interventions and on a HNC rehabilitation program developed in the Netherlands Cancer Institute [1,2]. Each dedicated healthcare professional was asked which key clinimetric tools and interventions for HNC rehabilitation are used [3]. Subsections were not completed in case this discipline did not participate in the dedicated rehabilitation team.

In Section 3, the reimbursement method was determined for each hospital by multiple choice questions, and it was asked whether reimbursement was sufficient or if there were financial restrictions to provide rehabilitation.

Barriers to and facilitators of rehabilitation provision in Section 4 were based on the six domains of the Institute of Medicine (IOM) and were categorized into clinical, economic (two parts), organizational and patient-related categories [4]. Each category was covered by multiple items (total of 43 items), which were assigned a 'barrier' or 'facilitator' designation according to whether they were regularly restrictive or facilitating, respectively, during the last six months. Other options were 'I don't know' or 'does not occur regularly in my situation'. An overview of the 43 items is provided in Appendix D.

Respondents were asked in Section 5 about their satisfaction regarding the rehabilitation provided; the added value of a multidisciplinary rehabilitation program and suggestions for future improvements. The latter was asked in an open question.

The survey was developed in collaboration with a panel of experts consisting of medical specialists and healthcare professionals involved in rehabilitation including the Dutch Working Group of Allied Healthcare (*Paramedische Werkgroep Hoofd-halstumoren* – PWHHT) (Section 1/2/4/5), managers/employees of the Financial Department and business specialists of a

healthcare insurer (Section 3/4). The extent to which the questions of Section 1 and Section 2 represented the cancer rehabilitation guideline was assessed by members of the IKNL.

References Appendix A

1. Beck A-JC, Passchier E, Retèl VP, et al. Study protocol of a prospective multicenter study comparing (cost-) effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo-or bioradiotherapy. *BMC cancer.* 2019;19(1):655.
2. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. *European Archives of Oto-Rhino-Laryngology.* 2016;273(6):1577-1587.
3. Federatie Medisch Specialisten (FMS). Guideline Head and Neck Tumors(2014). [in Dutch). Last accessed: 3-12-2019.; https://richtlijnendatabase.nl/richtlijn/hoofd-halstumoren/hoofd-halstumoren_-_korte_beschrijving.html
4. Wolfe A. Institute of Medicine Report: crossing the quality chasm: a new health care system for the 21st century. *Policy, Politics, Nursing Practice.* 2001;2(3):233-235.

Appendix B

Availability of clinimetrics and interventions provided during head and neck cancer rehabilitation in 14 Dutch centers.

Availability healthcare professional (% of centers)	Clinimetrics and interventions	Centers													
		A	B	C	D	E	F	G	H	I	J	K	L	M	N
SLP (100)															
	Audiogram	I						A	N					N	
	Tympanogram	I						A	N					N	
	Swallowing video	I	I	I	I	I	I	A		I	I	A	I	I	I
	FEES	I	I	I	I	I	I	I	I	I	I	A	I	I	I
	MMO			I	I	I		A		S		A	I	I	
	FOIS	A	I	A	A	S	S	A	I	S	I		I	S	S
	Swal-QoL		I	I	I		I	S			I			S	S
	MDADI		I		I		I	S							
	EAT-10		I			I	I		S						
	VHI	I	S	I	I	S		S	I	I	I		I	S	S
	SHI				I	I		S		I	I		I	I	
	SOAL							S							
	Swallowing rehabilitation	A	A	A	A	R	A	A	R	A	A	A	R	R	A
	Voice rehabilitation	A	R	R	A	R	A	A	R	A	A	R	R	R	R
	Speech and articulation rehabilitation	A	R	A	A	R	A	A	R	A	R	R	R	R	R
	Speech rehabilitation after TLE	A	P	P	A		A	A	R	P	A	A	P	A	R
	Trismus therapy		P	R	A	R	A	A					R	R	
	Olfactory rehabilitation after TLE	A	A	R	A		A	A		R	R	A	R	A	R
	Hearing test							A							
	Mime therapy	R		R	R	R		A		R	R		R	R	R
	Other														
Dietician (93)															
	Pinch strength test	I	A				I	I	A	A	I			A	
	SNAQ					S	S	S			I				S
	BMI	S	A			S	S	S	A	A	S	S	S	S	S
	BIS		I				I	I	A	I				A	
	PG-SGA							I							
	Monitoring weight	A	A		P	A	A	P	A	A	A	A	A	R	P
	Monitoring intake	A	A		P	A	A	P	A	A	A	A	A	R	P

	Advice on nutritional supplements	A	R		A	A	A	P	A	A	A	A	A	R	P
	Nutritional advice in general	A	A		P	A	A	P	A	A	A	A	A	R	P
	Nutritional advice during a physical program						R	R							
	Other														
Physiotherapist (86)															
	6MWT				I			I		A	I		I	I	
	Steep ram test				I			A			I		A	I	
	SPADI				I			I		A	A	I			I
	AROM	S	S		I			I		A	A	S	A	A	S
	MFI				I			A		I	I				
	PSC				I			A			I	I	A		I
	Borg RPE-scale	I			I			A			A		A		S
	Maximal exercise test with ECG and breath gas analysis				I			I		N					
	Improving physical condition	A	R		P			A			A	R	R	R	R
	Muscle strength training	A	R		P			A			A	R	R	R	P
	Trismus therapy				R					A		R		R	A
	Shoulder and neck exercise training	A	R		P			A		A	A	A	A	A	A
	Lymphedema therapy	R			R			A		A		R	R		R
	Other														
Medical social worker (57)															
	Distress thermometer						A	S			S			I	
	HADS						I	S				N		I	
	CED-D						I					N			
	Other														
	PE coping with cancer disease	R			R		R	R			R	A	A	R	
	PE partner/loves ones	R			R		R	R			R	A	A	R	
	Resumption of work	R			R		R	R			R	R	A	R	
	Mindfulness							R					A	R	
	Cognitive behavioral therapy				R			R			R		A	R	
	Other														
Psychologist (50)															
	UCL	I		I		I		S				I			
	HADS	I		I			I	S				I			
	CED-D			I		I	I	N				I			
	SCL-90	I		I		I		S							
	Other														

	PE coping with cancer disease	R		R	R	R	P	R				R
	PE partner/loved ones			R	R	R	P	R				R
	Psychological decompensation	R		R	R	R	R					R
	Cognitive behavioral therapy	R		R	R	R	R	R				R
	Psychological diagnostics	R		R	R	R	R	R				R
	EMDR	R		R	R	R	R	R				R
	Other											
Psychiatrist and psychiatric nurse (spe-cialist) (36)												
	UCL											
	HADS											
	CED-D											
	SCL-90			I								
	PE coping with cancer disease	R		R				R				
	PE partner/loved ones	R		R	R			R		R		
	Psychological decompensation/me-medication	A		A	A			A		R		
	Cognitive behavioral therapy	N								R		
	Psychiatric diagnostics	R		A	A			R		R		
	Drug rehabilitation	R		A	A			R				
	Other											
Occupational therapist (21)												
	COPM							S		I		
	USER-P							N		I		
	IPA							N				
	PSC							S				
	MFI							S				
	Other											
	PE on sleep							A		R		
	PE on fatigue/energy coaching							A		R		
	Ergonomics							A		R		R
	Resumption of work							A		R		
	Arm-hand function training							A				R
	Cognitive rehabilitation							A				R
	Training of ADL							A		R		R
	Other											
Art therapist (14)												
	HADS							S				
	CES-D											

Art therapy	R		R	
Reactivating daily activity	R			
Inventory patient’s medical queries	R		A	
Other				

Clinimetrics are displayed in white background; interventions in grey background.

Legends: Clinimetrics are displayed in grey; interventions in white. A black cell means the healthcare professional is available within the dedicated team; cell shading means unavailability. An empty grey or white cell reflects no use or not applicable. A, All (clinimetrics: standard use and on indication; interventions: on referral and according to protocol); I, on indication; N, not known; P, according to protocol; R, on referral; S, standard use based on the hospital’s guideline.

Abbreviations: 6 MWT, 6 minutes walking test; ADL, activities of daily living; AROM, active range of motion; Borg RPE-scale, borg rating of perceived exertion; BMI, body mass index; BIS, bio-electric impedance spectroscopy; CES-D, center or epidemiological studies depression scale; COPM, Canadian Occupational Performance Measure; EAT-10, Eating Assessment Tool; ECG, electrocardiogram; FEES, flexible endoscopic evaluation of swallowing; FOIS, functional oral intake scale; HADS, hospital anxiety depression scale; IPA, impact of participation and autonomy; MDADI, MD Anderson dysphagia inventory; MMO, maximal mouth opening; MFI, multidimensional fatigue index; PE, psycho-education; PG-SGA, patient-generated subjective global assessment; PSC, patient specific complaints; SCL-90, symptom checklist-90; SHI, speech handicap index; SLP, speech-language pathologist; SNAQ, short nutritional assessment questionnaire; SOAL, swallowing outcomes after laryngectomy; Swal-Qol, swallowing quality of life; SPASI, shoulder pain and disability index; TLE, total laryngectomy; UCL, Utrecht coping list; USER-P, Utrecht scale for evaluation of rehabilitation-participation; VHI, voice handicap index.

Appendix C

Financing of head and neck cancer rehabilitation care of healthcare professionals in 14 Dutch HNC centers.

The table displays the absolute number of centers that apply a certain coverage method for each healthcare professional (per center, multiple coverage methods were possible for one healthcare professional).

Healthcare professional	No. of centers						
	Diagnosis DRG	Symptom DRG	Rehabilitation DRG	Costs primary care	Projects/ subsides	Other	U
Art therapist	5	1	1	0	0	1	5
Dental hygienist	5	1	1	1	0	6	1
Dentist	1	0	0	1	0	7	2
Dietitian	10	1	1	0	0	0	1
Nurse	9	1	1	0	0	1	3
Nurse specialist	10	1	1	0	0	3	1
Occupational therapist	7	1	2	0	0	2	3
PM&R physician	2	0	5	0	0	3	3
Prosthetist	2	1	0	1	3	6	3
Psychiatrist	6	1	0	0	0	3	4
Psychologist	9	1	1	0	0	2	3
Social worker	9	1	1	0	0	1	3
SLP	11	1	1	0	0	1	1

The Dutch DRG is named a DBC (diagnose behandel combinatie).

Abbreviations: DRG, diagnosis-related group, U, unknown, PM&R, physical medicine and rehabilitation, SLP, speech-language pathologist.

Appendix D

An overview of the categories and items included in the survey to assess the barriers and facilitators of rehabilitation care provision.

No.	Category	Item
1	Clinical	Attitude of HP towards rehabilitation
2		Attitude of specialists towards rehabilitation
3		Effect evaluation of rehabilitation care
4		Evidence-based rehabilitation
5		Expertise/knowledge of medical specialists and HP
6		Knowledge of HP (in general) on rehabilitation
7		Knowledge of referrer on (in- and external) referral options regarding rehabilitation care
8		Knowledge of referrer on rehabilitation
9		Motivation of HP to provide rehabilitation
10		Motivation of medical specialists to provide rehabilitation
11		Stimulation of patient participation in rehabilitation care by HP
1	Economic: Part 1	Coverage structure for rehabilitation
2		Evaluation of cost-effectiveness of rehabilitation
3	Economic: Part 2*	Contractual agreements between health insurers and hospital
4		Financial support or subsidy within the hospital
5		Tariffs negotiated with the health insurers
1	Patient-related	Availability of patient information on rehabilitation
2		Expectations of patients regarding rehabilitation
3		Financial capacity of patients
4		Health literacy of patients
5		Language proficiency of patients
6		Motivation and therapy compliance of patients
7		Prioritization of rehabilitation care by patients
8		Psychiatric history and/or comorbidity
9		Social safety net/informal care for patients
10		Stimulation of patients by relatives and friends
11		Time for rehabilitation care in relation to social- and work-related activities
12		Transport to/from the hospital
13		Travel time to the hospital

1	Organizational	Accessibility of materials to provide rehabilitation care (e.g. instruments)
2		Alignment of interventions of HP
3		Applying the national cancer rehabilitation guideline
4		Available locations to provide rehabilitation
5		Availability of a contact person for patients
6		Capacity medical specialists and HP
7		Collaboration with the HP of the primary
8		Communication between medical specialists/HP
9		Educational opportunities regarding rehabilitation for HP
10		HP specialized in head and neck rehabilitation
11		Physical distance between medical specialists/HP (e.g. lack of integrated practice units)
12		Planning of rehabilitation
13		Protocol to provide rehabilitation
14		Timely inventory of care needs (screening)

Healthcare professionals reflect the persons who provide supportive care.
*Completed by the managers/employees of the Financial Department.

Abbreviations: HP, healthcare professionals.

Appendix Survey

#	Vraagoverzicht Organisatie van hoofd-hals nazorg copy
1	Geachte collega, Uit de praktijk is bekend dat de organisatie van ´hoofd-hals nazorg/ ondersteunende zorg´ verschillend is ingericht in Nederland**.** Om inzicht te krijgen in de **inhoud en organisatie van nazorg/ondersteunende zorg** , hebben wij een **online enquête** ontwikkeld, welke wordt ondersteund door de wetenschappelijke raad van de NWHHT. Deze enquête heeft als doel een overzicht te verkrijgen van de **organisatie**, **inhoud en financiering** van deze nazorg en tevens **belemmerende en bevorderende factoren** in het verlenen van nazorg te identificeren. In deze enquête verstaan we onder ´**nazorg/ ondersteunende zorg**´: *'Alle ondersteunende zorg/ herstelzorg/ revalidatie welke wordt ingezet met als doel het functioneren op psychisch, fysiek, sociaal en spiritueel vlak te bevorderen voor patiënten met hoofd-halskanker welke een oncologische behandeling (hebben) ondergaan met curatieve intentie'.* Deze zorg vindt meestal plaats na oncologische behandeling, maar kan ook al starten tijdens de behandeling (bijv. preventieve sliktherapie). De standaard oncologische nacontrole kan een rol spelen in de nazorg, maar wordt in deze enquête niet meegenomen. Het invullen van deze enquête duurt ongeveer **15 tot 20 minuten**. Alvast hartelijk dank voor het invullen! Mede namens prof. dr. M.W.M. van den Brekel en prof. dr. W.H. van Harten, Ann-Jean Beck en Ellen Passchier, PhD studenten Hoofd-halschirurgie AVL
2	Algemene gegevens Wat is uw geslacht? (Aanvinken wat van toepassing is) • Man • Vrouw
3	Algemene gegevens Wat is uw leeftijd? (Antwoord in jaren)
4	Algemene gegevens Waar bent u werkzaam? (Aanvinken wat van toepassing is) • Erasmus Medisch Centrum • Leids Universitair Medisch Centrum • Medisch Centrum Haaglanden • Medisch Centrum Leeuwarden • Medisch Spectrum Twente • Maastricht Universitair Medisch Centrum • Nederlands Kanker Instituut / Antoni van Leeuwenhoek ziekenhuis • Noordwest Ziekenhuisgroep • Radboud Universitair Medisch Centrum • St. Elisabeth Ziekenhuis • Universitair Medisch Centrum Groningen • Universitair Medisch Centrum Utrecht • Vrije Universiteit medisch centrum Amsterdam • Ziekenhuis Rijnstate
5	Algemene gegevens Hoelang bent u werkzaam op uw afdeling? (Antwoord in jaren)

6	Algemene gegevens In welke functie bent uw werkzaam? (Aanvinken wat van toepassing is) • Hoofd-halschirurg • Radiotherapeut • Oncoloog • Logopedist • Fysiotherapeut • Diëtist • Ergotherapeut • Vaktherapeut • Psychiater • Psycholoog • Medisch maatschappelijk werker • Revalidatiearts • Verpleegkundig specialist/ Verpleegkundige • Psychiatrisch verpleegkundige/ Verpleegkundig • psychiatrisch specialist • Manager Planning & Control • Medewerker afdeling Planning & Control •DBC consulent

7	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis In deze enquête is ´**nazorg/ ondersteunende zorg**´gedefinieerd als: 'Alle ondersteunende zorg/herstelzorg/revalidatiezorg welke wordt ingezet met als doel het functioneren op psychisch, fysiek, sociaal en spiritueel vlak te bevorderen voor patiënten met hoofd-halskanker welke een oncologische behandeling (hebben) ondergaan met curatieve intentie'. Gegeven deze definitie; hoe is de 'nazorg/ ondersteunende zorg' voor hoofd-halskanker patiënten georganiseerd binnen uw ziekenhuis? (Aanvinken wat van toepassing is)				
	• Op reguliere basis (bijv. protocollair vastgelegd)	• Op indicatie (Gaarne toelichten wat de indicatie criteria zijn)	• Op verzoek van de patiënt	• Anders, namelijk:	• Geen specifieke organisatie van nazorg/ ondersteunende zorg

8	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis Wanneer wordt er routinematig met de´nazorg/ ondersteunende zorg´gestart? (Meerdere antwoorden mogelijk)			
	• Voor de behandeling	• Tijdens de behandeling	• Na de behandeling	• Anders, namelijk:

9	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis Is het routinematig verlenen van ´nazorg/ ondersteunende zorg´ in uw ziekenhuis afhankelijk van subsite of stadium van de tumor? (Aanvinken wat van toepassing is)			
	• Ja	• Nee	• Weet ik niet	• Niet van toepassing

10	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis Zo ja, aan welke groepen verleent u routinematig ´nazorg/ ondersteunende zorg´? (Meerdere antwoorden mogelijk) Patiënten met de diagnose: • T1/T2 larynxcarcinoom • T1/T2 orofarynxcarcinoom • T1/T2 mondholtecarcinoom • T1/T2 nasofarynxcarcinoom • T1/T2 neusbijholtecarcinoom • T1/T2 speekselkliertumoren • T3/T4 larynxcarcinoom • T3/T4 orofarynxcarcinoom • T3/T4 mondholtecarcinoom • T3/T4 nasofarynxcarcinoom • T3/T4 neusbijholtecarcinoom • T3/T4 speekselkliertumoren • Anders, namelijk:

11	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis Is het routinematig verlenen van ´nazorg/ ondersteunende zorg´ in uw ziekenhuis afhankelijk van de oncologische behandeling? (bijv. alleen CRT patienten) (Aanvinken wat van toepassing is)				
	• Ja	• Nee	• Weet ik niet	• Niet van toepassing	• Anders, namelijk:

12	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis Zo ja, bij welke behandeling vanwege hoofd-halskanker verleent u routinematig ´nazorg/ ondersteunende zorg´? (Meerdere antwoorden mogelijk) Patiënten die behandeld worden met: • Chirurgie • Radiotherapie • Chemoradiatie • Fotodynamische therapie • Anders, namelijk:

13	Organisatie van ´nazorg /ondersteunende zorg´ in uw ziekenhuis Hanteert uw ziekenhuis een richtlijn of protocol voor het verlenen van ´nazorg/ ondersteunende zorg ´ aan hoofd-halskanker patiënten? (Meerdere antwoorden mogelijk) • Ja, de nationale richtlijn oncologische revalidatie • Ja, de nationale richtlijn detecteren behoefte psychosociale zorg • Ja, de nationale richtlijn herstel na kanker • Ja, de nota van de NWHHT • Ja, een ziekenhuis breed protocol • Ja, een eigen protocol op de afdeling • Nee • Weet ik niet • Anders namelijk:

14	Signalering van zorgbehoefte Worden in uw ziekenhuis fysieke of psychosociale problemen/ klachten bij hoofd-halskanker patiënten systematisch geinventariseerd en/of uitgevraagd (=signalering)? (Aanvinken wat van toepassing is en gaarne toelichting)				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

15	Signalering van zorgbehoefte Wie inventariseert/ vraagt de behoefte aan 'nazorg/ ondersteunende zorg' van hoofd-halskanker patiënten uit in uw ziekenhuis (=signalering)? (Meerdere antwoorden mogelijk) • Medisch specialist • Verpleegkundig specialist • Verpleegkundige / Casemanager Paramedicus • Niet van toepassing • Anders, namelijk:

16	Signalering van zorgbehoefte Op welke wijze wordt de behoefte aan 'nazorg/ ondersteunende zorg' bij hoofd-halskanker patiënten geinventariseerd/ uitgevraagd (=signalering)? (Meerdere antwoorden mogelijk)				
	• Lastmeter	• Gesprek	• Kwaliteit van leven vragenlijst (bijv. EORTC QLQ-C30)	• Weet ik niet	• Anders, namelijk:

17	Verwijzing naar ´nazorg/ ondersteunende zorg´ Wie verwijst in uw ziekenhuis hoofd-halskanker patiënten naar 'nazorg/ ondersteunende zorg'? (Meerdere antwoorden mogelijk)		
	• Hoofd-halschirurg • Radiotherapeut • Oncoloog • Logopedist • Fysiotherapeut • Diëtist • Ergotherapeut	• Vaktherapeut • Tandarts • Mondhygiënist • Prothetist • Psychiater • Psycholoog • Medisch maatschappelijk werker	• Revalidatiearts • Verpleegkundig specialist • Verpleegkundige • Er worden geen hoofd-halskanker patiënten verwezen naar nazorg/ ondersteunende zorg • Anders, namelijk:

18	Verwijzing naar ´nazorg/ ondersteunende zorg´ Naar welke (ondersteunende) zorgverleners wordt **routinematig** verwezen voor ´nazorg/ ondersteunende zorg´ aan hoofd-halskanker patiënten? (Gaarne per zorgverlener aangeven, er zijn meerdere antwoorden mogelijk)					
		Binnen eigen ziekenhuis	Naar de eerstelijnszorg	Naar een ander ziekenhuis	Ik verwijs niet naar deze ondersteunende zorg	Weet ik niet
	• Logopedist					
	• Fysiotherapeut: Orofaciaal therapeut					
	• Fysiotherapeut: Lymfoedeemtherapeut					
	• Diëtis					
	• Ergotherapeut					
	• Vaktherapeut					
	• Tandarts					
	• Mondhygiënist					
	• Prothetist					
	• Psychiater					
	• Psycholoog					
	• Medisch maatschappelijk werker					
	• Revalidatiearts					
	• Verpleegkundig specialist					
	• Verpleegkundige					
	• Anders					

19	Gaarne specificeren van uw antwoord ''Anders'':

20	Verwijzing naar ´nazorg/ ondersteunende zorg´ Hoe is het verwijzen vanuit uw ziekenhuis naar eerstelijnszorg ´nazorg/ ondersteunende zorg ´georganiseerd? (Meerdere antwoorden mogelijk)						
	• Protocollair, door middel van de nationale richtlijn oncologische revalidatie	• Protocollair, door middel van de nationale richtlijn detecteren behoefte psychosociale zorg	• Protocollair, door middel van een ziekenhuis breed protocol	• Protocollair, wij hanteren een eigen protocol op de afdeling	•Niet protocollair, ik verwijs op indicatie	• Weet ik niet	• Anders, namelijk:

21	Verwijzing naar ´nazorg/ ondersteunende zorg´ Is er tijdens het inventariseren/ uitvragen van de zorgbehoefte van hoofd-halskanker patiënten een evaluatiemoment om te bepalen of **multidisciplinaire** of **monodisciplinaire**´nazorg/ ondersteunende zorg´ noodzakelijk is? (Aanvinken wat van toepassing is) Onder multidisciplinaire zorg verstaan wij een geïntegreerde samenwerking van de (ondersteunende) zorgverleners. Indien patiënten door 1 of meerdere (ondersteunende) zorgverleners afzonderlijk, d.w.z. zonder onderlinge geïntegreerde samenwerking, worden behandeld valt dit onder monodisciplinaire zorg.				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

22	Verwijzing naar ´nazorg/ ondersteunende zorg' Is er een afdeling revalidatiegeneeskunde in uw ziekenhuis aanwezig? (Aanvinken wat van toepassing is)				
	• Ja		• Nee		• Weet ik niet

23	Verwijzing naar ´nazorg/ ondersteunende zorg´ Wordt een revalidatiearts betrokken in de ´nazorg/ ondersteunende zorg´ voor patiënten met hoofd-halskanker? (Aanvinken wat van toepassing is)				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

24	Verwijzing naar ´nazorg/ ondersteunende zorg´ Indien er een revalidatiearts betrokken is in de 'nazorg/ ondersteunde zorg', wat is zijn/haar rol in het nazorgtraject/revalidatiebehandeling? (Meerdere antwoorden mogelijk)	
	• Indicatie stellen revalidatiebehoefte • Intake/ Revalidatiebehandeling • Coördinatie nazorg/ ondersteunende zorg	• Ter consultatie •Anders, namelijk:

25	Verwijzing naar ´nazorg/ ondersteunende zorg´ Worden hoofd-hals kankerpatiënten weleens naar een revalidatiecentrum buiten uw ziekenhuis verwezen? (Aanvinken wat van toepassing is)				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

26	Evalueren van ´nazorg/ ondersteunende zorg´ Worden er in het kader van nazorg voor patiënten met hoofd-halskanker doelen door (ondersteunende) zorgverleners opgesteld en geëvalueerd? (Aanvinken wat van toepassing is)				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

27	Evalueren van ´nazorg/ ondersteunende zorg´ Welke methodiek dient als basis voor het opstellen van doelen, behandeling en/of evaluatie hiervan? (Aanvinken wat van toepassing is) • Specifiek, Meetbaar, Acceptabel, Realistisch, Tijdsgebonden (SMART) • International Classification of Functioning and disability and health (ICF) • Somatisch/ lichamelijk functioneren, Activiteiten dagelijks leven, Maatschappelijk functioneren, Psychisch functioneren, Communicatie/ waarneming (SAMPC) • Alle bovengenoemde methodieken • Weet ik niet • Anders, namelijk:

28	Evalueren van ´nazorg/ ondersteunende zorg´ Vindt er binnen uw ziekenhuis een standaard overleg plaats in teamverband betreffende nazorg voor hoofd-halskanker patiënten (bijv. multidisciplinair overleg)? (Aanvinken wat van toepassing is)				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

29	Evalueren van ´nazorg/ ondersteunende zorg´ Zo ja, wie nemen deel aan dit (multidisciplinaire) overleg betreffende nazorg? (Meerdere antwoorden mogelijk)		
	• Diëtist • Revalidatiearts • Logopedist •Oncoloog • Psychiater • Verpleegkundige • Psychiatrisch verpleegkundige	• Hoofd-halschirurg • Tandarts • Ergotherapeut • Verpleegkundig specialist • Prothetist • Fysiotherapeut	• Psycholoog • Medisch maatschappelijk werker • Mondhygiënist • Radiotherapeut • Vaktherapeut •Anders, namelijk: • Geen van allen

30	Evalueren van ´nazorg/ ondersteunende zorg´ Zo ja, hoe vaak vindt dit overleg plaats? (Meerdere antwoorden mogelijk)			
	• Wekelijks	• Op indicatie	• Maandelijks	• Anders, namelijk:

31	Evalueren van 'nazorg/ ondersteunende zorg' Wordt de patienttevredenheid van de ervaren 'nazorg/ ondersteunende zorg' binnen uw ziekenhuis geëvalueerd? (Aanvinken wat van toepassing is)				
	• Altijd	• Vaak	• Soms	• Nooit	• Weet ik niet

32	Evalueren van 'nazorg/ ondersteunende zorg' Zo ja, op welke wijze wordt de patiënttevredenheid geëvalueerd?

33	Evalueren van ´nazorg/ ondersteunende zorg´ Welke vragenlijsten worden in uw ziekenhuis afgenomen ten behoeve van het meten van de kwaliteit van leven betreffende 'nazorg/ ondersteunende zorg' voor hoofd-hals kankerpatiënten ? (Meerdere antwoorden mogelijk)	
	• EORTC QLQ-Cancer30 (C30) • EORTC QLQ-Head&Neck35 (H&N35) • 36-Item Short Form Health Survey (SF-36) EuroQol-5dimensions (EQ-5D)	• Weet ik niet • Anders, namelijk: • Er worden geen vragenlijsten afgenomen

34	Evalueren van ´nazorg/ ondersteunende zorg´ Zo ja, met welk doel worden deze kwaliteit van leven vragenlijsten afgenomen? (Meerdere antwoorden mogelijk)	
	• Ten behoeve van wetenschappelijk onderzoek • Ten behoeve van de Kwaliteitsregistratie (Dutch Head and Neck Audit) •Ten behoeve van effectevaluatie • Ten behoeve van kostenanalysen	• De resultaten worden teruggekoppeld aan de patiënt • Weet ik niet • Anders, namelijk:

35	Evalueren van ´nazorg/ ondersteunende zorg´ Zo ja, op welke tijdstippen worden de vragenlijsten afgenomen? (Meerdere antwoorden mogelijk)	
	• Baseline (diagnose) • 3 maanden na eind oncologische behandeling • 6 maanden na eind oncologische behandeling • 9 maanden na eind oncologische behandeling	• 12 maanden na eind oncologische behandeling • 24 maanden na einde oncologische behandeling • Anders, namelijk:

36	Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Worden de onderstaande interventies ingezet door u als logopedist? (Aanvinken wat van toepassing is)					
		Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
	• Slikrevalidatie					
	• Stembehandeling					
	• Spraakrevalidatie/ articulatiebehandeling					
	• Spraakrevalidatie na TLE					
	• Trismustherapie					
	• Reukrevalidatie na TLE					
	• Gehooronderzoek					
	• Mime therapie					
	• Anders					

37	Gaarne specificeren van uw antwoord ''Anders'':

38	Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)					
		Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
	• Audiogram					
	• Tympanogram					
	• likvideo					
	• Flexibele Endoscopische Evaluatie van het Slikken (FEES)					
	• Maximale mondopening (MMO)					
	• Functional Oral Intake Scale (FOIS)					
	• Swallowing Quality of Life (Swal-Qol)					
	• MD Anderson Dysfagia Inventory(MDADI)					
	• Eating Assessment Tool (EAT-10)					
	• Voice Handicap Index (VHI)					
	• Speech Handicap Index (SHI)					
	• Swallowing Outcomes After					
	• Laryngectomy (SOAL)					
	•Anders					

39	Gaarne specificeren van uw antwoord ''Anders'':

40 Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker
Worden de onderstaande interventies ingezet door u als diëtist? (Aanvinken wat van toepassing is)

	Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
• Monitoren gewicht					
• Monitoren volwaardige intake					
• Advies voedingssupplementen					
• Algemene voedingsadviezen					
• Voedingsadvies tijdens een beweegprogramma					
• Anders					

41 Gaarne specificeren van uw antwoord ''Anders'':

42 Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker
Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)

	Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
• Handknijpmeting					
• Short Nutritional Assessment					
• Questionnaire (SNAQ)					
• Body Mass Index (BMI)					
• Bio-elektrische Impedantie Analyse					
• (BIA)/ Bio-elektrische Impedantie					
• Spectroscopie(BIS)					
• Patient-Generated Subjective					
•Global Assessment (PG-SGA)					
•Anders					

43 Gaarne specificeren van uw antwoord ''Anders'':

44 <u>Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker</u>
Worden de onderstaande interventies ingezet door u als fysiotherapeut? (Aanvinken wat van toepassing is)

	Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
• Conditieverbetering					
• Spierkrachttraining					
• Trismustherapie					
• Schouder-nek oefentherapie					
• Lymfoedeemtherapie					
• Anders					

45 Gaarne specificeren van uw antwoord ''Anders'':

46	Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)					
		Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
	• 6 Minutes Walking Test (6 MWT) Steep ramp test					
	• Shoulder Pain And Disability Index					
	•(SPADI)					
	• Active Range Of Motion (AROM)					
	• Patiënt Specifieke Klachten (PSK) Multidimensionele Vermoeidheids					
	• Index (MVI)					
	• Borg Ratings of Perceived					
	• Exertion (Borg RPE-schaal)					
	• Maximale inspanningstest met ECG en ademgasanalyse					
	• Anders					

47	Gaarne specificeren van uw antwoord ''Anders'':

48	Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Worden de onderstaande interventies ingezet door u als ergotherapeut? (Aanvinken wat van toepassing is)					
		Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
	• Psycho-educatie slaap					
	• Psycho-educatie vermoeidheid/ energie coaching					
	• Ergonomie					
	• Werkhervatting					
	• Arm-hand functietraining					
	• Cognitieve revalidatie					
	• Training van ADL activiteiten					
	• Anders					

49	Gaarne specificeren van uw antwoord ''Anders'':

50	Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)					
		Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
	•Canadian Occupational Performance Measure (COPM)					
	•Utrechtse Schaal voor de Evaluatie van Participatie (USER-P)					
	•Impact op Participatie en Autonomie (IPA)					
	• Patiënt Specifieke Klachten (PSK)					
	•Multidimensionele Vermoeidheids Index (MVI)					
	•Anders					

51	Gaarne specificeren van uw antwoord ''Anders'':

52	Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Worden de onderstaande interventies ingezet door u als medisch maatschappelijk werker? (Aanvinken wat van toepassing is)					
		Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
	• Psycho-educatie omgaan met kanker					
	• Psycho-educatie partner/naasten					
	• Werkhervatting					
	• Mindfulness					
	• Cognitieve gedragstherapie					
	• Anders					

53	Gaarne specificeren van uw antwoord ''Anders'':

54	Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)					
		Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
	•Lastmeter					
	• Hospital Anxiety Depression Scale (HADS)					
	• Center for Epidemiological Studies Depression Scale (CES-D)					
	• Anders					

55	Gaarne specificeren van uw antwoord ''Anders'':

56	Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Worden de onderstaande interventies ingezet door u als vaktherapeut/activiteitenbegeleider? (Aanvinken wat van toepassing is)					
		Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
	• Vaktherapie					
	• Reactivering dagelijkse activiteiten					
	• Hulpvraag verheldering					
	• Anders					

57	Gaarne specificeren van uw antwoord ''Anders'':

58	Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)					
		Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
	• Hospital Anxiety Depression Scales (HADS)					
	• Center for Epidemiological Studies Depression Scale (CES-D)					
	• Anders					

59	Gaarne specificeren van uw antwoord ''Anders'':

60	Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Worden de onderstaande interventies ingezet door u als medisch psycholoog? (Aanvinken wat van toepassing is)					
		Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
	• Psycho-educatie omgaan met kanker					
	• Psycho-educatie partner/ naasten					
	• Psychische decompensatie Cognitieve gedragstherapie					
	• Psychologische diagnostiek					
	• Eye Movement Desensitization and Reprocessing (EMDR)					
	• Anders					

61	Gaarne specificeren van uw antwoord ''Anders'':

62 Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker

Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)

	Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
• Utrechtse Coping Lijst (UCL)					
• Hospital Anxiety Depression Scales (HADS)					
• Center for Epidemiological Studies					
• Depression Scale (CES-D)					
• Symptom Checklist-90 (SCL-90)					
• Anders					

63	Gaarne specificeren van uw antwoord ''Anders'':

64 Interventies ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker

Worden de onderstaande interventies ingezet door u als psychiater/psychiatrisch verpleegkundige/ verpleegkundig psychiatrisch specialist? (Aanvinken wat van toepassing is)

	Op verwijzing	Protocollair/ preventief	Protocollair/ preventief en op verwijzing	Niet van toepassing	Weet ik niet
• Psycho-educatie omgaan met kanker					
• Psycho-educatie partner/ naasten					
• Psychische decompensatie, medicatie					
• Cognitieve gedragstherapie					
• Psychiatrische diagnostiek • Verslavingsproblematiek					
• Verslavingsproblematiek					
• Anders					

65	Gaarne specificeren van uw antwoord ''Anders'':

66	Klinimetrie ´nazorg/ ondersteunende zorg´voor hoofd-hals kanker Vul van de onderstaande klinimetrie in of u het op indicatie, standaard of niet afneemt. (Aanvinken wat van toepassing is)					
		Afname op indicatie	Standaard afname	Standaard afname en op indicatie	Geen afname	Weet ik niet
	•Utrechtse Coping Lijst (UCL)					
	• Hospital Anxiety Depression Scales (HADS)					
	• Center for Epidemiological Studies					
	• Depression Scale (CES-D)					
	• Symptom Checklist-90 (SCL-90)					
	• Anders					

67	Gaarne specificeren van uw antwoord ''Anders'':

68	Financiering van 'nazorg/ ondersteunende zorg' voor hoofd-halskanker patiënten Gebruikt uw ziekenhuis een aparte DBC voor 'nazorg/ ondersteunende zorg'? (Gaarne toelichting)			
	• Ja	• Nee	• Weet ik niet	• Anders, namelijk

69	Financiering van 'nazorg/ ondersteunende zorg' voor hoofd-halskanker patiënten Kunt u aangeven hoe de kosten voor de (ondersteunende) zorgdisciplines in het kader van 'nazorg/ ondersteunende zorg' voor patiënten met hoofd-halskanker worden gedeclareerd in uw ziekenhuis? (Meerdere antwoorden mogelijk)							
		Behandel (diagnose) DBC/ DOT	Zorgvraag DBC/DOT	Revalidatie DBC (Zorgproduct-groep 99002)	Kosten eerstelijns-zorg	Project-subsidies	Overig	Weet ik niet
	• Logopedist							
	• Fysiotherapeut							
	• Diëtist							
	• Ergotherapeut							
	• Creatief therapeut							
	•Tandarts							
	•Mondhygiënist							
	• Prothetist							
	•Psychiater							
	• Psycholoog							
	• Maatschappelijk werker							
	• Revalidatiearts							
	• Verpleegkundig specialist							
	• Verpleegkundige							

70	Financiering van ´nazorg/ ondersteunende zorg´ voor hoofd-hals kankerpatienten Is het tarief voor zorgactiviteiten met betrekking tot 'nazorg/ ondersteunende zorg' voor patiënten met hoofd-halskanker in uw ziekenhuis dekkend? (Gaarne toelichting)		
	• Ja	• Nee	• Weet ik niet

71	Financiering van ´nazorg/ ondersteunende zorg´ voor hoofd-hals kankerpatienten Zijn er in uw ziekenhuis financiële beperkingen in het verlenen van nazorg voor patiënten met hoofd-halskanker? (Gaarne toelichting) • Ja • Nee • Weet ik niet

72	Financiering van ´nazorg/ ondersteunende zorg´ Komt het wel eens voor dat de 'nazorg/ ondersteunende zorg' die in uw ziekenhuis wordt gegeven valt buiten de ziekenhuisfinanciering (DBC), waardoor de patiënt zelf voor het consult moet betalen? (Meerdere antwoorden mogelijk) • Ja, patiënt moet zelf betalen per consult • Ja, patiënt wordt verwezen naar eerstelijnszorg • Nee • Weet ik niet • Anders, namelijk:

73	Financiele belemmerende/ bevorderende factoren in het verlenen van 'nazorg/ ondersteunende zorg' Kunt u aangeven of onderstaande factoren de **afgelopen 6 maanden in de meeste gevallen** (dus geen incidentele zaken) een **belemmerende** of een **bevorderende factor** zijn geweest bij het verlenen van nazorg/ ondersteunende zorg in uw situatie? (Aanvinken wat van toepassing is) Indien de factor geen belemmerende of bevorderende factor is, vinkt u ´Komt niet regelmatig voor in mijn situatie´ aan.

Financiele factoren

	Belemmerende factor	Bevorderende factor	Komt niet regelmatig voor in situatie	Weet ik niet
• Tarief ondersteunende-/nazorg onderhandeld met zorgverzekeraar				
• Algemene subsidie/financiële steun binnen ziekenhuis				
• Contractuele afspraken zorgverzekeraars en ziekenhuis				
• Anders				

74	Gaarne specificeren van uw antwoord ''Anders'':

75	Opinie Wat is uw mening over het aanbieden van een multidisciplinair medisch specialistisch oncologisch revalidatieprogramma voor patiënten met hoofd-halskanker? (Aanvinken wat van toepassing is) • Een multidisciplinair revalidatieprogramma lijkt mij WEL van meerwaarde voor patiënten met hoofd-halskanker. • Een multidisciplinair revalidatieprogramma lijkt mij NIET van meerwaarde voor patiënten met hoofd-halskanker. • Weet ik niet •Anders, namelijk:

76	Opinie Bent u tevreden over de wijze waarop nazorg voor patiënten met hoofd-halskanker in uw ziekenhuis is georganiseerd? (Aanvinken wat van toepassing is) • Zeer tevreden • Tevreden • Niet tevreden/niet ontevreden • Zeer ontevreden

77	Opinie Wat zou er volgens u nog verbeterd kunnen worden aan de nazorg in uw ziekenhuis? (Gaarne toelichting)

78 Klinische belemmerende/ bevorderende factoren in het verlenen van ´nazorg/ ondersteunende zorg´ Kunt u aangeven of onderstaande factoren **de afgelopen 6 maanden in de meeste gevallen** (dus geen incidentele zaken) een **belemmerende** of een **bevorderende factor** zijn geweest bij het verlenen van nazorg/ ondersteunende zorg in uw situatie? (Aanvinken wat van toepassing is)
Indien de factor geen belemmerende of bevorderende factor is, vinkt u ´Komt niet regelmatig voor in mijn situatie´ aan.

Klinische factoren

	Belemmerende factor	Bevorderende factor	Komt niet regelmatig voor in situatie	Weet ik niet
• Evalueren effect van ondersteunende-/nazorg (klinimetrie)				
• Evidence based ondersteunende- /nazorg (bijv. volgens evidence based richtlijn)				
• Expertise/kennis specialisten/(ondersteunende) zorgverleners				
• Attitude specialisten t.a.v. ondersteunende-/nazorg				
• Attitude (ondersteunende) zorgverleners t.a.v. ondersteunende-/nazorg				
• Motivatie specialisten t.a.v. ondersteunende-/ nazorg				
• Motivatie (ondersteunende) zorgverleners				
• Kennis zorgverlener over inhoud ondersteunende-/ nazorg				
• Kennis verwijzer over inhoud ondersteunende-/ nazorg				
• Kennis verwijzer over (in- en externe) verwijsmogelijkheden ondersteunende-/nazorg				
• Stimulatie patiënt deelname ondersteunende-/ nazorg door specialist/ (ondersteunende) zorgverleners				
• Anders				

79	Gaarne specificeren van uw antwoord ''Anders'':

80 Economische belemmerende/ bevorderende factoren in het verlenen van ´nazorg/ ondersteunende zorg´

Kunt u aangeven of onderstaande factoren **de afgelopen 6 maanden in de meeste gevallen** (dus geen incidentele zaken) een **belemmerende** of een **bevorderende factor** zijn geweest bij het verlenen van nazorg/ ondersteunende zorg in uw situatie? (Aanvinken wat van toepassing is)
Indien de factor geen belemmerende of bevorderende factor is, vinkt u ´Komt niet regelmatig voor in mijn situatie´ aan.

Economische factoren

	Belemmerende factor	Bevorderende factor	Komt niet regelmatig voor in situatie	Weet ik niet
• Vergoedingsstructuur ondersteunende-/ nazorg				
• Evalueren kosteneffectiviteit van ondersteunende- / nazorginterventies				
• Anders				

81 Gaarne specificeren van uw antwoord ''Anders'':

82 Financiering van ´nazorg/ ondersteunende zorg´

Zijn er in uw ziekenhuis beperkingen in het verlenen van nazorg voor patiënten met hoofd- halskanker, welke voortkomen uit financiële overwegingen? (Gaarne toelichting)

• Ja • Nee • Weet ik niet

83 Financiering van ´nazorg/ ondersteunende zorg´

Komt het weleens voor dat de nazorg die u verleent niet wordt vergoed, waardoor de patiënt per consult zelf moet betalen of wordt verwezen naar eerstelijnszorg? (Meerdere antwoorden mogelijk)

• Ja, patiënt moet zelf betalen per consult • Ja, patiënt wordt verwezen naar eerstelijnszorg • Nee • Weet ik niet • Anders, namelijk:

84 Patientgerelateerde belemmerende/ bevorderende factoren in het verlenen van ´nazorg/ ondersteunende zorg´

Kunt u aangeven of onderstaande factoren **de afgelopen 6 maanden in de meeste gevallen** (dus geen incidentele zaken) een **belemmerende** of een **bevorderende factor** zijn geweest bij het verlenen van nazorg/ ondersteunende zorg in uw situatie? (Aanvinken wat van toepassing is)
Indien de factor geen belemmerende of bevorderende factor is, vinkt u ´Komt niet regelmatig voor in mijn situatie´ aan.

Patiëntgerelateerde factoren

	Belemmerende factor	Bevorderende factor	Komt niet regelmatig voor in situatie	Weet ik niet
• Beschikbaarheid patiënteninformatie ondersteunende-/nazorg				
• Motivatie/therapietrouw van patiënt				
• Prioriteren ondersteunende-/nazorg door patiënt				
• Verwachtingen ondersteunende-/nazorg van patiënt				
• Reisafstand				
• Vervoer van/naar ziekenhuis				
• Financiële daadkracht (bijv. aanvullende verzekering, reiskostenvergoeding)				
• Gezondheidsvaardigheden van patiënt				
• Beheersing Nederlandse taal				
• Tijd voor ondersteunende-/ nazorg in verhouding tot andere werkgerelateerde/sociale activiteiten				
• Sociaal vangnet/mantelzorg Stimulering door naasten				
• Psychiatrische voorgeschiedenis/co-morbiditeit				
• Anders				

85	Gaarne specificeren van uw antwoord ''Anders'':

86 Organisatorische belemmerende/ bevorderende factoren in het verlenen van ´nazorg/ ondersteunende zorg´

Kunt u aangeven of onderstaande factoren **de afgelopen 6 maanden in de meeste gevallen** (dus geen incidentele zaken) een **belemmerende** of een **bevorderende factor** zijn geweest bij het verlenen van nazorg/ ondersteunende zorg in uw situatie? (Aanvinken wat van toepassing is)
Indien de factor geen belemmerende of bevorderende factor is, vinkt u ´Komt niet regelmatig voor in mijn situatie´ aan.

Organisatorische factoren

	Belemmerende factor	Bevorderende factor	Komt niet regelmatig voor in situatie	Weet ik niet
• Toepassen nationale richtlijn voor oncologische revalidatie				
• Protocol voor ondersteunende-/nazorg				
• Capaciteit specialisten/ (ondersteunende) zorgverleners				
• Hoofd-halsnazorg specialisatie (ondersteunende) zorgverleners				
• Scholingsmogelijkheden o.g.v. ondersteunende-/nazorg voor (para-) medici				
• Afstemmen interventies (ondersteunende) zorgverleners				
• Contactpersoon voor patiënt (bijv. casemanager)				
• Tijdig inventariseren zorgbehoeften (screening)				
• Planning van ondersteunende-/nazorg				
• Communicatie specialisten/ (ondersteunende) zorgverleners				
• Beschikbare ruimten t.b.v. verlenen ondersteunende-/nazorg				
• Ruimtelijke afstanden specialist/ (ondersteunende) zorgverleners (bijv. ontbreken van integrated practice units)				
• Materialen verlenen ondersteunende-/ nazorg (bijv. meetinstrumenten, oefenmateriaal, hulpmiddelen)				
• Samenwerking eerstelijnszorg				
• Anders				

87	Gaarne specificeren van uw antwoord ''Anders'':

88	Opinie Wat is uw mening over het aanbieden van een multidisciplinair revalidatieprogramma voor patiënten met hoofd-halskanker? (Aanvinken wat van toepassing is)			
	• Een multidisciplinair revalidatieprogramma lijkt mij WEL van meerwaarde voor patiënten met hoofd-halskanker.	• Een multidisciplinair revalidatieprogramma lijkt mij NIET van meerwaarde voor patiënten met hoofd-halskanker.	• Weet ik niet	• Anders, namelijk:

89	Opinie Bent u tevreden over de wijze waarop nazorg voor patiënten met hoofd-halskanker in uw ziekenhuis is georganiseerd? (Aanvinken wat van toepassing is)				
	• Zeer tevreden	• Tevreden	• Niet tevreden/niet ontevreden	• Ontevreden	• Zeer ontevreden

90	Opinie Wat zou er volgens u nog verbeterd kunnen worden aan de 'nazorg/ ondersteunende zorg' in uw ziekenhuis? (Gaarne toelichting)0

91	Dit is het einde van deze vragenlijst, hartelijk dank voor het invullen. Mocht u nog vragen of opmerkingen hebben dan kunt u contact opnemen met **a.beck@nki.nl** of **e.passchier@nki.nl**

Chapter 5

Study protocol of a prospective multicenter study comparing (cost-)effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo- or bioradiotherapy

Ann-Jean C.C. Beck*
Ellen Passchier*
Valesca P. Retèl
Martijn M. Stuiver
Lisette van der Molen
Willem M.C. Klop
Arash Navran
Wim H. van Harten
Michiel W.M. van den Brekel
*First author

BMC Cancer. 2019 Jul 3;19(1):655.
doi: 10.1186/s12885-019-5874-z.

Abstract

Background

Since 2011, a tailored, interdisciplinary head and neck rehabilitation (IHNR) program, covered by the basic healthcare insurance, is offered to advanced head and neck cancer (HNC) patients in the Netherlands Cancer Institute (NKI). This program is developed to preserve or restore patients' functioning, and to optimize health-related quality of life (HRQoL). It applies an integrated approach to define patients' individual goals and provide rehabilitation care throughout the cancer care continuum. The aim of the current study is to assess the (cost-) effectiveness of the IHNR approach compared to usual supportive care (USC) consisting of monodisciplinary and multidisciplinary care in advanced HNC patients.

Methods

This multicenter prospective observational study is designed to compare (cost-)effectiveness of the IHNR to USC for advanced HNC patients treated with chemoradiotherapy (CRT) or bioradiotherapy (BRT). The primary outcome is HRQoL represented in the EORTC QLQ-C30 summary score. Functional HRQoL, societal participation, utility values, return to work (RTW), unmet needs (UN), patient satisfaction and clinical outcomes are secondary outcomes, assessed using the EORTC QLQ-H&N35, USER-P, EQ-5D-5L, and study-specific questionnaires, respectively. Both patient groups (required sample size: 64 per arm) are requested to complete the questionnaires at: diagnosis (baseline; T0), 3 months (T1), 6 months (T2), 9 months (T3) and 12 months (T4) after start of medical treatment. Differences in outcomes between the intervention and control group will be analyzed using mixed effects models, Chi-square test and descriptive statistics. In addition, a cost-effectiveness analysis (CEA) will be performed by means of a Markov decision model. The CEA will be performed using a societal perspective of the Netherlands.

Discussion

This prospective multicenter study will provide evidence on the effectiveness and cost effectiveness of IHNR compared to USC. RTW and societal participation, included as secondary outcomes, have not been studied sufficiently yet in cancer rehabilitation. Interdisciplinary rehabilitation has not yet been implemented as usual care in all centers, which offers the opportunity to perform a controlled clinical study. If demonstrated to be (cost-)effective, national provision of the program can probably be advised.

Trial registration: The study has been retrospectively registered in the Netherlands Trial Registry on April 24th 2018 (NTR7140).

Background

In the Netherlands, approximately 3200 patients are diagnosed with head and neck cancer (HNC) annually [1]. Cancer of the head and neck is often treated curatively by (a combination of) surgery, radiotherapy and/or chemotherapy. As a consequence of the tumor and its treatment, impairment of functioning may occur concerning e.g. swallowing, speech, breathing and cancer-related fatigue, but also psychosocial problems such as altered body image, anxiety and depression. Additionally, patients may suffer from pre-existing comorbidity relating to physical and/or psychosocial functioning. Rehabilitation care can play an important role in restoring these functions, and may help to regain daily life activities and improve health-related quality of life (HRQoL) [2, 3].

Rehabilitation often comprises monodisciplinary interventions, also known in the Netherlands as 'usual supportive care' (USC), provided by specialized individual healthcare professionals. Nonetheless, monodisciplinary care does not always sufficiently meet patients' needs, as problems are often multifactorial and complex [2]. To optimize the rehabilitation of patients, an upcoming trend is to implement multidisciplinary rehabilitation care, the importance of which is underlined in the guideline on cancer rehabilitation developed by the Netherlands Comprehensive Cancer Organization (Integraal Kankercentrum Nederland – IKNL) [4]. The rationale is that a coordinated multidisciplinary approach, in which healthcare professionals cooperate to optimize patients' outcomes, might be more effective than healthcare professionals individually addressing patients' problems during conventional monodisciplinary rehabilitation care. In multidisciplinary care, different healthcare professionals have separate (sub)goals that are achieved during rehabilitation with the patient. When these goals are aligned with the objective to achieve one broader goal, such as regaining participation in society by the patient, this is defined as 'interdisciplinary care'. This type of care is assumed to be especially useful when patients have several interrelated and/or severe problems, which is often the case in advanced HNC [5–12]. However, it is also recognized that this type of rehabilitation can be more expensive.

The integrative, biopsychosocial, International Classification of Functioning, Disability and Health (ICF) model [7,13], developed by the World Health Organization, is often applied as a framework for interdisciplinary rehabilitation. The ICF model describes individual functioning in a broader context, consisting of two parts: (1) Functioning and Disability and (2) Contextual factors. Functioning and Disability encompasses the physical and functional status; Contextual factors are subdivided in environmental and personal factors (e.g. coping strategies). In addition, a distinction is made between capacity (the ability to execute a task or action) and performance (the actual task or activity performed in daily life). Discrepancies in current and desired status in each of these components determine a person's individual rehabilitation objective to be achieved, and consequently, the interdisciplinary interventions to apply. For example, a male

HNC patient treated with chemoradiotherapy (CRT), who cannot perform daily activities due to feeding tube dependency and fatigue. The activities (e.g. eating and drinking, walking and driving) this person wants to do, relate to the individual roles in his daily life (e.g. being a father, working as a bus driver). Both components determine which tailored interventions to apply. For example, to be able to perform daily activities such as eating and drinking, walking and driving, swallowing rehabilitation and physical exercise will be needed respectively, both combined with nutritional advice for a personalized, balanced diet. These interventions aim to optimize the patient's capacity. Besides optimizing the patient's capacity, especially if functional improvement is limited, rehabilitation goals can be achieved also by addressing behavioral and/or environmental factors. To optimize the patient's performance in order to resume his role as father and as bus driver, interventions such as energy coaching and family counseling could be applied. These interventions will address personal factors, such as coping, and will use cognitive behavioral therapy to improve the ability to adjust to limitations and improve social functioning. As both physical- and cognitive-based interventions are executed simultaneously within interdisciplinary rehabilitation care, this approach can have a synergistic effect. For HNC patients, a specific ICF HNC core set is available to facilitate interdisciplinary communication within rehabilitation [14].

A HNC-specific interdisciplinary rehabilitation program (IHNR) was developed in the Netherlands Cancer Institute (NKI) in 2010 (version 1.0), based on the ICF framework. IHNR consists of structured interdisciplinary interventions, tailored to the individual needs of the patient, with the primary aim to enable patients to regain their desired level of participation in society. This program is integrated into medical care, which means that the rehabilitation care is offered throughout cancer treatment. IHNR is a modular program (including swallowing rehabilitation module, eating module, bodyweight monitoring module, preventive shoulder rehabilitation module, physical exercise module, energy conservation module, guidance coping and adjustment module, art therapy module). Each module is based on the best available evidence. Healthcare professionals that can be consulted within IHNR, apart from the head and neck surgeon, radiotherapist, physical medicine and rehabilitation (PM&R) physician and dentist, are: the speech-language pathologist, dietician, physical therapist, occupational therapist, medical social worker and/or psychologist, and art therapist [15]. IHNR is implemented as standard care in the rehabilitation of HNC patients in the NKI. More details on this program are given in the Methods section.

The program was found feasible in a previous observational study. In this study, positive outcomes on HRQoL were observed in patients who participated with the IHNR compared to reference values [16]. Also, the time until recovery was shorter than usually observed for patients treated with USC (estimated approximately 1 year) [2]. In addition, the preventive (swallowing) exercise program (PREP) included in the IHNR, was found cost-effective compared to USC

in advanced HNC patients treated with CRT [17]. So far, there is limited uptake of this program by other HNC care providers, partly because of the character of the evidence, partly because insurance agencies for the same reason often do not want to engage in contracting additional services for this population.

The added value of interdisciplinary and multidisciplinary cancer rehabilitation compared to monodisciplinary care, in terms of effectiveness and cost-effectiveness, are reported scarcely in literature for cancer patients [18]. In addition, the effect of this integrated IHNR program on HRQoL, return to work (RTW), participation in society and cost-effectiveness compared to USC has not been studied previously in a controlled setting.

Therefore, the aim of our study is to investigate the effectiveness and cost-effectiveness of IHNR (intervention group) compared to USC (control group) in advanced HNC patients treated with concomitant CRT or bioradiotherapy (BRT) in a prospective controlled clinical study.

Prior to this study, we framed three hypotheses. First, we hypothesize that IHNR will shorten the time to regain (baseline) HRQoL [2]. Second, we hypothesize that the program will enhance the ability to resume work-related and daily activities, and will lead to a reduction in medical consumption (e.g. tube feeding) and adverse events (e.g. occurrence of pneumonias). Third, we expect that these improvements will result in a reduction of hospital- and society-related costs, resulting in a more cost-effective approach than USC [17].

Methods

Study design

We will perform a prospective controlled observational study comparing the effectiveness and cost-effectiveness of IHNR to USC for advanced HNC patients using Patient Reported Outcome Measures (PROMs). Primary objective is HRQoL. Secondary outcomes are functional HRQoL, return to work, societal participation, costeffectiveness, unmet needs, clinical outcomes and patient satisfaction. Before the start of the treatment, patients in the intervention group are offered to participate in the IHNR. The intervention group consists of all eligible consenting patients treated in the NKI, despite participating or not in the program. The control group consists of advanced HNC patients treated in six Dutch HNC centers which are representative for the USC in the Netherlands; three academic and three community centers, providing mono- or multidisciplinary care.

This study does not fall under the Medical Research Involving Human Subjects Act (*Wet Medisch Wetenschappelijk Onderzoek*) due to the non-invasive nature of the study, but is submitted to

and approved by the Dutch Medical Ethical Committees (registered: P16HNR). The study started in February 2017.

Study population: in- and exclusion criteria

Adult patients diagnosed with advanced head and neck squamous cell carcinoma (HNSCC; stage 3 and 4) are included in this study. Patients are eligible if they are to be treated with primary CRT (Cisplatin or Carboplatin) or BRT (Cetuximab) with intent to cure. IHNR takes place mainly at the Center for Quality of Life in the outpatient clinic of the NKI. Patients who are unwilling to cooperate in the study or unable to take part in the program due to a language barrier or an interfering psychiatric or psychological disorder are excluded from the study. Advanced HNC patients who are treated primarily with surgery are not eligible for the study, in order to control heterogeneity within the two arms and ensure comparability between the arms. At least 64 patients are needed per arm.

Study groups

IHNR – intervention group

Since 2011, IHNR is offered to HNC patients as standard rehabilitation care in the NKI, and it is reimbursed through the basic health care insurance package. Recently, the program has been updated to the newest scientific literature and clinical experience (HNR version 2.0, 2016) [15].

IHNR begins after diagnosis prior to or at the start of oncological treatment and continues until approximately 6months post treatment [2]. The PM&R physician defines in discussion with the patient relevant rehabilitation needs and goals, and the core problem that needs to be addressed during rehabilitation. Subsequently, the PM&R physician determines which treatment modules can be applied during treatment. Preventive swallowing rehabilitation combined with nutritional assessment and advice is routinely offered during CRT and BRT. Other interventions are initiated as deemed appropriate to achieve the intended and defined goals, and include physical exercise supervised by a physical therapist, energy counseling or RTW guidance by an occupational therapist, and psychosocial care by a medical social worker and/or psychologist, and art therapist. In conversation with the patient, expected length and frequency of the rehabilitation interventions and the various healthcare professionals to be involved are clarified. Thereafter, the PM&R physician refers to relevant healthcare professionals depending on the rehabilitation modules selected. Assessments are made before the start of rehabilitation treatment by each involved health professional. At the end of the intake phase, the patient's core problem and individual rehabilitation needs, as well as the results of the assessments are discussed in an interdisciplinary team meeting. Subsequently, several SMART (Specific, Measurable, Attainable, Realistic, Timebound) interdisciplinary rehabilitation (sub)goals are formulated. During IHNR, tailored interventions are offered to the patient that meet the individual goals. The interventions are provided individually, or in group sessions if applicable and indicated.

All goals are evaluated every 4 to 6 weeks within the rehabilitation team. Besides the PM&R physician and healthcare professionals, a head and neck surgeon and radiotherapist attend the rehabilitation interdisciplinary meetings to discuss interference of the oncological treatment, and its consequences for the individual rehabilitation plan. The dentist and oral hygienist can be involved as well. This integrated approach distinguishes IHNR from other rehabilitation programs [2].

USC – control group

The control group comprises 6 hospitals, all of which are members of the Dutch Head and Neck Society (DHNS). USC is mostly delivered by healthcare professionals who are affiliated with the Dutch working group of allied healthcare in HNC (PWHHT), and follow national guidelines for HNC supportive care [19]. Nevertheless, from practice, we know that the content and organizational structure between centers can vary between these national centers.

In one subpopulation of the control group, an academic center, HNC patients are offered multidisciplinary rehabilitation care 6 to 8 weeks after treatment. A personalized approach starts from the third chemotherapy cycle with monitoring by the speech-language pathologist and the dietician to offer advice when compensation is needed to guarantee safe and sufficient intake of liquid and food. Patients who become dependent on non-oral intake receive individual coaching to keep drinking sips of water regularly, despite pain. At 6 to 8 weeks after completion of the oncological treatment, the patient's condition is evaluated by a multidisciplinary team and when needed the patient is assessed by a PM&R physician, dietician, occupational therapist, physical therapist and speech-language pathologist, usually resulting in a rehabilitation plan. This subgroup is however reflected as usual care because it rather reflects common practice as patients are included after treatment and there is no structured interdisciplinary care present during rehabilitation.

In general, the other centers in the control group offer monodisciplinary rehabilitation care on indication during or after treatment. The disciplines involved during rehabilitation differ among the centers.

Recruitment and completion of PROMs

Patients' eligibility is assessed at the outpatient clinic by a healthcare professional at the department of the Head and Neck Surgery and Oncology, usually the head and neck surgeon or nurse practitioner. Eligible patients are informed about the study by the investigators of the study or a contact person in the respective centers, usually a healthcare professional of the rehabilitation team. Patient information, informed consent (patient and hospital copy) and a baseline (T0) questionnaire are handed to the patient at the outpatient clinic. Eligible patients who are willing to participate return written informed consent (hospital copy) and the completed baseline questionnaire to the outpatient clinic or by mail. The questionnaire comprises five

PROMs concerning HRQoL, societal participation, employment status, medical consumption, unmet needs and patient satisfaction. Follow-up (FU) questionnaires are send to the home address on paper on four different time points during FU within a one-year range: 3 (T1), 6 (T2), 9 (T3) and 12 (T4) months after start of treatment (Fig. 1).

Primary outcome

Effectiveness: quality of life

Primary outcome is assessed at all time points (T0 to T4), and consists of the summary score of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [20].

The EORTC QLQ-C30 comprises 30 questions, that relate to one global health status/QoL scale, five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three symptom scales (fatigue, nausea/vomiting and pain) and six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). In the EORTC QLQ-C30, each scale or item results in a score ranging from 0 to 100. An increasing score derived from functional scales indicates improved functioning, whereas an increase in symptom scores indicates worsening of symptoms [21, 22]. The EORTC QLQ- C30 summary score originates from all scales except for the global health status/QoL and financial difficulties scales. The score consists of an outcome between 0 and 100 and reflects the overall HRQoL [20].

Secondary outcomes

Secondary outcomes are assessed at all time points (T0 to T4), except for medical consumption, unmet needs and patient satisfaction with care. Information on medical consumption and unmet needs are obtained from T1 to T4; satisfaction by the patient will be assessed at T4.

Head and neck cancer-specific quality of life

HNC-specific HRQoL is assessed using the EORTC QLQ module for HNC; the EORTC QLQ-H&N35. This module contains seven symptom scales (pain, swallowing, senses problems, speech problems, trouble with social eating and social contact, and less sexuality) and eleven single-item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, weight gain), resulting in eighteen scores, ranging from 0 to 100, with higher scores indicating higher symptom burden [22, 23].

Cost-effectiveness: costs, life years and utilities

We will investigate the cost-effectiveness of IHNR versus USC from a societal perspective. We will determine life years, quality-adjusted life years (QALYs) and costs. Data on life years related to the survival of HNC patients will be sourced from the Netherlands Cancer Registry. QALYs are

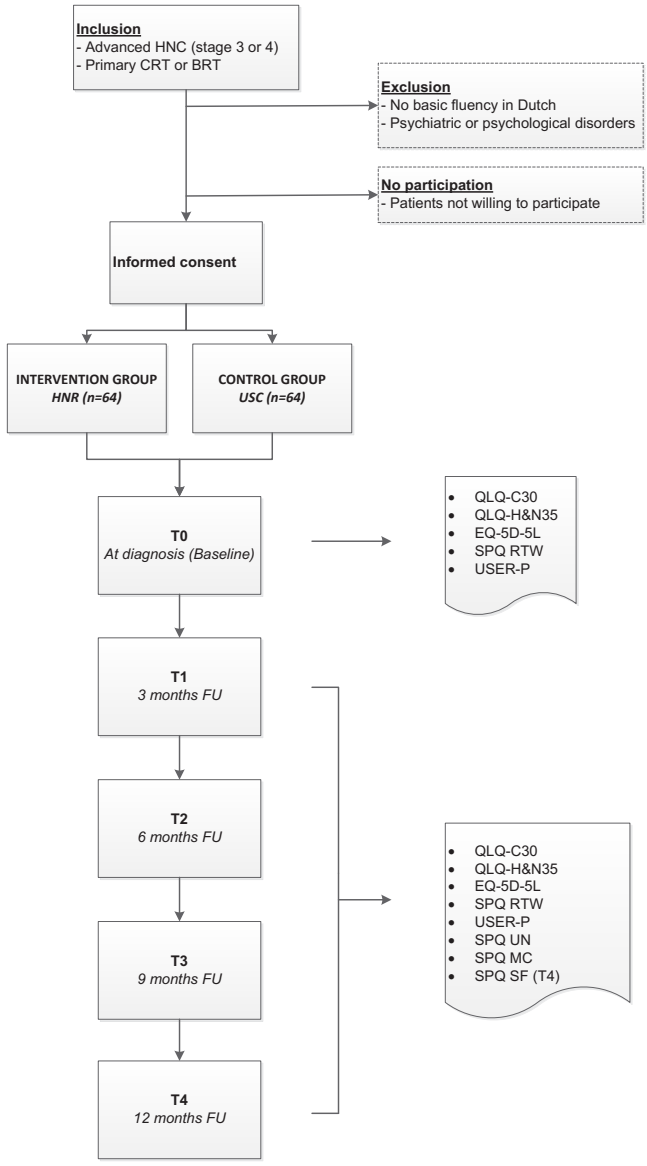

Figure 1. Flowchart of the study.

Abbreviations: BRT, bioradiotherapy; CRT, chemoradiotherapy; EQ-5D-5L, five-level EuroQol five-dimensional questionnaire; FU, follow-up; HNC, head and neck cancer; IHNR, interdisciplinary head and neck cancer rehabilitation program; MC, medical consumption; QLQ-C30, Quality of Life Questionnaire-Core30; QLQ-H&N35, Quality of Life Questionnaire-Head and Neck35; RTW, return to work; SF, satisfaction; SPQ, study-specific questionnaire; UN, unmet needs; USC, usual supportive care; USER-P, Utrecht Scale for Evaluation of Rehabilitation-Participation.

calculated by multiplying the life years with the utilities. A utility is a score that ranges from 0 to 1, derived from the five-level EuroQol five-dimensional questionnaire (EQ-5D-5L), a preference-based instrument. The EQ-5D-5L consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [24].

Direct and indirect costs will be included in the analysis. Costs related to healthcare services by healthcare professionals (e.g. physical therapy, nutritional advice, swallowing rehabilitation), medication use (e.g. painkillers, antibiotics) and dietary supplements (including feeding tube dependency). Direct costs for the intervention will be determined by means of the activity based costing (ABC) method [25]. In addition, work-related costs, such as production loss, costs related to primary care and domestic care will be taken into account. The concise version of the Dutch Medical Consumption Questionnaire (MCQ) will be combined with survival data derived from literature. The MCQ informs on the type and number of consultations by healthcare professionals in the primary and secondary care, domestic care, medication use and dietary supplements [26]. In this way, we can also check for potential crossover contamination between the two groups. To estimate the costs, the cost manual for economic evaluations and the overview of Dutch tariffs defined by the Dutch Healthcare Authority (NZa) are consulted [27, 28].

Return to work (RTW)

At baseline and FU, two study-specific questions regarding employment status (e.g. full time or part-time employee, self-employed, retired), adapted to the Dutch work-related legislation, and profession are included. In addition, the first item of the workability index (WAI) will be assessed. The WAI first item is an estimation of the individual employee of his or her work capacity on a scale from 0 to 10 (0 indicates that the patient is not capable of working and 10 indicates most optimal work capacity). This first item is commonly applied as an indicator of workability in previous studies. The outcome of the WAI has proved to be a good predictor of a person's employability [29, 30].

Societal participation

The Dutch Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) questionnaire will be used to assess societal participation. It contains questions about daily activities and satisfaction with the way in which patients can perform daily activities. The USER-P is a validated questionnaire, and the most commonly used PROM in rehabilitation care in the Netherlands. It comprises 32 items in three scales: frequency, restrictions and satisfaction. Items are accompanied by a five-optional Likert scale. With the algorithm, an average score is calculated between 0 and 100 for each scale. A higher score indicates a better level of societal participation [31].

Unmet needs of the patient

A study-specific question is included at T1 to T4 to identify whether there were important needs that remained unaddressed during the rehabilitation care, and if so, which healthcare professionals the patient wished to be involved. It comprises of a yes-no question to ask whether there were needs not addressed during the last 3 months. If yes, patients can appoint the healthcare provider involved in the need. At the end of the program, the distress thermometer and problem list (completion at start and end of treatment) will be discussed with the patient. In addition, during the multidisciplinary team meeting problems are identified which were not properly addressed at the various time points [32–34].

Patient satisfaction

Level of satisfaction concerning the IHNR or USC will be assessed using a five-point scale, with 0 indicating very unsatisfied and 5 is very satisfied.

Clinical outcomes

Clinical outcomes include adverse events (e.g. pneumonia) during and after treatment, hospital admissions and medication use. These data will be obtained from medical records and a study-specific concise version of the Medical Consumption Questionnaire (MCQ) [26].

Patient, tumor and treatment characteristics

Sociodemographic data (age, sex, marital status, educational background and employment status) of patients are gathered at baseline. Date of start of medical treatment is used to determine FU time points. Additional clinical data comprising treatment details of CRT and BRT (e.g. dose of systemic treatment, number of systemic cycles intended and provided) and tumor characteristics will be obtained from the medical record system. Information on progression of disease and recurrences will be evaluated throughout the study.

Power calculation

To estimate the sample size required for this study, we used a one sample t-test power calculation. The power calculation was based on a comparison between the intervention and control group at end of follow-up, using a power (β) of 0.8 and a significance level of 0.05. We will recruit until we have included 128 patients in total for this analysis (64 are needed per arm) to be able to detect the expected effect-size (Cohen's d) of 0.5 [35]. In our study we will use a repeated-measures design to allow for a more definitive evaluation of within-subject changes in the HRQOL summary score over time. Although, repeated measures can increase statistical power, we opted for a more conservative approach to sample size calculation by assuming a cross-sectional design. This should cover potential design effects such as attrition, or differences in baseline characteristics. Recruitment time is estimated at 2 years.

Statistical analysis

Scores on the HRQoL questionnaires and the USER-P will be calculated according to published scoring algorithms [22, 24,31].

We will look at group differences in HRQOL using a mixed effect growth model with random intercept and slope, nested within site (clusters of different hospitals). This approach takes into account the within and between person variability, and deals adequately with missing data [36]. If baseline differences are identified, these variables will be accounted for in the model. In case of non-ignorable dropout, which will be evaluated halfway during the study, we will correct the model for different patterns of missing values [37]. All analyses will be performed on an 'intention to treat' basis and will be adjusted for case mix by means of a propensity score analysis. Additional explorative analyses will be done on a 'per protocol' basis.

A generalized mixed-effects model using a logistic link function will be used to estimate the effects of IHNR on the proportion of patients at work, compared to USC, at each time point [38]. In this analysis, only patients are included who either are an employee, are self-employed, or do voluntary work at the baseline measurement.

Employment status, unmet needs and satisfaction of the patient will be analysed using descriptive statistics. Group differences in evaluation of satisfaction will be tested by means of the Chi-square test for trend. The unmet needs and the satisfaction of the patient will be evaluated crosssectional, at each time point and at T4 respectively.

Cost-effectiveness analysis

The cost-effectiveness of IHNR compared to USC will be assessed using a Markov model including three health states (disease free survival, progression of disease, death (death due to the HNC or other cause)), a three-month cycle duration and a time horizon of 1 year. One year was chosen because patients are likely to recover within 1 year [2]. Production losses will be analyzed by means of the friction cost method [39, 40]. The friction cost method calculates the costs over the friction period; the period in which the patient has not yet been replaced at work by another employee.

The incremental costs-effectiveness ratio (ICER) is calculated by dividing the difference in total costs of IHNR and USC by the difference in QALYs, and indicates the additional costs of IHNR per QALY gained. The mean together with the degree of uncertainty, represented in confidence intervals of the input parameters, will be estimated, and probabilistic sensitivity analyses will be carried out. Visualization of data will be realized by means of a cost-effectiveness plane and cost-effectiveness acceptability curve [41,42]. A ceiling ratio of €20.000/QALY, corresponding with the Dutch threshold for preventive care, will be used in this analysis [43].

Discussion

To our knowledge, this is the first prospective multicenter study to evaluate the added value of the integrated character of a HNC interdisciplinary rehabilitation program. The study takes into account important outcomes of rehabilitation, including RTW and societal participation, which have not been sufficiently studied to date. As IHNR is an integrated program which is tailored to patients' needs by individual and comprehensive assessment, we assume unmet needs are better addressed within this program.

The primary outcome expressed by the EORTC QLQC30 summary score, derived from the EORTC QLQC30 measurement instrument, offers a more reliable endpoint than the two-item overall QLQ-C30 score, often used in studies [20]. This study will take into account the variations in the provision of rehabilitation care between centers in the control group, due to the multicenter nature of this study including both academic and non-academic hospitals throughout the Netherlands. In addition, the cost-effectiveness analysis included in the study may provide valuable information to support decision-making concerning reimbursement of cancer rehabilitation programs in the Netherlands.

However, several limitations to the study need to be taken into account. Randomization in the current study design was considered not feasible as IHNR is provided as reimbursed standard care in the NKI, and is currently not provided in the other centers. Moreover, introducing randomization in the NKI with a "no supportive care" group raises ethical concerns. '
Therefore, this controlled observational study within different HNC centers was considered to be the most feasible design. To best approach the internal validity of a randomized study, we will adjust for case mix by using propensity score analysis [44]. Furthermore, the USC provided by the control group to HNC patients can vary among the different HNC centers. In this study, these centers are merged in one control group. Differentiation between subgroups of comparable USC will only be feasible in case sufficient number of patients is included in each of these subgroups, which will be challenging especially if one of these groups is relatively well represented in accrual numbers. To minimize the risk of selection bias we recruit sequential cohorts in all participating centers.

Another limitation of this study is the restriction of inclusion to advanced HNC patients treated with CRT or BRT. Patients treated with extensive primary surgery, such as a total laryngectomy, also have rehabilitation needs for which IHNR could be profitable. Nonetheless, we opted to select only patients treated with CRT or BRT to obtain a group as homogenous as possible. Also, as the benefits on effectiveness of interdisciplinary care compared to monodisciplinary and (in particularly) multidisciplinary care have not been proven yet, we will aim to investigate this using multiple outcome measurements. However, whether we can eventually prove these

benefits is not certain. If unmet needs arise from this study, this may be relevant for improvement of rehabilitation care an incentive to also follow-up with a study including qualitative methods or implementing a HNC-specific tool such as the Patient Concerns Inventory [45]. Still, patient's assessment of unmet needs can be difficult as patients are often not aware of the possibilities with regard to supportive care, with the result that some unmet needs remain unknown.

A phenomenon experienced in survivorship studies is the fact that awareness- and diffusion of knowledge on aspects of survivorship care, sometimes in the shape of general healthy living- and general psychosocial advice or it's availability on the internet, makes USC a kind of moving target [46]. This leads to difficulty in establishing the exact differences between the trial arms. Finally, patients who are eligible for this study are also eligible for several other ongoing studies. If patients are included in multiple clinical studies, this may have some influence on HRQoL outcomes. Due to the multicenter nature of most of the other studies, we do not expect these studies to cause relevant differences between centers. Therefore, we believe that the impact on the estimate of effect will be negligible.

With the outcomes of this study, we aim to get more insight into the applicability and efficiency of IHNR in practice. If IHNR proves more (cost-)effective compared to USC, the availability and nationwide reimbursement through basic health insurance will contribute to a better HRQoL in this vulnerable group of patients.

References

1. Netherlands Comprehensive Cancer Organisation. Incidence of head and neck cancer in the Netherlands. [in Dutch]. Available from: https://www.cijfersoverkanker.nl/selecties/Dataset_1/img5d19afb60a6fe. Accessed 1 July 2019.
2. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. Eur Arch Otorhinolaryngol. 2016;273(6):1577–87.
3. Giuliani M, McQuestion M, Jones J, Papadakos J, Le LW, Alkazaz N, et al. Prevalence and nature of survivorship needs in patients with head and neck cancer. Head Neck. 2016;38(7):1097–103.
4. Netherlands Comprehensive Cancer Organisation. Cancer Guideline (2011). Available from: https://www.oncoline.nl/medisch-specialistische-revalidatiebij-oncologie. Accessed 1 July 2019.
5. Licitra L, Keilholz U, Tahara M, Lin J-C, Chomette P, Ceruse P, et al. Evaluation of the benefit and use of multidisciplinary teams in the treatment of head and neck cancer. Oral Oncol. 2016;59:73–9.
6. Clarke P, Radford K, Coffey M, Stewart M. Speech and swallow rehabilitation in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S176–S80.
7. Eadie TL. The ICF: a proposed framework for comprehensive rehabilitation of individuals who use alaryngeal speech. Am J Speech-Lang Pathol. 2003; 12(2):189–97.
8. Eades M, Murphy J, Carney S, Amdouni S, Lemoignan J, Jelowicki M, et al. Effect of an interdisciplinary rehabilitation program on quality of life in patients with head and neck cancer: review of clinical experience. Head Neck. 2013;35(3):343–9.
9. van Weert E, Hoekstra-Weebers J, Grol B, Otter R, Arendzen HJ, Postema K, et al. A multidimensional cancer rehabilitation program for cancer survivors: effectiveness on health-related quality of life. J Psychosom Res. 2005;58(6):485–96.
10. Dieperink KB, Johansen C, Hansen S, Wagner L, KA K, Minet LR, et al. Male coping through a long-term cancer trajectory. Secondary outcomes from a RTC examining the effect of a multidisciplinary rehabilitation program (RePCa) among radiated men with prostate cancer. Acta Oncol. 2017;56(2):254–61.
11. Leclerc AF, Foidart-Dessalle M, Tomasella M, Coucke P, Devos M, Bruyere O, et al. Multidisciplinary rehabilitation program after breast cancer: benefits on physical function, anthropometry and quality of life. Eur J Phys Rehabil Med. 2017;53(5):633–42.
12. Khan F, Amatya B, Drummond K, Galea M. Effectiveness of integrated multidisciplinary rehabilitation in primary brain cancer survivors in an Australian community cohort: a controlled clinical trial. J Rehabil Med. 2014;46(8):754–60.
13. WHO. International Classification of Functioning, Disability and Health (ICF). Available from: http://www.who.int/classifications/icf/en/. Accessed 19 Mar 2018.
14. Tschiesner U, Rogers S, Dietz A, Yueh B, Cieza A. Development of ICF core sets for head and neck cancer. Head Neck. 2010;32(2):210–20.
15. Netherlands Cancer Institute. HNR 2.0 (version 2006). Available from: https://www.avl.nl/flipbooks/HHR-HNR%202.0/index.html#p=1. Accessed 19 Mar 2018.

16. Scott NW, Fayers P, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, et al. EORTC QLQ-C30 reference values manual. 2008.

17. Retèl VP, van der Molen L, Hilgers FJ, Rasch CR, l'Ortye AA, Steuten LM, et al. A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemoradiotherapy. BMC Cancer. 2011;11(1):475.

18. Mewes JC, Steuten LM, IJzerman MJ, Van Harten WH. Effectiveness of multidimensional cancer survivor rehabilitation and cost-effectiveness of cancer rehabilitation in general: a systematic review. Oncologist. 2012;17(12):1581–93.

19. Dutch Society for Otorhinolaryngology. Guideline for head and neck tumors. [in Dutch]. https://richtlijnendatabase.nl/richtlijn/hoofdhalstumoren/hoofdhalstumoren_-_korte_beschrijving.html. Accessed 1 July 2019.

20. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol. 2016; 69:79–88.

21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.

22. Fayers PM, Aaronson NK, Bjordal K, Grønvold M, Curran D, Bottomley A. EORTC QLQ-C30 scoring manual; 2001.

23. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) quality of life head and neck module (QLQ H&N35). Arch Otolaryngol Head Neck Surg. 2000;126(4):459–67.

24. Szende A, Oppe M, Devlin N. EQ-5D value sets: inventory, comparative review and user guide. Berlin: Springer Science & Business Media; 2007. https://doi.org/10.1007/1-4020-5511-0.

25. Lievens Y, Van den Bogaert W, Kesteloot K. Activity-based costing: a practical model for cost calculation in radiotherapy. Int J Radiat Oncol Biol Phys. 2003;57(2):522–35.

26. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens J, Brouwer W. Manual of the iMTA medical consumption questionnaire (iMCQ). Rotterdam: iMTA, Erasmus University Rotterdam; 2013.

27. Hakkaart-Van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Swan Tan SK. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg [manual for economic evaluations: methods and standard cost prices for economic evaluations in health care]. Rotterdam: Institute for Medical Technology Assessment, Erasmus MC; 2015.

28. Dutch Health Authority (NZa). DBC product finder for tariffs (2017). Available from: https://puc.overheid.nl/nza/doc/PUC_236092_22/1/. Accessed 1 July 2019.

29. De Zwart B, Frings-Dresen M, Van Duivenbooden J. Test–retest reliability of the work ability index questionnaire. Occup Med. 2002;52(4):177–81.

30. De Boer A, Verbeek J, Spelten E, Uitterhoeve A, Ansink A, De Reijke T, et al. Work ability and return-to-work in cancer patients. Br J Cancer. 2008;98(8):1342.

31. Post MW, van der Zee CH, Hennink J, Schafrat CG, Visser-Meily JM, van Berlekom SB. Validity of the Utrecht scale for evaluation of rehabilitation-participation. Disabil Rehabil. 2012;34(6):478–85.

32. Ma X, Zhang J, Zhong W, Shu C, Wang F, Wen J, et al. The diagnostic role of a short screening tool—the distress thermometer: a meta-analysis. Support Care Cancer. 2014;22(7):1741–55.

33. Carlson LE, Waller A, AJ M. Screening for distress and unmet needs in patients with cancer: review and recommendations. J Clin Oncol. 2012; 30(11):1160–77.

34. National Comprehensive Cancer Network. National Comprehensive Cancer Network, NCCN clinical practice guidelines in oncology: distress management. US; 2008. Available from: https://www.nccn.org/patients/resources/life_with_cancer/pdf/nccn_distress_thermometer.pdf. Accessed June 2019

35. Cohen J. Statistical power analysis for the behavioral sciences. Hilsdale: Lawrence Earlbaum Associates; 1988. p. 2.

36. Diggle P. Analysis of longitudinal data. Oxford: Oxford University Press; 2002. https://doi.org/10.2307/2291352.

37. Son H, Friedmann E, Thomas SA. Application of pattern mixture models to address missing data in longitudinal data analysis using SPSS. Nurs Res. 2012;61(3):195–203.

38. Steyerberg EW. Clinical prediction models: a practical approach to development,validation, and updating. New York: Springer Science & Business Media; 2008. https://doi.org/10.1007/978-0-387-77244-8.

39. Garrison LP, Mansley EC, Abbott TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR drug cost task force report—part II. Value Health. 2010;13(1):8–13.

40. Koopmanschap MA, Rutten FF, van Ineveld BM, Van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ. 1995; 14(2):171–89.

41. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation: Handbooks in Health Economic E; 2006.

42. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of costeffectiveness acceptability curves. Health Econ. 2001;10(8):779–87.

43. Raad voor de Volksgezondheid en Zorg aan de minister van Volksgezondheid, Welzijn en Sport. Zinnige en duurzame zorg. Zoetermeer; 2006. https://www.raadrvs.nl/documenten/publicaties/2006/06/07/zinnigeen-duurzame-zorg. Accessed 1 July 2019.

44. d'Agostino RB. Tutorial in biostatistics. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17(19):2265–81.

45. Ghazali N, Kanatas A, Bekiroglu F, Scott B, Lowe D, Rogers SNJTBotRCoSoE. The Patient Concerns Inventory: a tool to uncover unmet needs in a cancer outpatient clinic. 2013;95(3):1–6.

46. van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, et al. Effect of low-intensity physical activity and moderate-to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomizedclinical trial. J Clin Oncol. 2015;33(17):1918–27.

Abbreviations

ABC	Activity based costing
BRT	Bioradiotherapy
CEA	Cost-effectiveness analysis
CRT	Chemoradiotherapy
DHNS	Dutch Head and Neck Society
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	Five-level EuroQol five-dimensional questionnaire
FU	Follow-up
HNC	Head and neck cancer
HNSCC	Head and neck squamous cellcarcinoma
HRQol	Health-related quality of life
ICER	Incremental costseffectiveness ratio
ICF	International Classification of Functioning Disability and Health
IHNR	Interdisciplinary head and neck cancer rehabilitation
IKNL	Netherlands Comprehensive Cancer Organization – *Integraal Kankercentrum Nederland*
MCQ	Medical Consumption Questionnaire
NKI	Netherlands Cancer Institute
NZA	Dutch Healthcare Authority – *Nederlandse Zorgauthoriteit*
PREP	Preventive (swallowing) exercise program
PROM	Patient reported outcome measure
PWHHT	Dutch working group of allied healthcare in head and neck cancer – *Paramedische Werkgroep voor Hoofd-Halstumoren*
QALY	Quality-adjusted life year
QLQ-C30	Quality of life questionnaire-core 30
RTW	Return to work
UN	Unmet needs
USERP	Dutch Utrecht Scale for Evaluation of Rehabilitation-Participation – *Utrechtse Schaal voor Evaluatie van Revalidatie-Participatie*
USC	Usual supportive care
WAI	Workability index

Acknowledgements

Not applicable.

Authors' contributions

AB, EP, VR, MS, LM, MK, AN, WH and MB contributed to the design of the study protocol. All authors read and approved the manuscript.

Author details

1 Department of Head and Neck Surgery and Oncology, the Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands.
2 Division of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute, Amsterdam, the Netherlands.
3 Center for Quality of Life, Netherlands Cancer Institute, Amsterdam, the Netherlands.
4 ACHIEVE Center of Applied Research, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands.
5 Department of Health Technology and Services Research, University of Twente, Enschede, the Netherlands.
6 Rijnstate Hospital, Arnhem, the Netherlands.
7 Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands.
8 Institute of Phonetic Sciences, University of Amsterdam, Amsterdam, the Netherlands.
9 Department of Oral and Maxillofacial Surgery, Amsterdam University Medical Center (Amsterdam UMC), Amsterdam, the Netherlands

Author's information

Not applicable.

Availability of data and materials

The dataset used and analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

AB, EP and MS are supported by a non-restricted research grant from ATOS Medical Sweden contributing to the existing infrastructure for health-related quality of life research of the department of Head and Neck Oncology and Surgery. ATOS Medical Sweden had no involvement in the development of the study protocol.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study (registration number: P16HNR) has received ethical approval from the Medical Ethical Committee of the participating hospitals. The participating hospitals are: Maastricht University Medical Center (MUMC+)/ MAASTRO Clinic, Maastricht; Medical Center Haaglanden (MCH), The Hague; Medisch Spectrum Twente (MST); Netherlands Cancer Institute (NKI), Amsterdam; Radboud university medical center (Radboudumc) Nijmegen, University Medical Center Utrecht (UMCU), Utrecht; Rijnstate Hospital, Arnhem. A written informed consent is obtained from all participants upon participation.

Funding

The study is funded by the Netherlands Cancer Institute (Plesmanlaan 121, 1066CX, Amsterdam, the Netherlands). AB, EP and MS are supported by a non-restricted research grant from ATOS Medical Sweden.

Chapter 6

Cost-effectiveness of surgery versus organ preservation in advanced laryngeal cancer

Ann-Jean C.C. Beck
Wim H. van Harten
Michiel W.M. van den Brekel
Arash Navran
Valesca P. Retèl

Accepted at Laryngoscope
doi: 10.1002/lary.28954.

Abstract

Objective

Treatment decision-making for patients with laryngeal cancer consists of a complex trade-off between survival and quality of life. For decision makers on coverage and guidelines, costs come in addition to this equation. Our aim was to perform a cost-effectiveness analysis of surgery (laryngectomy with or without radiotherapy) versus organ preservation (OP: radiotherapy, chemo- and/or bioradiation) in advanced laryngeal cancer patients from a healthcare perspective.

Methods

A cost-effectiveness analysis was conducted using a Markov model. For each modality, data on survival and quality-adjusted life years (QALYs) were sourced from relevant articles in agreement with experts, and national benchmark cost prices were included regarding treatment, follow-up, adverse events and rehabilitation.

Results

Total QALYs of the surgical approach (6.59) were substantially higher compared to the OP approach (5.44). Total lifetime costs were higher for the surgical approach compared to the OP approach, namely €95,881 versus €47,233. The surgical approach was therefore more effective and more costly compared to OP, resulting in an incremental cost-effectiveness ratio of €42,383/QALY.

Conclusion

Based on current literature, surgical treatment was cost-effective compared to OP in advanced laryngeal cancer within most willingness-to-pay thresholds. The study provides information on the survival adjusted for quality of life in combination with costs of two different approaches for advanced laryngeal cancer, relevant for patients, physicians and policy makers. As financial toxicity is a relevant aspect in this population, collection of real-world data on country-specific costs and utilities is strongly recommended to enable further generalization.

Introduction

Worldwide, the incidence of laryngeal cancer is estimated to be 177,000 and accounts for 94,000 deaths per year [1]. Cancer of the larynx is accountable for approximately one-third of the head and neck cancers (HNCs) [2]. The disease and treatment have a detrimental impact on a patient's life and often patients have to cope with significant morbidity after treatment [3].

In laryngeal cancer, choosing the right individual treatment is dependent on multiple aspects including patient-related (e.g. age, comorbidity) and treatment-related factors (e.g. intensity, duration, toxicity). This is especially difficult when treatment options have similar survival rates. In example, most studies on patients with T3 laryngeal carcinoma do not report significant differences in overall survival (OS) between surgery and organ preserving (OP) modalities [4]. Not only survival outcomes, but also treatment effects on quality of life (QoL) and physical and psychosocial functioning are crucial in decision-making [5]. In advanced laryngeal cancer patients, no significant differences in QoL outcome were reported between treatment with either total laryngectomy or chemoradiation. However, they do have different toxicities: e.g. the chemoradiation group had more problems with dry mouth whereas the laryngectomy group suffered from disturbances in smell, use of painkillers and taste and coughing [3]. In addition, most long-term QoL studies in laryngectomy patients report that these patients have a relatively high overall QoL due to factors such as adequate counseling and coping [6,7]. Overall, the tradeoff between treatment-related QoL and survival outcomes makes selecting a treatment challenging for the patient and physician. Combining QoL and survival in one effectiveness outcome such as the quality-adjusted life years (QALY) outcome could be relevant information in clinical practice.

In a cost-effectiveness analysis, all these relevant aspects are combined in the trade-off. This information can serve as input for guideline development, optimization of treatment choices in individual decision-making and at a political level, in the decision whether or not to reimburse certain treatments. Taking into account costs for the total treatment trajectory – including costs for treatment of adverse events (AE) and rehabilitation into - is necessary, especially nowadays due to growing numbers of cancer survivors and healthcare costs as a whole. Medical expenses, in terms of financial toxicity, impact this financially strained population for whom coverage is not always assured [8]. The literature on cost-effectiveness research in the laryngeal cancer field is scarce. Morton et al. reported on cost-effectiveness in 1997 showing the trade-off between the modalities of guidelines at that time [9]. A cost minimization study evaluating total laryngectomy with radiotherapy (RT) versus induction chemotherapy and RT resulted in cost savings in the surgery group [10]. This study only focused on short-term AE. In addition, economic burden was reported in two studies, with substantially high (outpatient) chemoradiation costs in the United States [11,12].

Currently, a complete overview of patients' survival, detailed AE, function (QoL) and cost data is lacking in literature. Using a cost-effectiveness model, all relevant information available in literature could be combined, and (cost-)effectiveness outcomes could be used as relevant information to support clinical and policy decision-making.

Therefore, the aim of this study is to evaluate the cost-effectiveness of surgery, comprising of total laryngectomy with or without postoperative RT, compared to organ preservation (OP), consisting of RT, chemoradiation (CRT with Cisplatin) and bioradiation (BRT with Cetuximab), including short and long-term AE in advanced (stage 3 and 4) laryngeal cancer.

Materials and methods

Patient groups

Two patient groups were compared in the model: patients with advanced (stage 3 and 4) laryngeal cancer treated with curative intent with surgery with or without RT versus OP (RT/CRT/BRT). Weighted averages were applied to patients with or without treatment with RT (surgery group) and patients treated with RT, CRT or BRT (OP group). For the surgery group, this means that a proportion of patients – in accordance to literature – received postoperative RT. This portion of patients had additional costs related to e.g. RT treatment, follow-up and treatment of RT-specific AE (fibrosis). As the model input data derived from literature – including the survival-specific data – was not available for stage 3 and stage 4 separately, we could not build separate models based on stage.

The study was assessed and approved by the Medical Ethical Committee of the Netherlands Cancer Institute (NKI-AVL) registration number: METC18.0916/P18CEA).

Model description

A Markov decision model was developed from a healthcare perspective including three mutually exclusive health states: disease-free survival, progression of disease (POD) and death (due to laryngeal cancer or other causes) (Figure 1). By means of Monte Carlo simulation, a hypothetical cohort of 5000 patients was simulated with a lifetime horizon using a one-year cycle time. The survival data (progression of disease), cost data and treatment regimens were based on the Dutch perspective.

Input data

The input parameters were obtained from various key international articles, carefully selected on relevant criteria in consensus with a group of experts. An overview of the input parameters is shown in Table 1. Detailed information on the methods regarding the input data is provided in full text in Appendix A.

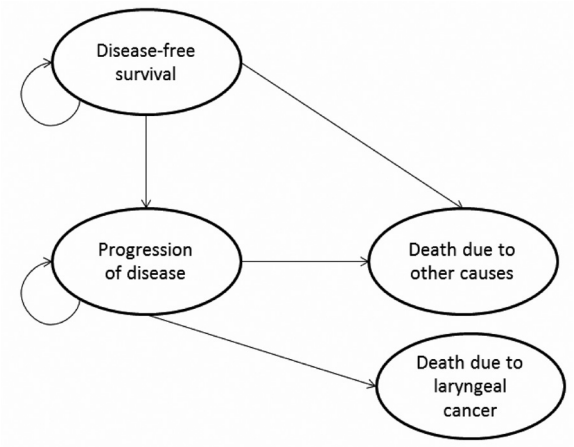

Figure 1. Health states of the Markov model.

The relevant criteria were: tumor group ((at least) inclusion of advanced laryngeal cancer), sample size (at least 50 per subgroup (except for five subgroups; see 'sample size' in Appendix B)), availability of AE/QoL data using a (validated) measurement tool (e.g. EuroQol five-dimensional questionnaire (EQ-5D)) [13], time point of assessment of AE/QoL (preferably at least 6 months post-treatment) and quality of the study (e.g. (randomized) controlled trial) to obtain comparable input data. Literature-based input data comprised of survival data, (primary and secondary) treatment probabilities and most incidental long-term AE.

The health effects, expressed in QALYs, were calculated by multiplying the life years gained times the associated EQ-5D utilities, and sourced from literature.

When literature was not sufficient or available regarding probabilities for the BRT group, they were assumed to be similar to the CRT group based on expert elicitation. Also, the probability of managing fibrosis for postoperative RT and RT group was assumed to be similar to CRT and BRT respectively by the experts.

All literature-based input data were confirmed and assessed for generalizability with a panel of experts in the HNC field consisting of head and neck surgeons, radiotherapist, medical oncologist, speech-language pathologist, physiotherapist, dietician, physician assistant and nurse specialists. Additional information of the specifications (e.g. sample size, tumor group, time point of measurement) of the included articles and sourcing of the probabilities is provided in Appendix B.

National cost prices were linked to the 2018 Dutch diagnosis-related groups (DRGs) (sub)codes (Table 1) [14]. Costs for medication and nutritional support were calculated with online prices [15,16].

Table 1. Model input parameters per year. The table includes the probabilities, health effects ((dis)utilities) and costs used in the model to obtain the deterministic model outcomes. Treatment probabilities, adverse events, utilities, treatment(-related) costs, adverse events costs and rehabilitation are provided for the surgery and organ preservation group separately. To conduct the simulations, random numbers were drawn for each parameter from the beta (probabilities/utilities) and gamma (costs/frequencies) to account for the uncertainty within the parameters.

Probabilities (range 0-1)	Mean	SE	Distribution	Source
Survival				
Progression of disease – Surgery	0.133	0.043	Beta	See appendix B
Progression of disease – OP	0.176		Beta	See appendix B
RT	0.178	0.038		
CRT	0.163	0.081		
BRT	0.163	0.081		
Death due to laryngeal cancer†	0.249	0.022	Beta	See appendix B
Treatment probabilities - Surgery				
PORT (1 cycle)‡	0.797	0.012	Beta	See appendix B
Secondary treatment (curative) of recurrent disease (1 cycle)	0.125	0.042	Beta	See appendix B
Secondary treatment (palliative) of recurrent disease† (1 cycle)	0.300	0.034	Beta	See appendix B
Treatment probabilities - OP				
Secondary treatment (curative) of recurrent disease (1 cycle)	0.164	0.033	Beta	See appendix B
Adverse events – Surgery				
Dysphagia – oral supplements (continuous cycles)	0.417	0.081	Beta	See appendix B
Fibrosis (2 cycles)	0.069	0.033	Beta	See appendix B
Hypothyroidism (continuous cycles)	0.108	0.050	Beta	See appendix B
Neopharyngeal spasm (1 cycle)	0.124	0.029	Beta	See appendix B
Neopharyngeal stenosis (3 cycles)	0.233	0.019	Beta	See appendix B
Tracheostomal stenosis (1cycle)	0.130	0.023	Beta	See appendix B

Adverse events – OP				
Dysfunctional larynx – total laryngectomy (1 cycle)	0.041		Beta	See appendix B
RT	0.041	0.018		
CRT	0.041	0.018		
BRT	0.041	0.018		
Dysfunctional larynx – tracheostomy (1 cycle)	0.020		Beta	See appendix B
RT	0.020	0.013		
CRT	0.020	0.013		
BRT	0.020	0.013		
Dysphagia – oral supplements (1 cycle)	0.336		Beta	See appendix B
RT	0.335	0.032		
CRT	0.327	0.063		
BRT	0.394	0.034		
Dysphagia – tube feeding (1 cycle)	0.132		Beta	See appendix B
RT	0.100	0.013		
CRT	0.330	0.026		
BRT	0.239	0.062		
Fibrosis (2 cycles)	0.024		Beta	See appendix B
RT	0.018	0.018		
CRT	0.069	0.033		
BRT	0.018	0.018		
Hypothyroidism (continuous cycles)	0.086		Beta	See appendix B
RT	0.086	0.027		
CRT	0.086	0.027		
BRT	0.086	0.027		
Laryngeal edema (1 cycle)	0.074		Beta	See appendix B
RT	0.074	0.031		
CRT	0.074	0.031		
BRT	0.074	0.031		

Table 1. Continued

Pneumonia (continuous cycles)	0.117		Beta	See appendix B	
RT	0.100	0.007			
CRT	0.213	0.023			
BRT	0.213	0.023			
Frequencies (range >0)	**Mean**	**SE**	**Distribution**		
Treatment-related frequencies - Surgery					
Yearly number of voice prosthesis replacements	5.214	0.665	Gamma		
Health effects (utility values, range 0-1)	**Mean**	**SE**	**Distribution**	**Source**	
Utility DFS – Surgery	0.890	0.020	Beta	[17]	
Utility DFS – OP	0.846		Beta		
RT	0.847	0.024		[18]	
CRT	0.840	0.011		[19]	
BRT	0.840	0.011		EE	
Disutility Progression	0.130	0.070	Beta	[18]	
Costs (€)	**Mean**	**SE**	**Distribution**	**Source**	**Content diagnostics/treatment**
Treatment costs – Surgery					
Total laryngectomy	16 692	2 129	Gamma	[14]	
PORT	6 678	852	Gamma	[14]	
ICU (per day)	2 325	297	Gamma	[14]	
Total costs Surgery	24 339		Gamma	[14]	
Diagnostics progression of disease†	345	44	Gamma	[14]	Laryngoscopy, CT-scan of the head and neck, ultrasound of the neck with FNAC, PET-CT (only in patients treated with curative intention)
Secondary treatment (curative) of recurrent disease	1 459	186	Gamma	[14]	Neck dissection
Secondary treatment (palliative) of recurrent disease†	40 659	5 186	Gamma	[14,15]	Chemotherapy (Carboplatin) or immunotherapy (Nivolumab) with tracheostomy placement in a portion of the patients

Treatment costs – OP					
RT	9 246	1 179	Gamma	[14]	
CRT	11 408	1 455	Gamma	[14,15]	
BRT	20 970	2 675	Gamma	[14,15]	
Diagnostics	1 453	185	Gamma	[14]	Laryngoscopy, CT-scan of the head and neck, chest X-ray, OPT, ultrasound of the neck with FNAC, PET-CT, examination under general anesthetics (including one-day admission)
Total costs OP	11 311		Gamma	[14]	
Secondary treatment (curative) of recurrent disease	22 997	2 933	Gamma	[14]	Total laryngectomy and flap reconstruction (including 1 ICU day)
Treatment-related costs - Surgery					
Voice prosthesis replacements first year (total)	3 281	418	Gamma	[14]	
Voice prosthesis replacements FU (costs per replacement)	778	99	Gamma	[14]	
FU consultation specialist year 0[†]	63	8	Gamma	[14]	
FU consultation specialist year 1	216	28	Gamma	[14]	
FU consultation specialist year 2	171	22	Gamma	[14]	
FU consultation specialist year 3-5	108	14	Gamma	[14]	
Treatment-related costs - OP					
FU consultation specialist year 1	206	26	Gamma	[14]	
FU consultation specialist year 2	143	18	Gamma	[14]	
FU consultation specialist year 3-5	103	13	Gamma	[14]	
Adverse events costs – Surgery					
Dysphagia – oral supplements	3 048	389	Gamma	[14,16]	VFSE, consultation speech-language pathologist and dietician, oral supplements (every 3 months)
Fibrosis[†,§]	153	19	Gamma	[14]	Consultation physiotherapist (every 4 months)

Table 1. Continued

Hypothyroidism FU year 1-5†	489	62	Gamma	[14,15]	Consultation internist, Thyrax supplementation (every 6 months)
Hypothyroidism FU after 5 years†	244	31	Gamma	[14,15]	Consultation internist, Thyrax supplementation (every 12 months)
Neopharyngeal spasm	283	36	Gamma	[14,15]	Consultation head and neck surgeon, Botox injection
Neopharyngeal stenosis	2 565	327	Gamma	[14]	VFSE, dilatation
Tracheostomal stenosis	4 104	523	Gamma	[14]	Stomaplasty
Adverse events costs – OP					
Dysfunctional larynx – total laryngectomy	16 692	2 129	Gamma	[14]	Total laryngectomy
Dysfunctional larynx – tracheostomy	2 013	257	Gamma	[14]	Tracheostomy and PRG placement
Dysphagia – oral supplements	1 327	169	Gamma	[14,16]	VFSE, consultation speech-language pathologist and dietician, oral supplements (6 months max)
Dysphagia – tube feeding	6 973	889	Gamma	[14], hospital costs	VFSE, PRG placement, consultation speech-language pathologist and dietician, tube feeding (12 months)
Laryngeal edema	1 460	186	Gamma	[14]	Tracheostomy placement
Pneumonia	3 063	391	Gamma	[14]	Antibiotics during hospital admission
Rehabilitation – Surgery	4 091	522	Gamma	[14]	Outpatient clinic healthcare providers (e.g. speech-language pathologist, physiotherapist, occupational therapist), diagnostics (e.g. blood count. X-ray)
Rehabilitation – OP	1 588		Gamma	[14]	Outpatient clinic healthcare providers (e.g. speech-language pathologist, physiotherapist, occupational therapist), diagnostics (e.g. blood count. X-ray)
RT	1 146	146			
CRT	4 091	522			
BRT	4 091	522			

The number of simulation cycles applied to the AE is provided between brackets.
The FU consultations with specialists refer to the head and neck surgeon and radiotherapist.
All treatments include diagnostics (except for primary OP treatment), treatment, hospital admission (if applicable), medication use, consultations healthcare providers including specialists, acute complications and the first outpatient consultation. The content of diagnostics for the OP group, treatments of AE, secondary treatments and rehabilitation care are specified in the content column.
Probabilities and costs for OP are weighted averages. Survival rates were converted to one-year probabilities with the formulas: rate = -[ln(1-probability)]/time and 1-year probability=1-exp(-rate*1) [20].

Abbreviations: BRT, bioradiation; CRT, chemoradiation; CT-scan, *Computed Tomography* scan; EE, expert elicitation; FNAC, fine needle aspiration cytology; FU, follow-up; OP, organ preservation; OPT, panoramic radiograph; PET-CT, Positron emission tomography–*computed tomography;* PORT, postoperative radiotherapy; PRG, percutaneous radiologic gastrostomy; RT, radiotherapy; SE, standard error; VFSE, video fluoroscopic swallowing exam; X-ray, electromagnetic radiation.

†Similar between Surgery and OP group.
‡The proportion of patients receiving RT in the surgery group. The additional costs related to RT treatment, FU and AE are included in the total costs for the surgery group based on this proportion (through a weighted average).
§Only applies to patients with postoperative RT.

Deterministic analysis

The incremental cost-effectiveness ratio (ICER) was used as a primary outcome. The ICER is calculated by dividing the difference in total lifetime costs of both strategies by the QALY difference. The ICER is expressed in costs per QALY gained. The willingness-to-pay (WTP) threshold reflects how much the Dutch population is willing to pay for a gain in effect (QALY), and is situated at €80 000 currently in the Netherlands [21].

A discount rate of 4% and 1,5% was applied to the costs and health outcomes respectively according to Dutch guidelines [22].

Probabilistic sensitivity analysis

Uncertainty within the input probabilities was handled probabilistically through distributions for each of the parameters (Table 1). Random numbers were drawn from the distributions to simulate the outcomes of 5000 patients. The simulations were visualized by a cost-effectiveness (CE) plane, consisting of four quadrants, in which the incremental costs (y-axis) and QALYs (x-axis) indicate whether the treatment in question is more or less costly or effective compared to usual care. The cost-effectiveness acceptability curve (CEAC) displays the probability (y-axis) of a strategy being cost-effective (a.k.a. the highest net monetary benefit) at the various thresholds in costs/QALY (x-axis) [20,23].

The analysis was performed in Microsoft Excel version 2010.

Sensitivity analyses

A tornado diagram was constructed to show the sensitivity of uncertain parameters and for identification of most influential parameters on the ICER, costs and QALYs. Margins of +/- 20% were applied to obtain the parameter ranges. Specific scenario analysis were performed for: 1) rehabilitation care, because this type of care is provided but is not (yet) standardized, and 2) the number of cycles of chemotherapy because these may be discontinued due to AE including nephrotoxicity (Appendix C).

Results

Mean results

Over the lifetime period, the surgical approach was more effective but more costly than the OP group (Table 2). In the surgery versus OP group, the LY and QALY gain were 0.91 (7.80 versus 6.89) and 1.15 (6.59 versus 5.44) respectively. The total lifetime healthcare costs per patient were higher with the surgical approach (€95 881) compared to OP (€47 233).

Table 2. Model outcomes of cost-effectiveness of the analysis surgery compared to organ preservation in advanced laryngeal cancer from a healthcare perspective.

Treatment modality	Costs (€)	QoL (QALY)	Survival (LY)	ICER (€QALY)
Surgery	95 881	6.59	7.80	
OP	47 233	5.44	6.89	
Increments	48 647	1.15	0.91	
Surgery compared to OP				42 383

Abbreviations: BRT, bioradiotherapy; CRT, chemoradiation; ICER, incremental cost-effectiveness ratio; LY, life year; OP, organ preservation; QALY, quality-adjusted life year; QoL, quality of life; RT, radiotherapy.

Uncertainty analysis

The CE plane shows that the majority of simulations (86%) is situated in the cost-effective quadrant (displayed northeast), which means that surgery is more effective and more costly (Figure 2). The surgical approach is cost-effective at a WTP threshold of more than €40 000 (Figure 3). At the Dutch WTP threshold of €80 000/QALY, the surgical approach is cost-effective with a probability of 70%.

One-way sensitivity analysis

The tornado diagrams in Figure 4a-c show most influential input parameters (ranked most influential from top to bottom). The diagrams display the impact of changing a certain parameter in the model (+/- 20%) on the ICER (Figure 4a), incremental costs (Figure 4b) and incremental QALYs (Figure 4c).

Overall, model outcomes proved to be robust against parameter changes, as the surgical approach remained the most cost-effective approach. Taking into account costs for rehabilitation care and a reduction in systemic therapy costs through discontinuation of Cisplatin cycles did not impact the cost-effectiveness outcomes from the model.

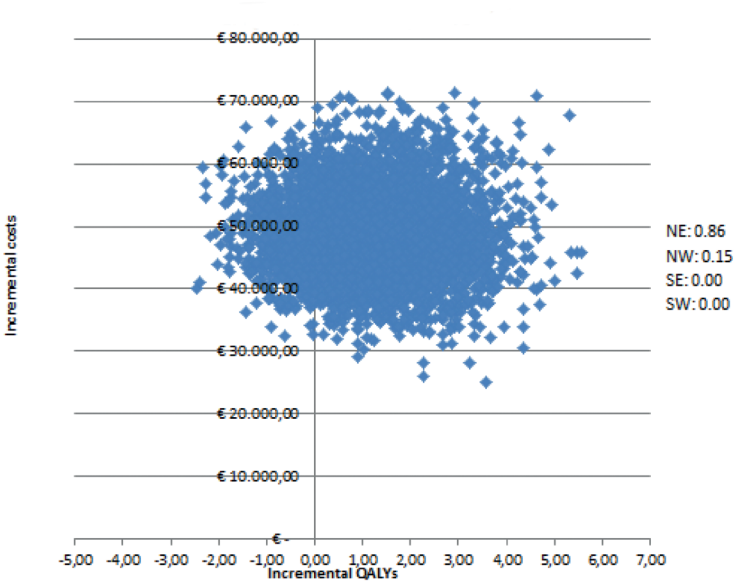

Figure 2. Cost-effectiveness (CE) plane of surgery versus OP. The scatter dots each represent incremental costs and QALYs of the 5000 simulations. NE, northeast quadrant; NW, northwest quadrant (dominated); SE, southeast quadrant (dominant); SW, southwest.

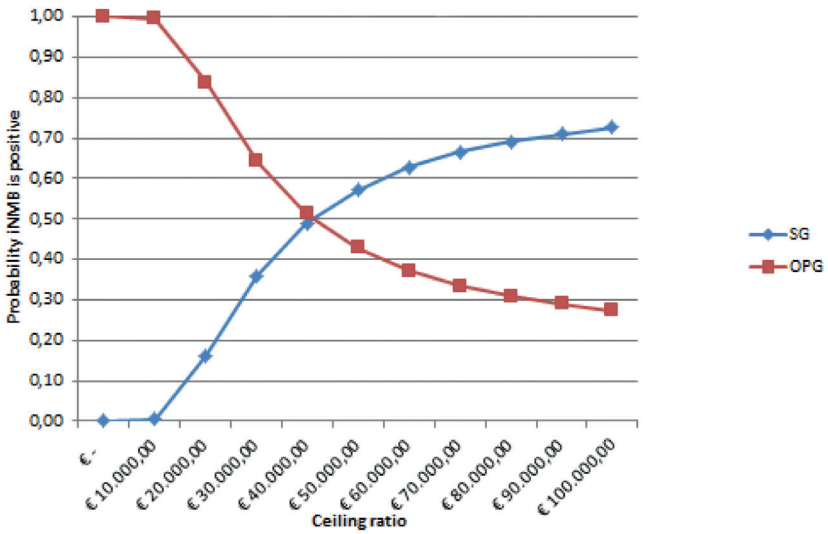

Figure 3. Cost-effectiveness acceptability curves (CEAC) of surgery versus OP. The curve represents the probability of surgery being cost-effective at various willingness-to-pay thresholds (ceiling ratios).

Abbreviations: OPG, organ preservation group; SG, surgery group.

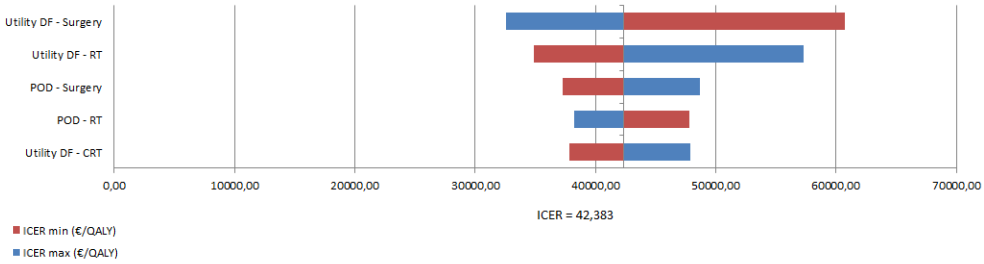

Figure 4a. Influence on the incremental cost-effectiveness ratio (ICER).

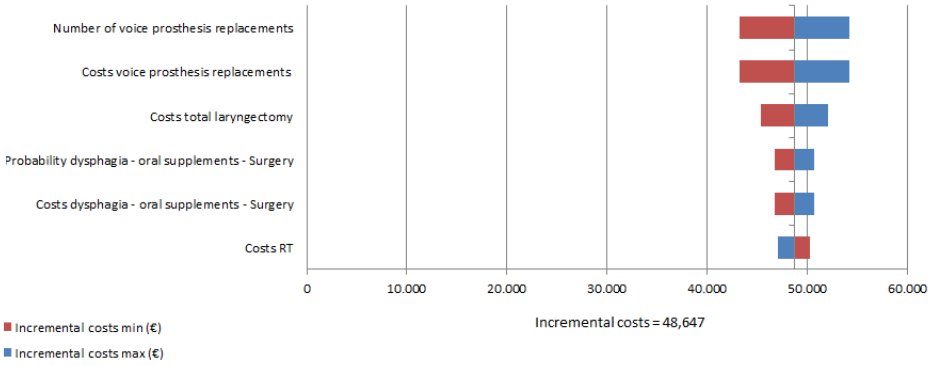

Figure 4b. Influence on the incremental costs.

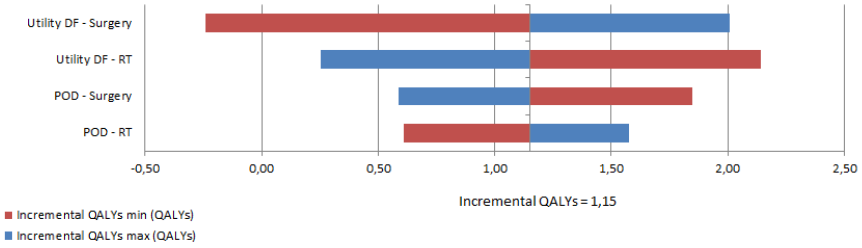

Figure 4c. Influence on the incremental quality adjusted life years (QALYs).

Figure 4. Tornado diagrams including most influential input parameters incorporated in the model. For the input parameters, ranges of +/- 20% were used to calculate the maximum and minimum (for the POD and utility values clinically relevant ranges of +/- 5% were applied). In the three figures, the influence of the parameters' maximum (blue bars) and minimum (red bars) on the ICER (Figure 4a), incremental costs (Figure 4b) and incremental QALYs (Figure 4c) outcomes are visualized. The deterministic outcomes for the ICER (42,838), incremental costs (48,647) and QALYs (1.15) are displayed below the x-axis.

Abbreviations: CRT, chemoradiation; DF, disease-free; DFP, POD, progression of disease; RT, radiotherapy.

Discussion

Our results showed that the surgical approach was cost-effective compared to OP with an ICER of €42 383/QALY. Total QALYs of the surgical approach were higher compared to the OP approach; 6.59 and 5.44 respectively, which is substantial. We also see this in literature; this might be a result of coping well with and acceptance of the disability by laryngectomies [3,7,24]. Total lifetime costs were higher for the surgical approach (€95 881) compared to the OP approach (€47 233). For policy decision-making, taking the substantial higher QALY into account against the relative additional costs, it would be advised to make surgery the preference choice of treatment for this population. On the individual- and shared decision-making level, the tornado diagram can give additional information when changing certain parameters.

Compared to the existing literature, our findings on the QoL were similar [9]. However on the cost-side, we included much more detail on AE, which makes the trade-off more clear for both strategies [9-12]. Obviously, the costs of healthcare in different countries are difficult to compare. However, overall, the effects (e.g. survival in Western Europe) and the cost ratio between primary treatment costs of surgery and OP (RT) in the studies available in literature were in accordance to our study data [9,10,25]. This is an argument for international generalizability of our results in Western Europe. It should be acknowledged that, as the survival data, data on treatment regimens and costs are sourced from the Netherlands, this model will be most relevant to the Dutch perspective and countries in which the healthcare delivery models are similar. It could be valuable to source survival data from large studies e.g. Surveillance, Epidemiology and End results (SEER-) based in future cost-effectiveness analyses [26]. Additionally, access to large databases would facilitate precision of the estimates on survival data and improve quality of the model.

In this study, several limitations have to be considered. First, the input data was sourced from various controlled studies making it challenging to achieve comparability between modalities and contributes to the uncertainty of the outcomes. The input parameters sourced from the different studies were chosen based on a set of criteria and checked with an experienced panel in the field. However, we must emphasize that these results are heavily dependent on the choice of sources used for the input parameters. Access to large national databases with tumor-specific information would be helpful to overcome this. Second, it was difficult to find studies in literature reporting on AE data specifically to the laryngeal cancer population in order to estimate the exact AE differences between modalities. Third, the large uncertainty around the incremental QALYs captured in the CE plane resulted from the low sample sizes used in the literature. Fourth, with regard to the surgery group, we assumed that voice prosthesis use was applicable to the whole laryngectomy group because this is true for the majority of Dutch patients. However, from a worldwide perspective, use of the esophageal speech should also be included in a portion of patients [27]. This will result in lower costs for this patient population due to the lack of voice

prosthesis replacements, whereas the QoL of these patients is lower compared to patients with voice prosthesis use [28,29]. This could lead to a more favorable cost-effectiveness ratio for surgery (lower ICER) in certain countries. Fifth, in the scenario analyses, the impact of the discontinuation of cisplatin cycles had an impact on the costs but did not lead to changes in effectiveness (survival and QoL). In future research, it would be advised to take this information into account whenever available, because survival changes could have an impact on relative effectiveness and cost-effectiveness outcomes. A strength of the study is that, to the best of our knowledge, this is the first study to evaluate the cost-effectiveness of surgery versus OP in HNC patients with a robust Markov model-based analysis using all relevant literature available regarding the indirect costs for AE treatments. The input parameters were carefully selected from literature and were validated with a panel of clinical experts in the HNC field. Regarding the OP group, the parameters consisted of weighted averages calculated with individual data for each modality to enhance the precision of the estimates for the OP group. In addition, using the Dutch benchmark cost prices provided a good representation of the actual costs (in contrast to tariff prices) [14].

Conclusion

From this study, several research implications have to be considered for further research. From a patient perspective, preferably in a prospective study, it would be of value to collect and process data including e.g. the effects of rehabilitation e.g. return to work, participation in society and more specific data regarding AE specifically to laryngeal cancer patients to analyze this from a societal perspective. Methodologically, we encourage the development of HNC-specific utilities which would enhance the precision of QoL estimates in HNC patients (and decrease uncertainty as visualized in the tornado diagrams (Figure 4)) [30].

Practical implications that could come forth from this study are focused on clinical practice as well as policy-making. Nowadays, aside from patient's survival, there is increased focus on regaining QoL and daily activities after treatment [31]. Decision-making can vary among patients for which each case requires individual evaluation. Therefore, it is of great value to make adequate information available regarding QALY differences between surgery and OP treatments to facilitate the survival versus QoL tradeoff and improve shared, personalized decision-making. Presently a decision-aid for laryngeal cancer treatment is being developed [5] and implementing adequate QALY data in the tool could improve (objective) information provided to patients. Additionally, the uncertainty presented in the CEAC is mostly due to the higher surgery costs. It would be interesting to calculate possible scenarios resulting from the decision-aid, in order to get more insight into the cost-effectiveness based on patient preferences. Additionally, collection of country-specific costs will support additional analyses.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians.* 2018;68(6):394-424.
2. Koroulakis A, Agarwal M. Cancer, Laryngeal. In: *StatPearls [Internet].* StatPearls Publishing; 2018.
3. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Archives of Otolaryngology–Head Neck Surgery.* 2004;130(7):875-879.
4. Timmermans AJ, van Dijk BA, Overbeek LI, et al. Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. *Head neck.* 2016;38(S1):E1247-E1255.
5. Petersen JF, Berlanga A, Stuiver MM, et al. Improving decision making in larynx cancer by developing a decision aid: A mixed methods approach. *The Laryngoscope.* 2019.
6. Arenaz Búa B, Pendleton H, Westin U, Rydell R. Voice and swallowing after total laryngectomy. *Acta oto-laryngologica.* 2018;138(2):170-174.
7. Deleyiannis FWB, Weymuller Jr EA, Coltrera MD, Futran N. Quality of life after laryngectomy: are functional disabilities important? *Head Journal for the Sciences Specialties of the Head Neck.* 1999;21(4):319-324.
8. Massa ST, Osazuwa-Peters N, Boakye EA, Walker RJ, Ward GM. Comparison of the financial burden of survivors of head and neck cancer with other cancer survivors. *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):239-249.
9. Morton RP. Laryngeal cancer: Quality-o-life and cost-effectiveness. *Head Neck: Journal for the Sciences Specialties of the Head Neck.* 1997;19(4):243-250.
10. Davis GE, Schwartz SR, Veenstra DL, Yueh B. Cost comparison of surgery vs organ preservation for laryngeal cancer. *Archives of Otolaryngology–Head Neck Surgery.* 2005;131(1):21-26.
11. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CLJP. The economic burden of head and neck cancer: a systematic literature review. *Pharmacoeconomics.* 2014;32(9):865-882.
12. Day AT, Chang HY, Quon H, et al. Treatment, short-term outcomes, and costs associated with larynx cancer care in commercially insured patients. *The Laryngoscope.* 2018;128(1):91-101.
13. Oppe M, Devlin NJ, Szende A. *EQ-5D value sets: inventory, comparative review and user guide.* Springer; 2007.
14. Logex healthcare analytics. Last accessed: 20-11-2019.; https://www.logex.com/nl/.
15. Dutch Pharmacy Purchase Price. Last accessed: 20-11-2019.; http://www.medicijnkosten.nl.
16. Supply nutritional support. Last accessed: 20-11-2019.; https://www.sorgente.nl/webwinkel/drinkvoeding?voedingswaarde=Energie-+en+eiwitverrijkt
17. Jansen F, Coupé VM, Eerenstein SE, Leemans CR, Verdonck-de Leeuw I. Costs from a healthcare and societal perspective among cancer patients after total laryngectomy: are they related to patient activation? *Supportive Care in Cancer.* 2018;26(4):1221-1231.
18. Simons PA, Ramaekers B, Hoebers F, et al. Cost-effectiveness of reduced waiting time for head and neck cancer patients due to a lean process redesign. *Value in Health.* 2015;18(5):587-596.

19. Truong MT, Zhang Q, Rosenthal DI, et al. Quality of life and performance status from a substudy conducted within a prospective phase 3 randomized trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for locally advanced head and neck carcinoma: NRG Oncology Radiation Therapy Oncology Group 0522. *International Journal of Radiation Oncology* Biology* Physics.* 2017;97(4):687-699.

20. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation.* OUP Oxford; 2006.

21. Smulders Y, Thijs A. Kostprijs per gewonnen levensjaar: Trends en tegenstrijdigheden. *Nederlands tijdschrift voor geneeskunde.* 2006;150(45):2467-2470.

22. Roijen L, Linden N, Bouwmans C, Kanters T, Tan. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. *Zorginstituut Nederland The Netherlands: Zorginstituut Nederland.* 2015.

23. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health economics.* 2001;10(8):779-787.

24. Morton RP. Studies in the quality of life of head and neck cancer patients: results of a two-year longitudinal study and a comparative cross-sectional cross-cultural survey. *The Laryngoscope.* 2003;113(7):1091-1103.

25. Gatta G, Botta L, Sánchez MJ, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. *European journal of cancer.* 2015;51(15):2130-2143.

26. Eskander A, Blakaj DM, Dziegielewski PT. Decision making in advanced larynx cancer: an evidenced based review. *Oral oncology.* 2018;86:195-199.

27. Staffieri A, Mostafea BE, Varghese BT, et al. Cost of tracheoesophageal prostheses in developing countries. Facing the problem from an internal perspective. *Acta Otolaryngolica.* 2006.

28. van Sluis KE, van der Molen L, van Son RJ, Hilgers FJ, Bhairosing PA, van den Brekel MW. Objective and subjective voice outcomes after total laryngectomy: a systematic review. *European Archives of Oto-Rhino-Laryngology.* 2018;275(1):11-26.

29. Beck A, Retèl V, van den Brekel M, van Harten W. Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries. *Oral oncology.* 2019;91:56-64.

30. Beck A-JC, Kieffer JM, Retèl VP, et al. Mapping the EORTC QLQ-C30 and QLQ-H&N35 to the EQ-5D for head and neck cancer: Can disease-specific utilities be obtained? *PloS one.* 2019;14(12).

31. Beck A-JC, Passchier E, Retèl VP, et al. Study protocol of a prospective multicenter study comparing (cost-) effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo-or bioradiotherapy. *BMC cancer.* 2019;19(1):655.

Acknowledgements

We would like to thank R. Meissner, C. Apol, W. Stegeman, J.P. de Boer, W.M.C. Klop, M.M. Stuiver, S. Tjon A Joe, L. van der Molen, K.E. van Sluis, S. Onderwater and M. Jonker for their support in conducting the study.

Conflict of interest statement

This work was supported by Atos Medical AB (Malmö Sweden). Atos Medical AB had no involvement in the development or writing of the study. Atos Medical AB had no involvement in the development of the study.

Funding

This work was supported by Atos Medical AB (Malmö Sweden). Atos Medical AB had no involvement in the development or writing of the study.

Appendix A

Input parameters of the model.

Input data: Treatment-related probabilities

An overview of the input parameters is provided in Table 1. Most probabilities were retrieved from various articles because no study was available in literature comprising data for all different treatment modalities at once. Relevant articles were included based on tumor group ((at least) inclusion of advanced laryngeal cancer), sample size, objectification of AE/QoL with a (validated) measurement tool (e.g. EuroQol five-dimensional questionnaire (EQ-5D-5L)) [13], time point of assessment of AE/QoL (preferably at least 6 months post-treatment) and quality of the study (e.g. (randomized) controlled trial). An overview of the specifications of the included articles is provided in Appendix B (Figure B.1).

The occurrence of most incidental (>5%) long-term adverse events (AE) was taken into account for the surgery as well as for the OP modalities, starting within the first year after treatment. The AE comprised of neopharyngeal spasm, tracheostomal stenosis, neopharyngeal stenosis, – solely for the surgery group - dysphagia, fibrosis, hypothyroidism, pneumonia – for all groups – and dysfunctional larynx and laryngeal edema – solely for the OP group. Treatment of dysphagia and dysfunctional larynx was separated into two groups: nutritional support by means of oral supplements versus tube feeding and total laryngectomy versus tracheostomy with percutaneous radiological gastrostomy (PRG) respectively. A probability for the treatment of AE was assigned to each of the modalities, which was derived from literature [4,14-17,19,32-49]. Costs for AE occurring within 42 days after treatment (e.g. nephrotoxicity, fistula formation) were included in the total costs of primary treatment. The frequency of voice prosthesis replacements was also used as input parameter to estimate costs for treatment maintenance after laryngectomy.

Probabilities for adjuvant treatment with RT in the surgery group and the ratio between the different OP treatment modalities used to establish a weighted average was sourced from Timmermans et al. [4]. For the progression health state, probabilities to estimate the number of patients treated with either curative (surgery) or palliative treatment (chemo- or immunotherapy) were gained from the experts.

When literature was not sufficient, probabilities of BRT were assumed to be similar to CRT based on expert elicitation. Also, the probability of the occurrence of fibrosis for PORT and RT group was assumed to be similar to CRT and BRT respectively by the experts.

All input parameters were assessed on generalizability and checked by a panel of experts consisting of head and neck surgeons, radiotherapist, medical oncologist, speech-language pathologist, physiotherapist, dietician, physician assistant and nurse specialists.

Input data: Health effects

QALYs are defined as the life years corrected for the level of disease burden. QALYs are calculated by multiplying the life years gained times the associated utilities.

One-year survival probabilities for POD and cancer-related death were calculated for each treatment individually from rates derived from a Dutch national study with survival data on advanced laryngeal patients (Table 1, Appendix B) [20,38]. The rate for death due to laryngeal cancer in the progression group was assumed to be similar for all modalities [37]. The utilities for the surgery, RT and CRT modalities were sourced from literature and were based on outcomes reported by patients through the EuroQol five-dimensional questionnaire (EQ-5D) [13,17-19]. The utility value for the BRT group was unavailable in literature and assumed to be similar to CRT based on expert elicitation. A disutility was applied for POD [18,49].

Input data: Costs

Costs were calculated with national cost data (Table 1) [14]. In the Netherlands, hospitals are paid through Dutch DBCs (*Diagnose Behandel Combinaties*) by private health insurers, similar to diagnosis-related groups (DRGs). The DBC Hospital tariffs are negotiated with the health insurer based on the actual DBC costs: the cost prices.

For all treatment modalities, we used the national benchmark cost prices associated with the treatment DBCs in 2018 [14]. The costs prices of the DBC profiles are an average of the actual costs for treatment of advanced laryngeal cancer patients in 2018. The costs are derived from more than 45 hospitals, comprising mostly non-academic and three academic hospitals (38% of total academic hospitals). These profiles reflect the care provided since diagnosis until 42 days after last day of primary treatment (in case of OP) or hospital admission (in case of surgery). The profiles of the treatment modalities - separated for the Division of Head and Neck Surgery, Radiotherapy and Internal Medicine - contain subcodes for care activities reflecting costs for diagnostics (included in the DBC for surgical treatment), treatment (primary or secondary), first outpatient follow-up consultation and treatment for AE within that period. Most treatments for long-term AE were also covered by a DBC profile. The content of the DBC profiles were validated with the profiles of a random sample of laryngeal patients treated in 2018. Costs for Cisplatin and Cetuximab medication were calculated separately with the prices available online [15].

The micro-costing method was used to optimize precision estimates of the costs during the follow-up period [50]. The costs for follow-up consultations of healthcare providers, diagnostics and treatment for long-term AE (if no appropriate DBC was available), and diagnostics for the OP group were obtained from costs derived from (a combined set of) care activity subcodes. Costs for medication (e.g. against hypothyroidism and neopharyngeal spasm) and nutritional support in case of dysphagia were retrieved online at the Pharmacy Purchase Price and wholesaler website respectively [15,16].

The costs were expressed in 2019 Euros; costs originating from 2018 were corrected for inflation [51].

References Appendix A

1. Oppe M, Devlin NJ, Szende A. EQ-5D value sets: inventory, comparative review and user guide: Springer; 2007.
2. Lefebvre JL, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. J Clin Oncol. 2013;31(7):853-9.
3. Dutch Pharmacy Purchase Price. Last accessed: 20-11-2019. Available from: http://www.medicijnkosten.nl.
4. Logex healthcare analytics. Last accessed: 20-11-2019. Available from: https://www.logex.com/nl/.
5. Supply nutritional support. Last accessed: 20-11-2019. Available from: https://www.sorgente.nl/webwinkel/drinkvoeding?voedingswaarde=Energie-+en+eiwitverrijkt
6. Kawai S, Yokota T, Onozawa Y, Hamauchi S, Fukutomi A, Ogawa H, et al. Risk factors for aspiration pneumonia after definitive chemoradiotherapy or bio-radiotherapy for locally advanced head and neck cancer: a monocentric case control study. BMC cancer. 2017;17(1):59.
7. Dietz A, Rudat V, Nollert J, Helbig M, Vanselow B, Weidauer H. Chronic laryngeal edema as a late reaction to radiochemotherapy. Hno. 1998;46(8):731-8.
8. Boomsma MJ, Bijl HP, Christianen ME, Beetz I, Chouvalova O, Steenbakkers RJ, et al. A prospective cohort study on radiation-induced hypothyroidism: development of an NTCP model. International Journal of Radiation Oncology* Biology* Physics. 2012;84(3):e351-e6.
9. Truong MT, Zhang Q, Rosenthal DI, List M, Axelrod R, Sherman E, et al. Quality of life and performance status from a substudy conducted within a prospective phase 3 randomized trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for locally advanced head and neck carcinoma: NRG Oncology Radiation Therapy Oncology Group 0522. International Journal of Radiation Oncology* Biology* Physics. 2017;97(4):687-99.
10. Petersen JF, Lansaat L, Timmermans AJ, van der Noort V, Hilgers FJ, van den Brekel MW. Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period. Head neck. 2019;41(3):623-31.
11. Brandstorp-Boesen J, Falk RS, Boysen M, Brøndbo K. Impact of stage, management and recurrence on survival rates in laryngeal cancer. PloS one. 2017;12(7):e0179371.
12. Timmermans AJ, de Gooijer CJ, Hamming–Vrieze O, Hilgers FJ, van den Brekel MW. T3-T4 laryngeal cancer in The Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol. Head neck. 2015;37(10):1495-503.
13. Ward E, Bishop B, Frisby J, Stevens M. Swallowing outcomes following laryngectomy and pharyngolaryngectomy. Archives of Otolaryngology–Head Neck Surgery. 2002;128(2):181-6.
14. Skóra T, Nowak-Sadzikowska J, Mucha-Małecka A, Szyszka-Charewicz B, Jakubowicz J, Gli-ski B. Postoperative irradiation in patients with pT3-4N0 laryngeal cancer: results and prognostic factors. European Archives of Oto-Rhino-Laryngology. 2015;272(3):673-9.
15. Palmer B, Gaggar N, Shaw H. Thyroid function after radiotherapy and laryngectomy for carcinoma of the larynx. Head neck surgery. 1981;4(1):13-5.

16. Singer MI, Blom ED. Selective myotomy for voice restoration after total laryngectomy. Archives of Otolaryngology–Head. 1981;107(11):670-3.
17. Petersen JF, Pézier TF, van Dieren JM, van der Noort V, van Putten T, Bril SI, et al. Dilation after laryngectomy: Incidence, risk factors and complications. Oral oncology. 2019;91:107-12.
18. Kuo M, Ho CM, Wei WI, Lam KH. Tracheostomal stenosis after total laryngectomy: An analysis of predisposing clinicalfactors. The Laryngoscope. 1994;104(1):59-63.
19. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. The lancet oncology. 2010;11(1):21-8.
20. Nguyen N, Moltz C, Frank C, Vos P, Smith H, Karlsson U, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Annals of Oncology. 2004;15(3):383-8.
21. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiotherapy oncology. 2003;66(3):253-62.
22. Koutcher L, Sherman E, Fury M, Wolden S, Zhang Z, Mo Q, et al. Concurrent cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. International Journal of Radiation Oncology* Biology* Physics. 2011;81(4):915-22.
23. Timmermans AJ, van Dijk BA, Overbeek LI, van Velthuysen MLF, van Tinteren H, Hilgers FJ, et al. Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. Head neck. 2016;38(S1):E1247-E55.
24. Ramaekers BL, Joore MA, Grutters JP, Van Den Ende P, De Jong J, Houben R, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. Oral oncology. 2011;47(8):768-74.
25. Jansen F, Coupé VM, Eerenstein SE, Leemans CR, Verdonck-de Leeuw I. Costs from a healthcare and societal perspective among cancer patients after total laryngectomy: are they related to patient activation? Supportive Care in Cancer. 2018;26(4):1221-31.
26. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation: OUP Oxford; 2006.
27. Simons PA, Ramaekers B, Hoebers F, Kross KW, Marneffe W, Pijls-Johannesma M, et al. Cost-effectiveness of reduced waiting time for head and neck cancer patients due to a lean process redesign. Value in Health. 2015;18(5):587-96.
28. Xu X, Nardini HKG, Ruger JP. Micro-costing studies in the health and medical literature: protocol for a systematic review. Systematic reviews. 2014;3(1):47.
29. NVZ price index. Last accessed: 20-11-2019. Available from: https://nvz-ziekenhuizen.nl/prijsindexcijfers.

Appendix B

Specifications of model input parameters.

Probabilities	Sample size (n)	Tumor group (stage)	Time point (months after treatment)	Measurement	Source
Survival					
Progression of disease – Surgery	60	Larynx (3/4)	NA	RRR	[38]
Progression of disease – OP					
RT	102	Larynx (3/4)	NA	RRR	[38]
CRT	20	Larynx (3/4)	NA	RRR	[38]
BRT	NA	NA	NA	RRR	EE
Death due to laryngeal cancer[a]	369	Larynx (All)	60	RRR	[37]
Treatment probabilities - Surgery					
PORT	1172	Larynx (3/4)	NA	RRR	[4]
Secondary treatment (curative) of recurrent disease	NA	NA	NA	NA	EE
Secondary treatment (palliative) of recurrent disease[a]	NA	NA	NA	NA	EE
Treatment probabilities - OP					
Secondary treatment (curative) of recurrent disease	122	Larynx (3/4)	NA	NA	[38]
Adverse events – Surgery					
Dysphagia – oral supplements	36	NK[b]	(+/-) 36	RRR: Dietary status	[39]
Fibrosis	NA	NA	NA	NA	EE
Hypothyroidism	37	Larynx (NK)	4	Serum T4 and TSH levels	[41]
Neopharyngeal spasm	129	NK[b]	NA	Esophageal insufflation test	[42]
Neoparyngeal stenosis	477	Larynx/Hypopharynx/Other (All)	NA	RRR	[43]
Tracheostomal stenosis	207	Larynx-Hypopharynx (NK)	NA	RRR: tube placement or revision of stoma	[44]

Adverse events – OP

Dysfunctional larynx – total laryngectomy					
RT					
CRT	122	Larynx (3/4)	120	RRR	[38]
BRT	122	Larynx (3/4)	120	RRR	[38]
	NA	NA	NA	NA	EE
Dysfunctional larynx – tracheostomy	NA	NA	NA	NA	EE
Dysphagia – oral supplements					
RT	212	Oro-/Hypopharynx/Larynx (3/4)	2	RTOG grading	[45]
CRT	55	Oro-/Hypo-/Naso-pharynx/Larynx/Oral cavity (3/4)	NA	SPS	[46]
BRT	208	Oro-/Hypopharynx/Larynx (3/4)	2	RTOG grading	[45]
Dysphagia – tube feeding					
RT	500	All[c] (All)	NK	NK	[47]
CRT	319	All[c] (All)	NK	NK	[47]
BRT	46	Oro/Hypopharynx/Larynx (All)	9	Common Terminology Criteria for AE	[48]
Fibrosis					
RT	NA	NA	NA	NA	EE
CRT	58	Larynx/Hypopharynx (3/4)	At least 6	RTOG grading	[32]
BRT	56	Larynx/Hypopharynx (3/4)	At least 6	RTOG grading	[32]
Hypothyroidism					
RT	105	All[d] (All)	NA	Serum T4 and TSH levels	[35]
CRT	105	All[d] (All)	NA		[35]
BRT	NA	NA	NA	Serum T4 and TSH levels	EE
				NA	
Laryngeal edema					
RT	68	Oro-/Hypopharynx (3/4)	NA	Clinical investigation/	[34]
CRT	68	Oro-/Hypopharynx (3/4)	NA	CT	[34]
BRT	NA	NA	NA	Clinical investigation/ CT	EE
				NA	

Pneumonia					
RT	8002	Oro-/Hypopharynx/Larynx/Oral cavity (NK)	36	RRR	[52]
CRT	305	All[c] (3/4)	24	RRR	[33]
BRT	305	All[c] (3/4)	24	RRR	[33]

Frequencies	**Sample size (n)**	**Tumor group (stage)**	**Time point (months after treatment)**	**Measurement**	**Source**
Treatment-related frequencies – Surgery					
Yearly number of voice prosthesis replacements	70 days (median device time)	Larynx/Oro-/Hypopharynx (NK)	NA	RRR	[36]

Health effects	**Sample size (n)**	**Tumor group (stage)**	**Time point (months after treatment)**	**Measurement**	**Source**
Utility DFS – Surgery	240	Larynx/Hypopharynx (NK)	Cross-sectional	EQ-5D	[17]
Utility DFS – OP					
RT	44	Larynx (3/4)	At least 6	EQ-5D	[18]
CRT	246	Larynx/Oro-/Hypopharynx (3/4)	12	EQ-5D	[19]
BRT	NA	NA	NA	NA	EE
Disutility Progression	NA	NA	NA	NA	[18]

Survival rates were converted to one-year probabilities with the formulas: rate = -[ln(1-probability)]/time and 1-year probability=1-exp(-rate*1) [20].

Abbreviations: AE, adverse events; BRT, bioradiation; CT, *Computed Tomography* scan; CRT, chemoradiation; EE, expert elicitation; EQ-5D, EuroQol five-dimensional questionnaire; NA, not applicable; NK, not known; OP, organ preservation; PORT, postoperative radiotherapy; SPS, Swallowing Performance Scale; RRR, retrospective record review; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; T4, thyroxine; TSH, thyroid-stimulating hormone.

[a] Similar for Surgery and OP group.

[b]Patients who underwent (pharyngo)laryngectomy.

[c]Oro-/Hypo-/Nasopharynx/Larynx/Oral cavity/Paranasal sinuses/Unknown or Other.

[d]Oro-/Hypopharynx/Larynx/Oral cavity/Salivary gland/Skin/Unknown primary/Paranasal sinuses/Sarcoma in neck.

References Appendix B

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians.* 2018;68(6):394-424.
2. Koroulakis A, Agarwal M. Cancer, Laryngeal. In: *StatPearls [Internet].* StatPearls Publishing; 2018.
3. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Archives of Otolaryngology–Head Neck Surgery.* 2004;130(7):875-879.
4. Timmermans AJ, van Dijk BA, Overbeek LI, et al. Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. *Head neck.* 2016;38(S1):E1247-E1255.
5. Petersen JF, Berlanga A, Stuiver MM, et al. Improving decision making in larynx cancer by developing a decision aid: A mixed methods approach. *The Laryngoscope.* 2019.
6. Arenaz Búa B, Pendleton H, Westin U, Rydell R. Voice and swallowing after total laryngectomy. *Acta oto-laryngologica.* 2018;138(2):170-174.
7. Deleyiannis FWB, Weymuller Jr EA, Coltrera MD, Futran N. Quality of life after laryngectomy: are functional disabilities important? *Head Journal for the Sciences Specialties of the Head Neck.* 1999;21(4):319-324.
8. Massa ST, Osazuwa-Peters N, Boakye EA, Walker RJ, Ward GM. Comparison of the financial burden of survivors of head and neck cancer with other cancer survivors. *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):239-249.
9. Morton RP. Laryngeal cancer: Quality-of-life and cost-effectiveness. *Head Neck: Journal for the Sciences Specialties of the Head Neck.* 1997;19(4):243-250.
10. Davis GE, Schwartz SR, Veenstra DL, Yueh B. Cost comparison of surgery vs organ preservation for laryngeal cancer. *Archives of Otolaryngology–Head Neck Surgery.* 2005;131(1):21-26.
11. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CLJP. The economic burden of head and neck cancer: a systematic literature review. *Pharmacoeconomics.* 2014;32(9):865-882.
12. Day AT, Chang HY, Quon H, et al. Treatment, short-term outcomes, and costs associated with larynx cancer care in commercially insured patients. *The Laryngoscope.* 2018;128(1):91-101.
13. Oppe M, Devlin NJ, Szende A. *EQ-5D value sets: inventory, comparative review and user guide.* Springer; 2007.
14. Logex healthcare analytics. Last accessed: 20-11-2019.; https://www.logex.com/nl/.
15. Dutch Pharmacy Purchase Price. Last accessed: 20-11-2019.; http://www.medicijnkosten.nl.
16. Supply nutritional support. Last accessed: 20-11-2019.; https://www.sorgente.nl/webwinkel/drinkvoeding?voedingswaarde=Energie-+en+eiwitverrijkt
17. Jansen F, Coupé VM, Eerenstein SE, Leemans CR, Verdonck-de Leeuw I. Costs from a healthcare and societal perspective among cancer patients after total laryngectomy: are they related to patient activation? *Supportive Care in Cancer.* 2018;26(4):1221-1231.
18. Simons PA, Ramaekers B, Hoebers F, et al. Cost-effectiveness of reduced waiting time for head and neck cancer patients due to a lean process redesign. *Value in Health.* 2015;18(5):587-596.

19. Truong MT, Zhang Q, Rosenthal DI, et al. Quality of life and performance status from a substudy conducted within a prospective phase 3 randomized trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for locally advanced head and neck carcinoma: NRG Oncology Radiation Therapy Oncology Group 0522. *International Journal of Radiation Oncology* Biology* Physics.* 2017;97(4):687-699.

20. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation.* OUP Oxford; 2006.

21. Smulders Y, Thijs A. Kostprijs per gewonnen levensjaar: Trends en tegenstrijdigheden. *Nederlands tijdschrift voor geneeskunde.* 2006;150(45):2467-2470.

22. Roijen L, Linden N, Bouwmans C, Kanters T, Tan. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. *Zorginstituut Nederland The Netherlands: Zorginstituut Nederland.* 2015.

23. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health economics.* 2001;10(8):779-787.

24. Morton RP. Studies in the quality of life of head and neck cancer patients: results of a two-year longitudinal study and a comparative cross-sectional cross-cultural survey. *The Laryngoscope.* 2003;113(7):1091-1103.

25. Gatta G, Botta L, Sánchez MJ, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. *European journal of cancer.* 2015;51(15):2130-2143.

26. Eskander A, Blakaj DM, Dziegielewski PT. Decision making in advanced larynx cancer: an evidenced based review. *Oral oncology.* 2018;86:195-199.

27. Staffieri A, Mostafea BE, Varghese BT, et al. Cost of tracheoesophageal prostheses in developing countries. Facing the problem from an internal perspective. *Acta Otolaryngolica.* 2006.

28. van Sluis KE, van der Molen L, van Son RJ, Hilgers FJ, Bhairosing PA, van den Brekel MW. Objective and subjective voice outcomes after total laryngectomy: a systematic review. *European Archives of Oto-Rhino-Laryngology.* 2018;275(1):11-26.

29. Beck A, Retèl V, van den Brekel M, van Harten W. Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries. *Oral oncology.* 2019;91:56-64.

30. Beck A-JC, Kieffer JM, Retèl VP, et al. Mapping the EORTC QLQ-C30 and QLQ-H&N35 to the EQ-5D for head and neck cancer: Can disease-specific utilities be obtained? *PloS one.* 2019;14(12).

31. Beck A-JC, Passchier E, Retèl VP, et al. Study protocol of a prospective multicenter study comparing (cost-) effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo-or bioradiotherapy. *BMC cancer.* 2019;19(1):655.

32. Lefebvre JL, Pointreau Y, Rolland F, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. *J Clin Oncol.* 2013;31(7):853-859.

33. Kawai S, Yokota T, Onozawa Y, et al. Risk factors for aspiration pneumonia after definitive chemoradiotherapy or bio-radiotherapy for locally advanced head and neck cancer: a monocentric case control study. *BMC cancer.* 2017;17(1):59.

34. Dietz A, Rudat V, Nollert J, Helbig M, Vanselow B, Weidauer H. Chronic laryngeal edema as a late reaction to radiochemotherapy. *Hno.* 1998;46(8):731-738.

35. Boomsma MJ, Bijl HP, Christianen ME, et al. A prospective cohort study on radiation-induced hypothyroidism: development of an NTCP model. *International Journal of Radiation Oncology* Biology* Physics.* 2012;84(3):e351-e356.

36. Petersen JF, Lansaat L, Timmermans AJ, van der Noort V, Hilgers FJ, van den Brekel MW. Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period. *Head neck.* 2019;41(3):623-631.

37. Brandstorp-Boesen J, Falk RS, Boysen M, Brøndbo K. Impact of stage, management and recurrence on survival rates in laryngeal cancer. *PloS one.* 2017;12(7):e0179371.

38. Timmermans AJ, de Gooijer CJ, Hamming–Vrieze O, Hilgers FJ, van den Brekel MW. T3-T4 laryngeal cancer in The Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol. *Head neck.* 2015;37(10):1495-1503.

39. Ward E, Bishop B, Frisby J, Stevens M. Swallowing outcomes following laryngectomy and pharyngolaryngectomy. *Archives of Otolaryngology–Head Neck Surgery.* 2002;128(2):181-186.

40. Skóra T, Nowak-Sadzikowska J, Mucha-Małecka A, Szyszka-Charewicz B, Jakubowicz J, Gli-ski B. Postoperative irradiation in patients with pT3-4N0 laryngeal cancer: results and prognostic factors. *European Archives of Oto-Rhino-Laryngology.* 2015;272(3):673-679.

41. Palmer B, Gaggar N, Shaw H. Thyroid function after radiotherapy and laryngectomy for carcinoma of the larynx. *Head neck surgery.* 1981;4(1):13-15.

42. Singer MI, Blom ED. Selective myotomy for voice restoration after total laryngectomy. *Archives of Otolaryngology–Head.* 1981;107(11):670-673.

43. Petersen JF, Pézier TF, van Dieren JM, et al. Dilation after laryngectomy: Incidence, risk factors and complications. *Oral oncology.* 2019;91:107-112.

44. Kuo M, Ho CM, Wei WI, Lam KH. Tracheostomal stenosis after total laryngectomy: An analysis of predisposing clinicalfactors. *The Laryngoscope.* 1994;104(1):59-63.

45. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *The lancet oncology.* 2010;11(1):21-28.

46. Nguyen N, Moltz C, Frank C, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. *Annals of Oncology.* 2004;15(3):383-388.

47. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiotherapy oncology.* 2003;66(3):253-262.

48. Koutcher L, Sherman E, Fury M, et al. Concurrent cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. *International Journal of Radiation Oncology* Biology* Physics.* 2011;81(4):915-922.

49. Ramaekers BL, Joore MA, Grutters JP, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. *Oral oncology.* 2011;47(8):768-774.

50. Xu X, Nardini HKG, Ruger JP. Micro-costing studies in the health and medical literature: protocol for a systematic review. *Systematic reviews.* 2014;3(1):47.

51. NVZ price index. . Last accessed: 20-11-2019.; https://nvz-ziekenhuizen.nl/prijsindexcijfers.

52. Francis DO, Weymuller Jr EA, Parvathaneni U, Merati AL, Yueh B. Dysphagia, stricture, and pneumonia in head and neck cancer patients: does treatment modality matter? *Annals of Otology, Rhinology Laryngology.* 2010;119(6):391-397.

Appendix C

Specific scenario analyses.

Because provision of rehabilitation care is heterogeneous in the Netherlands and the exact content of rehabilitation care is unknown for the different modalities, a specific scenario analysis was conducted with estimations of rehabilitation care provided for each modality to show the potential effect on the outcomes. We used the rehabilitation medium (4-9 hours of care) and maximum (>9 hours of care) weighted DBC profile to represent the costs. We assumed the RT group to be treated within the medium-weighted DBC and the other modalities within the maximum rehabilitation profile. Additionally, because we know from practice that Cisplatin is often discontinued due to AE (e.g. acute nephrotoxicity), we performed a sensitivity analysis with simulated patients treated with 1 (5%), 2 (20%) or 3 (75%) cycles of Cisplatin in the OP arm.

Chapter 7

Cost-effectiveness analysis of using the heat and moisture exchangers compared to alternative stoma covers in laryngectomy rehabilitation: A US perspective

Ann-Jean C.C. Beck
Valesca P. Retèl
Glenn Bunting
Rosh K.V. Sethi
Daniel G. Deschler
Michiel W.M. van den Brekel*
Wim H. van Harten*
*Last author

Accepted at Head&Neck

Abstract

Background

This study aims to evaluate the cost-effectiveness of using heat moisture exchangers (HME) versus alternative stoma covers (ASC) following laryngectomy in the US.

Methods

A cost-effectiveness and budget impact analysis were conducted including uncertainty analyses using real-world survey data with pulmonary events and productivity loss.

Results

HME use was more effective and less costly compared to ASCs. Quality-adjusted life years were slightly higher for HME-users. Total costs per patient (life time) were $59,362 (HME) and $102,416 (ASC). Pulmonary events and productivity loss occurred more frequently in the ASC-users. Annual budget savings were up to $40,183,593. Costs per pulmonary event averted were $3770.

Conclusions

HME utilization in laryngectomy patients was cost-effective. Reimbursement of HME devices is thus recommended. Utilities may be underestimated due to the generic utility instrument used and sample size. Therefore, we recommend development of a disease-specific utility tool to incorporate in future analyses.

Introduction

Removal of the larynx during a total laryngectomy results in an altered anatomy in which a newly formed permanent tracheostoma is created in the neck, and therefore the upper respiratory tract is bypassed [1]. After total laryngectomy, disruption of the upper respiratory tract can cause significant pulmonary symptoms associated with increased sputum production, involuntary coughing and forced expectoration. These symptoms can have a great impact on daily life of patients, as they can negatively influence physical functioning, quality of voice and psychosocial well-being [2-5]. The functioning of the upper respiratory tract can be restored by certain devices to optimize pulmonary rehabilitation such as the heat and moisture exchanger (HME) providing stoma coverage, and to some extent alternative stoma covers (ASC, e.g. as foam pads or cloth bibs) [3,6]. For more than two decades, the HME has been established to optimize laryngectomy rehabilitation by reducing pulmonary complaints. The HME is a medical device that consists of a housing/cassette containing material that provides a large surface for condensation and evaporation of moisture during exhalation and inhalation, respectively. In order to improve its water exchange capacity, the HME material contains a hydroscopic salt, mostly calcium chloride [7,8]. The HME housing/cassette directly covers the stoma housed within the airtight adhesive or cannula [4]. This medical device diminishes complaints caused by the functional loss of the upper respiratory tract of laryngectomy patients by providing humidification, and to some extent heating and filtering of inhaled air [1,3,4,9]. The ASC is made of material or foam (e.g. scarf, cloth cover or foam pad) and placed in front of the stoma and held in place with a neck strap (cloth cover) or adhesive strip (foam pad). The covers provide a degree of stoma coverage and to some extent also humidification and heating of breathing air just like. a shawl does covering nose and mouth on a cold winter day. The difference between the HME and the ASC is that the HME provides an airtight seal over the stoma which makes heat and water exchange more reliable and facilitates stoma closure for speaking for those patients using a voice prosthesis. Moreover, with ASC the breathing air can easily bypass the cover, diminishing its efficacy [6]. In general, patients prefer HMEs for comfort and hygiene.

In the literature, very few studies have investigated the effectiveness of HME use compared to ASC in laryngectomy patients. One study that used valid measurements [6], looked at the moisture exchange capacity of both groups of appliances. The study results supported the use of the HME over the ASC. In this study, it was shown that patients preferred airtight HME's, as they provided more comfort, patients didn't like the feeling of a wet cloth with phlegm against their skin, and they communicated with more ease using voice prostheses. Moreover, the ASCs always have air leaks in daily practice, thereby significantly decreasing its efficacy [6].

The benefits of the HMEs have also been demonstrated in previous studies, including level 1 based evidence [4,9-11]. Histologically, the HME diminishes changes in the airways including loss

of tracheal ciliated cells, occurrence of hyperplasia and metaplasia, and deficiencies in airway clearance [12,13]. In practice, the HME has shown to contribute to an improvement in pulmonary functioning of patients by decreasing mucus accumulation, frequent daily coughing, irritation of the respiratory tract, and infection of the airways (especially in the cold winter months) [1,2,5,9,14-16]. In one study, an improvement in breathing was reported by 88% of laryngectomy patients [11]. A randomized controlled study (RCT) by Mérol et al. showed fewer pulmonary complaints, significantly fewer sleeping disturbances and a higher level of satisfaction among patients using the HME [10]. Similar results were found in RCTs evaluating the long-term effects of the HME [9,11,17]. In addition, hygiene around the stoma is improved by avoidance of skin contact resulting in the prevention of peristomal crust formation and mucus secretion [14,18]. Stoma closure using the HME not only ensures greater hygiene for the patient but also leads to fewer psychosocial problems [18]. The HME increases patients' quality of life (QoL) by improving social contact and fewer complaints of fatigue and insomnia, and secondarily has been reported to improve voice quality in 81% of laryngectomy patients [2,9,11,19-23].

Despite accumulating evidence on the effectiveness of the HME, the cost of this device is not always reimbursed for patients in certain countries including the United States (US), Italy and Poland [3,24]. The reason for this is multifactorial, including the increased costs of HME use over use of the ASC and the lack of evidence on cost-effectiveness necessary for reimbursement decision-making [24].

Absence of reimbursement is often a key barrier for patients accessing these devices [3]. Results of previous studies showed that healthcare costs related to HME use were lower compared to external air humidification in the postoperative setting [10,16,19]. An earlier cost-effectiveness analysis concluded the use of the HME to be cost-effective in Poland. In this analysis, the occurrence of pulmonary events was estimated based on a survey conducted by physicians, and QoL was sourced from a study using a time-series design [25]. Hence the result of this study cannot be translated to a US setting due to substantial differences between provision of laryngectomy rehabilitation and the healthcare systems in US and many countries within Europe. As physicians and speech pathologists in the US frequently recommend HMEs as well as ASC in practice, QoL outcomes can be studied by means of a controlled study rather than a time-series design with patients only using HMEs.

The cost-effectiveness of HMEs from a US perspective needs to be investigated to inform the political decision-making regarding reimbursement and promote device access to patients in the US. In addition, especially in the US the financial burden for patients and society is significant due to the healthcare system (mostly private insurance) in which only part of the population has insurance hence healthcare costs can be a burden for many patients [26]. Therefore, the aim of this study was to evaluate: 1) the cost-utility (generic), expressed in costs per quality-

adjusted life years (QALYs) and 2) the cost-effectiveness (disease-specific), expressed in costs per pulmonary event averted, of the HME compared to ASC in laryngectomy patients. We have conducted this study in the US because of the large national population size of laryngectomy patients and the fact that both pulmonary rehabilitation approaches (HME & ASC) are frequently applied and therefore a comparative analysis is possible. The analysis was performed from a societal perspective, from which the latter is defined by the inclusion of indirect costs related to productivity losses (e.g. work absence) [27].

Material and methods

Patient groups and data collection

Patients were recruited from the Massachusetts Eye and Ear Infirmary (Boston, US) during their follow-up visit at the outpatient clinic (Voice and Speech Lab). HME-users and ASC-users were recruited from September until the end of December 2018.

To ensure only established HME-users involved, only patients who were at least six-month post surgery and were wearing the HME for at least six hours per day were eligible for participation in the intervention group. HME-users were compared to ASC-users consisting of patients who were are least six months after total laryngectomy using a foam pad, foam bib, cloth bib or no stoma coverage. Patients who were unable to speak and understand English were excluded from the study. Eligible patients were informed written and orally. Written informed consent was obtained prior to participation.

The study was assessed and approved by the Institutional Review Board (IRB) of the Massachusetts Eye and Ear (registration number: 1310028-1).

Questionnaire

Patients completed a single study-specific questionnaire either via paper or online via RedCap [28]. The questionnaire was developed to collect input data for the model and compare equality between both groups. The study-specific questionnaire was based on the Ackerstaff-Hilgers questionnaire [20,23] and consisted of 80 questions in eight sections: 1) patient and treatment/ device use characteristics (including employment status), 2) medical history, 3) quality of life, 4) pulmonary rehabilitation, 5) current pulmonary complaints, 6) current fatigue complaints, 7) speech and 8) current psychosocial well-being.

Data was prospectively collected including pulmonary events of both groups to incorporate in the economic model. In addition, questions were added on the coverage and reimbursement of the HME and ASC for patients. Questions related to device use were included regarding: type of

device (e.g. HME, cloth bib, foam pad); device utilization per week during the day and night and total hours of device utilization per day (over 24 hours).

QoL data assessed by the EQ-5D

The utility index scores of patients (section 3of the questionnaire) were derived from the five-level EuroQol five-dimensional questionnaire (EQ-5D-5L) [29]. The utilities were obtained from the EQ-5D-5L, a generic preference-based measure. The EQ-5D-5L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and results in a utility score ranging from 0 (dead) to 1 (full health) [29]. In this study, the US tariff was used [29].

Data from medical records

Additional data obtained from medical records included treatment characteristics, comorbidity, occurrence of pulmonary events, medication use, hospital admissions and consultations by healthcare providers (head and neck surgeons, speech and language pathologists (SLPs)).

Model description

A Markov decision model was developed with three mutually exclusive health states, reflecting the disease trajectory. These disease models are often used in oncology because of decisive differences in QoL, survival and costs between the states relevant for the analysis: disease-free survival, progression of disease and death (Figure 1). A hypothetical cohort of 5000 patients was established by Monte Carlo simulation with a one-cycle lifetime horizon [30,31]. All simulated patients of both groups start at the disease-free survival. Each year (cycle), a proportion of patients transit to the progression of disease and death state. Prospective data on both groups from the questionnaire was used as input parameters in the model. The model was based on a US healthcare and societal perspective.

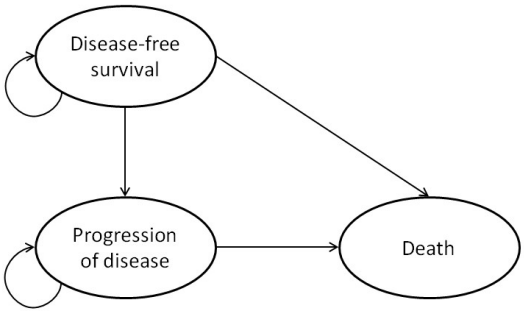

Figure 1. Health states incorporated in the Markov model.

Model input: Clinical variables (parameters)

Several input parameters were incorporated in the model including device and equipment (e.g. suction system, nebulizer) use, occurrence of pulmonary events (e.g. acute tracheobronchitis after laryngectomy, airway infections such as pneumonia), symptoms (e.g. coughing, mucus production, pain due to extensive coughing, insomnia) treated with medication and productivity loss (i.e. hours of absenteeism from work) secondary to the health condition. Occurrence of- and treatment for pulmonary events was reported over a six-monthly period. Treatment of daily symptoms were reported by means of current medication use and frequency of use at the time of questionnaire completion.

Model input: Costs

The micro-costing method was used to optimize precision estimates of the costs of both groups [32]. Annual device costs were sourced from the price lists of most prominent device manufacturers and distributors in the field and calculated through weighted averages. Aside from the HME or ASC, cost of accessories (e.g. housing device including the baseplate/adhesive, laryngectomy tube, shower aid) and equipment were also included in the economic model. Hospital costs were obtained from publically available data from Centers for Medicare & Medicaid Services (CMS) [33,34]. Medication prices were sourced from IBM Micromedex RED BOOK [35]. These costs were in 2019 US dollars. Productivity losses were calculated according to the human capital approach, multiplying annual lost working hours times the median US hourly wage [36-40].

Model input: Health effects

QALYs reflect the life years corrected for the level of disease burden. QALYs are calculated by multiplying the life years gained times the utility scores. The survival probabilities after laryngectomy were derived from literature and assumed to be similar for both groups.

Disutilities are utility decrements that reflect the adverse effect of a certain condition on a patient's QoL by subtracting the disutility from the patient's utility value. In this analysis, disutilities were applied for progressive disease, daily extensive coughing and mucus production. For the latter two, a weighted disutility was calculated for each group based on four categories based on the frequency of symptoms defined as the number of times coughing or mucus production occurred per week: category 1: 0-10 times/week; category 2: 11-73; category 3: 74-137; category 4: ≥138).

Analysis of cost-effectiveness

The incremental cost-effectiveness ratio was used to evaluate the cost-utility of the HME system. The incremental cost-effectiveness ratio is calculated by dividing the difference in total costs of both treatment strategies by the difference in QALYs. The incremental cost-effectiveness ratio represents the additional costs of HME use per QALY gained. The cost-effectiveness analysis, in terms of costs per pulmonary event averted, was calculated to reflect the pulmonary

outcomes during laryngectomy rehabilitation, as the cost per QALY is a rather generic outcome. Budget savings were calculated by multiplying incremental cost savings by the total number of laryngectomees in the US. The willingness-to-pay threshold is the amount a society is willing to pay for a gain in effect (QALY). In the US, the willingness-to-pay threshold is situated at $100,000/QALY [41].

A discount rate of 3% was applied to both costs and health outcomes [41].

Probabilistic and one-way sensitivity analysis

Uncertainty in the estimation of input probabilities was handled probabilistically by providing distributions for each of the parameters. From these confidence intervals, random numbers were drawn to calculate the outcomes of 5000 simulated patients. Outcomes were displayed by means of a cost-effectiveness plane and cost-effectiveness acceptability curve [42,43].

A tornado diagram was created to test the sensitivity of uncertain parameters and to identify the most influential ones on the incremental cost-effectiveness ratio, costs and QALYs. High and low parameter estimates were decided upon ranges within the data or margins of +/- 20%.

The analyses were conducted in Microsoft Excel version 2010.

Results

Patient demographics and device use

An overview of the patient characteristics is provided in Table 1. In total, 40 HME-users and 22 ASC-users were included in this study. All patients underwent a laryngectomy. From available medical reports (reports of seven patients unavailable from other institutions) 47patients underwent total laryngectomy and eight underwent pharyngolaryngectomy. Patients with ASC underwent a laryngectomy a longer time ago on average (10.5 years) than the HME-users (4.8 years). Most patients (83%) started using the HME during the (immediate-) postoperative period. Seven patients started using HMEs on average 51 days postoperatively (range 2-100). At the time of questionnaire completion, these seven patients were on average 5.5 years post laryngectomy (range 1.6-10.9). Most participants were male (n=47) and previous smokers (n=40). Significantly more females (p=0.004) and patients who were divorced/widow(er) (p=0.035) were ASC-users. The HME-users were more highly educated (not significant). Device utilization during the day was on average 6.7 (range: 4-7) and 4.9 (0-7) days/week for the HME-users and ASC-users (including non-users) respectively. During the night, this number was 5.5 (0-7) and 2.6 (0-7) nights/week respectively. The average number of hours of utilization per day (24 hours) was 20.2 (5.5-24) and 11.9 (0-24) hours respectively.

Table 1. Patient, tumor and treatment characteristics.

Characteristics	No. of patients using HME (%)	No. of patients using ASC (%)	*p* value
Mean age, y (range)	65.4 (37.9 - 88.9)	67.7 (40.7- 88.6)	0.474
Median age, y (range)	66.8 (37.9 - 88.9)	69.3 (40.7- 88.6)	
Sex			0.004
Male	35 (88)	12 (55)	
Female	5 (13)	10 (45)	
Marital status			0.035
Single	11 (28)	4 (18)	
Married	23 (58)	7 (32)	
Divorced, separated	3 (8)	3 (14)	
Widow(er)	2 (5)	6 (27)	
In partnership	1 (3)	1 (5)	
Missing	0 (0)	1 (5)	
Education level			0.111
Elementary school	0 (0)	3 (14)	
High school	16 (40)	8 (36)	
Community college	7 (18)	5 (23)	
University	17 (43)	6 (27)	
Employment status before treatment			1.000
Fulltime	28 (70)	16 (73)	
Part-time	3 (8)	2 (9)	
Retired	7 (18)	3 (14)	
Unemployed	2 (5)	1 (5)	
Smoking			1.000
Yes	2 (5)	1 (5)	
No	6 (15)	3 (14)	
Stopped	32 (80)	18 (82)	
Pulmonary history	16 (40)	11 (50)	
Asthma	2 (5)	2 (9)	0.610
COPD	7 (18)	8 (36)	0.097
Legionnaires' disease	1 (3)	0 (0)	1.000
Lung carcinoma	3 (8)	1 (5)	1.000
Pneumothorax	1 (3)	0 (0)	1.000
Pulmonary embolism	2 (5)	0 (0)	0.535
Years after laryngectomy			0.000
Mean, range	4.8 (0.5 – 20.2)	10.5 (1.2-25.2)	
Median, range	4.0 (0.5 – 20.2)	8.3 (1.2-25.2)	

Table 1. Continued

Pulmonary rehabilitation			
HME use	40 (100)	1 (5)*	0.000
Immediate postoperative use	*33 (83)*		
Start of use after surgery	*7 (18)*		
Cloth bib	7 (18)	5 (23)	0.740
Foam pad	7 (18)	9 (41)	0.068
Foam bib	0 (0)	2 (9)	0.122
None	0 (0)	4 (18)	0.013
Mask	0 (0)	1 (5)	0.355
Preferred voice restoration			0.049
TE speech	32 (80)	13 (59)	
Esophageal speech	1 (3)	1 (5)	
Electrolarynx	5 (13)	2 (9)	
TE + esophageal speech	1 (3)	0 (0)	
Whisper/no voice	0 (0)	2 (9)	
Missing	1 (3)	4 (18)	
Treatment prior to laryngectomy			0.882
RT	11 (28)	3 (14)	
CRT	11 (28)	11 (50)	
Surgery and RT	3 (8)	1 (5)	
None	9 (23)	2 (9)	
Unknown	6 (15)	5 (23)	
Postoperative treatment			0.882
RT	3 (8)	1 (5)	
CRT	6 (15)	2 (9)	
None	31 (78)	19 (86)	
Primary health insurer			0.624
Aetna	1 (3)	0 (0)	
Blue Cross Blue Shield	9 (23)	2 (9)	
BMC Healthnet Plan	0 (0)	1 (5)	
Harvard Pilgrim	2 (5)	0 (0)	
MaineCare	0 (0)	1 (1)	
Mass Health	3 (8)	1 (5)	
Medicare Part A & B	18 (45)	11 (50)	
Tufts Health Plan	2 (5)	2 (9)	
Unicare State Indemnity Plan	1 (3)	0 (0)	
United Healthcare	3 (8)	3 (14)	
Unknown	1 (3)	1 (5)	

Sources: Study-specific questionnaire and medical records.

Abbreviations: ASC, alternative stoma covers; COPD, chronic obstructive pulmonary disease; CRT, chemoradiotherapy; FU, follow-up; HME, heat and moisture exchanger; HNC, head and neck cancer; RT, radiotherapy; TE, tracheoesophageal.
*HME-usage less than six hours per day.

Patient-reported issues and quality of life (health effects)

Table 2 provides an overview of the input parameters [44-61]. QoL was similar for HME (0.833, SE=0.134) and ASC (0.839, SE=0.100), with overlapping intervals. Complaints of coughing and mucus production occurred more frequently in ASC-users, resulting in higher disutilities (utility decrements) (0.027 versus 0.019; 0.085 versus 0.069 respectively). Pulmonary events also occurred more often in ASC-users (including 20% airway infections and 10% tracheobronchitis). As the recording of pulmonary events were limited to six months prior to the study, acute postoperative infections were not included. The pulmonary symptoms questioned are chronic and persistent in the lives of laryngectomy patients, and therefore this would not alter in patients who have been operated a longer time ago as is the case with the ASC-users. Medication use was more prevalent in HME -users, except for sleeping medication. Productivity loss was reported more frequent in patients using ASC (probability of 0.682 in the first year, thereafter 0.545 compared to 0.425 and 0.200 respectively in HME-users). For HME-users, mean annual hours of productivity loss (absenteeism from work) was 1119 hours in the first year and 1616 hours thereafter, compared to 1366 hours and 1538 hours respectively in patients using ASC.

During questionnaire completion, 97% of HME-users reported to benefit from the device; HME use was equally valued or more pleasant in 78% compared to no stoma coverage; and 94% found speaking while using an HME easier or similar to not using a HME. Fourteen percent of HME-users reported that the HME is not reimbursed by their healthcare provider (and for HME accessories the percentage is higher), and in some cases only a certain type of HME is reimbursed. In addition, ASC were not reimbursed for 75% of participants in the control group.

Table 2. Model input data (parameters) per year.

Probabilities	**Mean (probability)**		**SE**		**Distribution**	**Source**
	HME	ASC	HME	ASC		
Survival						
POD	0.122	0.122	0.008	0.008	Beta	[44,45]
Death due to HNC	0.249	0.249	0.022	0.022	Beta	[44]
Pulmonary events						
Airway infection inpatient	0.026	0.200	0.025	0.087	Beta	SSQ
Annual number of airway infections inpatient*	2	2	n/a	n/a	Fixed	SSQ
Airway infection outpatient	0.026	0.000	0.025	0.000	Beta	SSQ
Annual number of airway infections outpatient*	4	0			Fixed	SSQ
Tracheobronchitis	0.051	0.100	0.035	0.065	Beta	SSQ
Annual number of tracheobronchitis*	2	2	n/a	n/a	Fixed	SSQ
Medication use						
Anti-cough	0.103	0.000	0.048	0.000	Beta	SSQ
Anti-mucus	0.150	0.100	0.056	0.065	Beta	SSQ
Pain killers	0.051	0.000	0.035	0.000	Beta	SSQ
Sleeping medication	0.211	0.300	0.065	0.100	Beta	SSQ
Productivity loss						
Work loss (first year)	0.425	0.682	0.077	0.097	Beta	SSQ
Work loss	0.200	0.545	0.062	0.104	Beta	SSQ
Hours loss (first year)	1119	1366	143	174	Gamma	SSQ
Hours loss	1616	1538	206	196	Gamma	SSQ
Health effects	**Mean (utility)**		**SE**		**Distribution**	**Source**
	HME	ASC	HME	ASC		
Utilities†						
DFS	0.833	0.839	0.134	0.100	Beta	EQ-5D-5L
Disutilities						
Coughing	0.019	0.027	0.011	0.011	Beta	[46]
Mucus production	0.069	0.085	0.013	0.013	Beta	[47]
Disutility progression	0.130	0.130	0.070	0.070	Beta	[48]

Costs		Mean ($)		SE ($)		Distribution	Source
		HME	ASC	HME	ASC		
Costs							
	Devices‡	2,031	498	259	63	Gamma	49-55
	Equipment§	653	649	83	83	Gamma	49,50,56-59
Costs FU-		464	464	n/a	n/a	Fixed	33
Costs POD¶		622	622	n/a	n/a	Fixed	33
Costs pulmonary events							
	Airway infection inpatient	5,975	5,975	1,524	1,524	Gamma	33-35,60
	Airway infection outpatient	100	100	51	51	Gamma	33,35,60
	Tracheobronchitis	86	86	22	22	Gamma	33,35,60
Cost medication							
	Anti- cough/ mucus	231	231	29	29	Gamma	35
	Pain killers	23	23	3	3	Gamma	35
	Sleeping medication	38	38	5	5	Gamma	35
Productivity loss							35
	Median US hourly wage (all occupations, 2018)	19	19	n/a	n/a	Fixed	61

The probabilities, (dis)utilities and costs that were used in the model to obtain the model outcomes without taking into account the parameters' uncertainty. To conduct the simulations, random numbers were drawn from the distributions (probabilities/utilities: beta distribution; costs: gamma distribution) for each parameter, taking into account the uncertainty within the parameter. Parameters consisting of absolute numbers obtained from our study were fixed (no distribution). Gamma distributions were established with +/-20% upper and lower values.

Abbreviations: ASC, alternative stoma cover; D&D, device manufacturers and distributors; DFS, disease-free survival; FU, follow-up; HME, heat and moisture exchanger; HNC, head and neck cancer; n/a, not applicable; POD, progression of disease; SE, standard error; SLP, speech-language pathologist; SSQ, study-specific questionnaire; US, United States.

*Six-monthly number was doubled to obtain yearly number.

†The utility data of two HME patients with very low quality of life (utility < 0.5) were excluded, because these low outcomes were caused by bipolar disease and severe depression.

‡Content HME package: HME device, baseplate/adhesive, skin wipes, remover wipes, laryngectomy tube, tube brush, shower aid. Content ASC package: Foam pad, foam bib, cloth bib, no coverage, shower aid.

§Content: Suction system, nebulizer, saline use, other stoma covers (part of HME-users who also use ASC).

-Content: Consultations head and neck surgeon and SLP.

¶Content: Consultation head and neck surgeon, CT-scan of head and neck, ultrasound with fine needle biopsy, chest X-ray, Pet-scan.

Costs, cost-effectiveness and sensitivity analysis

In the cost-utility analysis, the HME use was less costly and more effective (healthcare perspective: incremental cost-effectiveness ratio =$-11,833/QALY; societal perspective: incremental cost-effectiveness ratio =$-306,551/QALY) over the calculated time period (20 cycles) (Table 3). Total lifetime costs per patient were lower for HME-users than ASC-users from a healthcare ($29,889 versus $31,551) and societal ($59,362 versus $102,416) perspective. HME use resulted in 0.14 QALY gain (5.30 versus 5.15). The cost-effectiveness, expressed in costs per pulmonary event averted, was $3770 in total ($188 per year). Hence, total budget savings per year were $1,551,083 (healthcare) and $40,183,593 (societal) for the laryngectomy population in the US (almost 19,000 patients).

Regarding the probabilistic sensitivity analyses, the cost-effectiveness plane shows a similar distribution over the quadrants from a healthcare perspective, whereas from a societal perspective HME use is dominant (less costly and more effective) in 54% of the cases (Figure 2a and 2b). The cost-effectiveness acceptability curve shows a probability of 54% (Figure 3a) and 68% (Figure 3b) of HME use respectively being cost-effective at a US willingness-to-pay threshold of $100,000/QALY [41]. HME use is cost-effective starting from a threshold of approximately $10,000.

Regarding the one-way sensitivity analyses, most important model input parameters (ranked most influential from top to bottom) are displayed in the tornado diagrams (Figure 4a-c). The diagrams show the effect of changing a certain parameter (to the minimum or maximum value of the range) on the incremental cost-effectiveness ratio (Figure 4a), incremental costs (Figure 4b) and incremental QALYs (Figure 4c). Those related to (dis)utilities and productivity loss were most influential in the sensitivity analyses. The model outcomes proved to be robust despite uncertainty in these parameters, as HME use is still cost-effective at a US willingness-to-pay threshold of $100,000/QALY.

Table 3. Model outcomes of cost-effectiveness of HME versus ASC from a healthcare and societal perspective.

	Healthcare perspective			Societal perspective		
	HME	ASC	Incremental	HME	ASC	Incremental
Total costs per patient* ($)	29,889	31,551	-1,662	59,362	102,416	-43,054
Total QALYs per patient*	5.30	5.15	0.14	5.30	5.15	0.14
ICER ($/QALY)	n/a	n/a	-11,833	n/a	n/a	-306,551
Annual budget savings ($)	n/a	n/a	1,551,083	n/a	n/a	40,183,593
Total costs per pulmonary event averted*,† ($)	n/a	n/a	3770	n/a	n/a	3770

Abbreviations: ASC, alternative stoma covers; HME, heat and moisture exchanger; ICER, incremental cost-effectiveness ratio; n/a, not applicable; QALYS, quality-adjusted life years;.
*Total costs are calculated over a lifetime horizon.
†Costs are equal in the healthcare and societal setting.

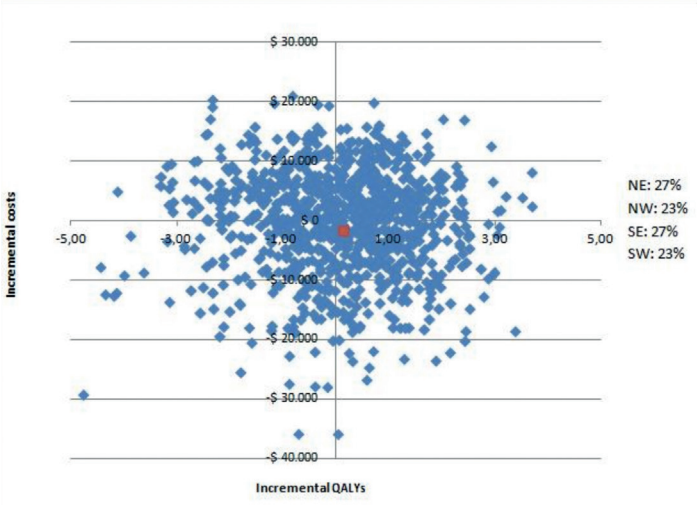

Figure 2a.

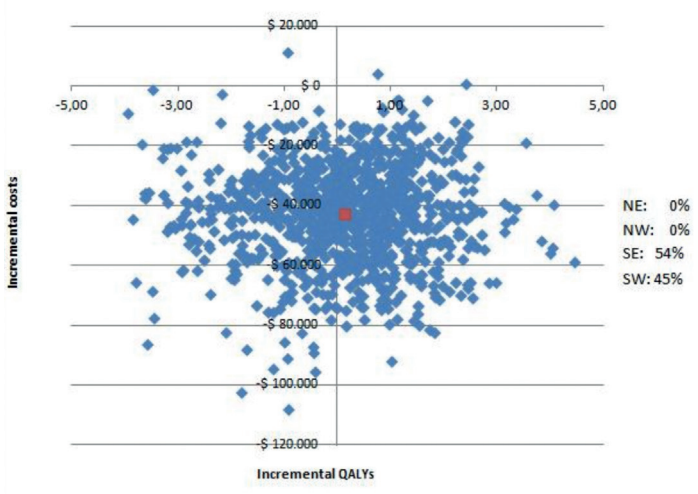

Figure 2b.

Figure 2. Cost-effectiveness (CE) plane of HME versus ASC from a healthcare (2a) and societal (2b) perspective. The scatter dots each represent incremental costs and QALYs of the 5000 simulations. The red dot shows the cost-effectiveness analysis without including the uncertainty of the parameters.

Abbreviations: ASC, alternative stoma covers; HME, heat and moisture exchanger; NE, northeast quadrant; NW, northwest quadrant (dominated); QALYS, quality-adjusted life years; SE, southeast quadrant (dominant); SW, southwest.

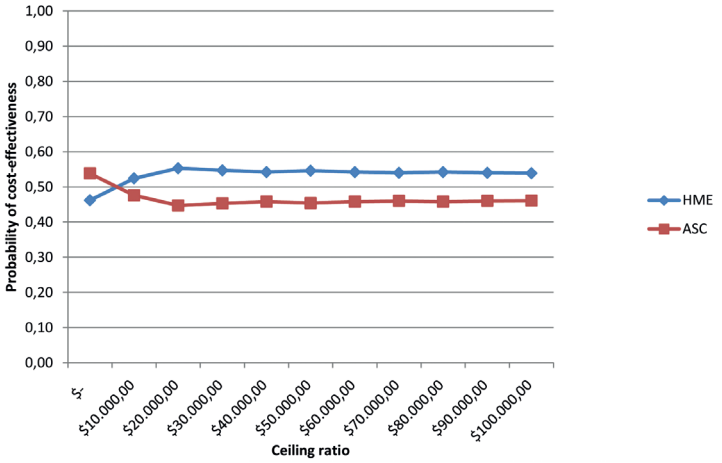

Figure 3a.

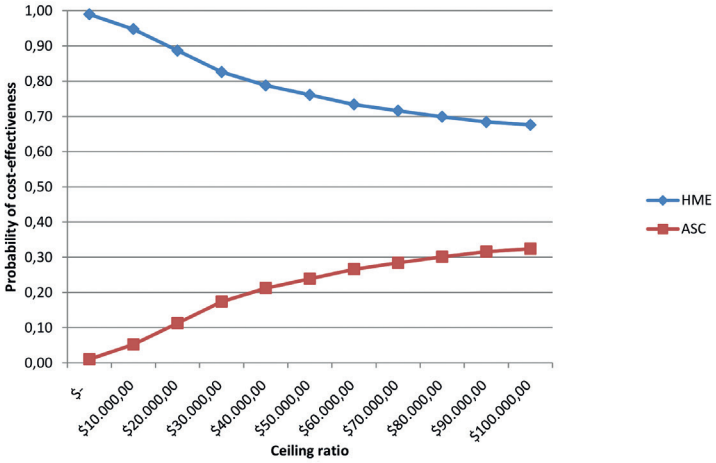

Figure 3b.

Figure 3. Cost-effectiveness acceptability curves (CEAC) of HME versus ASC from a healthcare (3a) and societal (3b) perspective. The curve represents the probability of HME being cost-effective (on the y-axis) at various willingness-to-pay thresholds (also known as ceiling ratios). The willingness-to-pay thresholds (costs/QALY) reflect the amount the population in the United States is willing to pay for a QALY gain.

Abbreviations: ASC, alternative stoma covers; HME, heat and moisture exchanger.

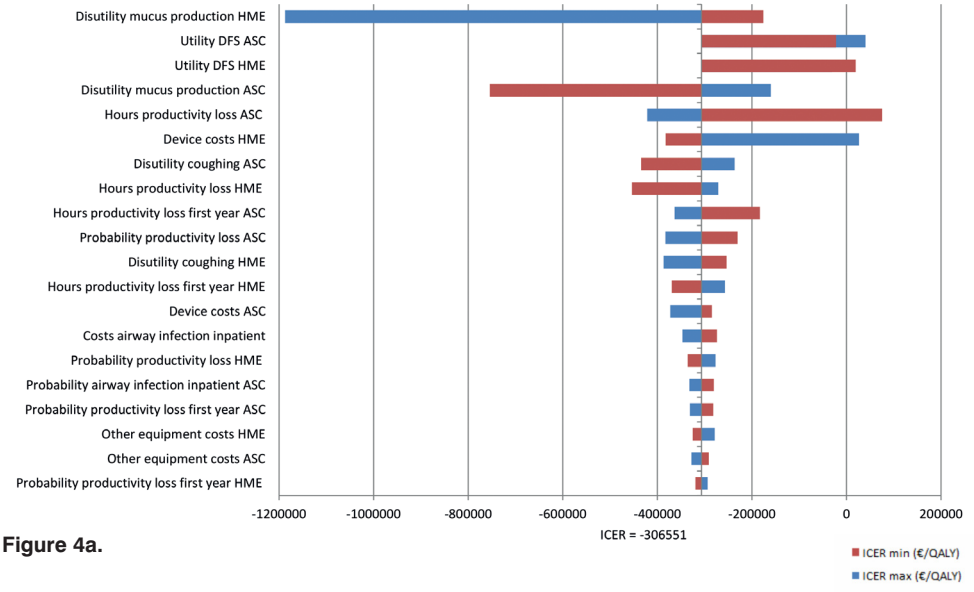

Figure 4a.

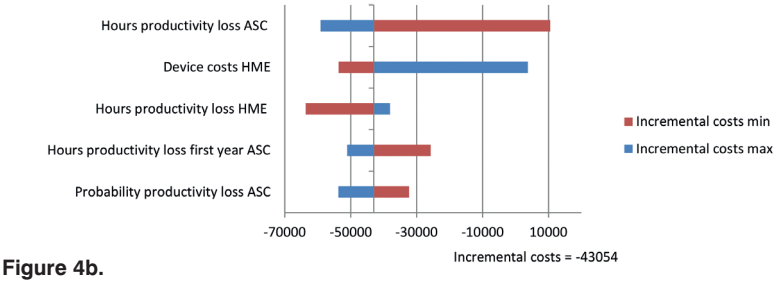

Figure 4b.

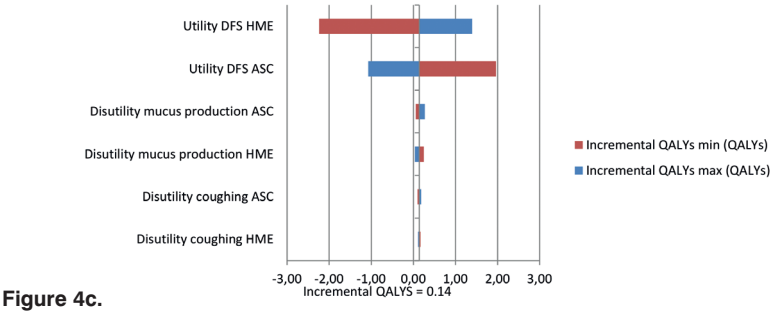

Figure 4c.

Figure 4. Tornado diagrams displaying most influential parameters from the sensitivity analyses expressed in the ICER (4a), incremental costs (4b) and incremental QALYs (4c). The effect of changing one of the parameters (with a minimum or maximum of +/-20% margin) on the outcomes (ICER, incremental costs and QALYs) is visualized in each of the bars in the figures. The values resulted from the cost-effectiveness analysis without including the uncertainty of the parameters for the ICER (-306,551), incremental costs (-43,054) and QALYs (0.14) are displayed below the x-axis.

Discussion

This is the first study to evaluate HME use compared to ASC use in laryngectomy rehabilitation, with new information regarding pulmonary events, return to work and prospective data on QoL. Outcomes of both the cost-utility and cost-effectiveness analysis were in favor of HME use relating to healthcare as well as the societal setting against a US willingness-to-pay threshold of $100,000/QALY. In total, annual budget savings were up to $40,183,593 when adopting the HME approach.

Our study results showed that HME-users reported fewer occurrences of pulmonary events (airway infections and tracheobronchitis) postoperatively compared to ASC-users, which is in line with other study results. In the literature, the occurrence of pulmonary events has been studied retrospectively by De Boer et al., showing pulmonary events to be more prevalent in non-HME-users [15]. Improvements in mucus production, stated by Foreman et al., led to a reduction in consumption of chest physiotherapy, and were also found in this study [16].

Return to work in HNC survivors has been described in literature to be up to 83% [62,63]. More recently, the study of Costa et al. investigated return to work specifically in laryngectomy patients. Fifty-three percent of patients returned to work, associated with voice prosthesis use and a high to intermediate skilled job. However, the authors did not investigate the impact of pulmonary rehabilitation methods on productivity loss [64]. In our study, patients using HME reported to have less productivity loss postoperatively, which established a cost reduction for the society. Although more HME-users communicated with a voice prosthesis, we also do believe that the HME device has a positive effect on returning to work.

With regard to QoL, the positive impact of HME use on QoL has already been recognized in several other studies focusing on factors such as improvement in social interaction and reduction in insomnia [1,2,5,21]. In our study, total QALYs (increment 0.14) were higher for HME- than ASC-users in our study, whereas the improvement in QoL was not clearly observed in the utility measures in our analysis (HME: 0.833; ASC: 0.839). This may be caused by the fact that these factors are not directly addressed by the EQ-5D-5L. The same applies for the reduction in coughing and mucus production. Therefore, we translated symptoms of coughing and mucus production into disutilities. Both for coughing and mucus production, a weighted disutility was calculated by multiplying the literature-based disutility assigned to each of the four categories times the percentage of patients reported to be in that category.

Our results with regard to the cost-effectiveness (cost-utility analysis) are consistent with earlier findings of the study of Retèl et al. [25]. This was the first study to assess cost-effectiveness of HME-use compared to usual care in Poland. Results showed less pulmonary infections, hospital

admissions and sleeping problems of HME-users, which is similar to our results. Contrary to this study, we did not include the use of external humidifiers, as these are not used in clinical practice in the US. The utility scores used in this study were sourced from an Italian study [22] and concluded that the QoL score was significantly higher in HME-users. This was calculated using EQ-5D data that was obtained using a time-series design in which HME-use and non-use was evaluated within the same cohort of Italian patients [22]. When comparing this with our study, we were able to assess the EQ-5D data in long-term HME-users (with a greater sample size) as well as in a control group – the ASC-users – which leads to more representative results. In addition, we included patients at least six months after laryngectomy, which may provide a better reflection of long-term pulmonary rehabilitation than at least three months posttreatment in the Italian study [22]. Finally, the study also concluded the HME to be being cost-effective (-12,264/QALY) from a healthcare perspective [25]. The HME use was more costly but more effective, as in accordance to our study results. To improve quality of the (cost-)effectiveness data and enable access to more data for critical comparison, further research is advised where data of HME and ASC use is prospectively collected at a national level, e.g. by means of a registry, and conducted at a national US level.

Additionally, our study provided insight showing the positive effect of HME use on return to work and the reduction of pulmonary events. In this way, HME use could positively impact societal participation of laryngectomy patients. In addition, our results revealed cost benefits for society (incremental cost-effectiveness ratio =$-11,833/QALY from a societal perspective), costs of $188 per pulmonary event averted per year (the incremental costs ($13,127) divided by the incremental pulmonary events (3.48) over a period of 20 cycles) and prospective real-world patient-reported data on pulmonary events combined with medical records rather than limited to only professional opinion.

Several limitations are acknowledged. The costs may have been underestimated by using the lower prices from REDBook and CMS public data, which only covers a fraction of the actual healthcare costs. Overall, the ASC-users were observed to be a somewhat financially weaker group in this study, as they were more frequently divorced/widow(er), female, and less highly educated . Higher social economic status of the HME-users could explain why they more often used medication. Medication use by ASC-users may be underestimated if these patients could not afford their medications. The fact that ASC-users were operated a longer time ago could have led to more progression of late effects of radiotherapy in this group – impacting utility outcomes – and less accurate reporting of patient-reported outcomes such as employment status. Finally, even though this sample was representative for this population and its outcomes were checked with experts, the sample size is rather small. In the model, this increases uncertainty. In view of this, these results should be considered as preliminary and confirmed with a larger study.

Strengths of the study include the prospective real-world data collection of HME-users and ASC-users (various product types) on QoL from the same facility, including pulmonary events and productivity. We applied the micro-costing method to induce precision in the costs estimates. Also, we analyzed the results from both the healthcare and societal perspective.

Research implications that come forth from this study focus mainly on decreasing the uncertainty found in the utility outcomes. The overlap of the rather wide intervals of the utility measurements in both groups resulted in uncertainty in the cost-effectiveness acceptability curves and the cost-effectiveness planes. As there is ample evidence in literature on the positive influence of HME-use on QoL, our analysis might have underestimated this through evaluation usingthe generic EQ-5D. Laryngectomy patients often suffer from HNC-specific problems, which are not directly assessed by the EQ-5D. Further research could overcome this problem by means of mapping HNC-specific outcomes to the EQ-5D or by creating a HNC-specific utility [65]. Inclusion of more patients would also enhance more precision in the estimates and allow subgroup analysis of the groups.

The most important implication for clinical practice is our recommendation for nationwide reimbursement of HME and accessories. Until now, irrespective of the benefits of HME including adequate pulmonary rehabilitation and cost savings, reimbursement is not secured. Reimbursement could increase access for patients in two ways. First, at a patient level, this vulnerable group of patients suffer the most from financial toxicity – defined as negative financial impact of cancer and treatment among patients who are underinsured – from all HNC patients [66,67]. The study of Massa et al. showed that HNC patients specifically have a higher financial burden including higher relative out-of-pocket payments (3.93% versus 3.07) and annual medical expenses ($8384 versus $5978) compared to patients with other cancers [26]. As a result, laryngectomy patients often cannot afford costs related to pulmonary rehabilitation, resulting in decreased function and productivity, isolation and an increase in hospital visits [68]. Providing reimbursement will therefore enhance access to (a larger portion of) patients and will be beneficial for societal participation and costs. Second, at an organizational level, not all hospitals can handle the financial loss of providing care to these patients by ‘eating’ (paying) the costs in case reimbursement is not provided. Reimbursement could encourage more US hospitals to provide this specific laryngectomy rehabilitation, and will ultimately will ultimately provide greater rehabilitation outcomes.

Conclusions

HME use scores favorably on cost-effectiveness compared to the ASC use in the pulmonary rehabilitation after laryngectomy in the US healthcare and societal setting. The HME use resulted in fewer occurrences of pulmonary events, fewer complaints of mucus production and extensive coughing, and less productivity loss. Annual hospital budget savings (per nearly 19,000 patients) calculated in this study were up to $40,183,593 (societal perspective). QoL differences between both groups were not clearly observed by means of generic utility outcomes. Further research on HNC-specific utilities or the use of mapping functions should be encouraged. In practice, nationwide reimbursement of the HME and its accessories is recommended in the US to facilitate accessibility for patients and thereby improve their pulmonary state and QoL.

Role of funding source

Atos Medical AB (Malmö, Sweden) had no involvement in the development of the study.

Conflict of interest statement

This work was supported by a non-restricted research grant from Atos Medical AB (Malmö, Sweden) contributing to the existing infrastructure for health-related quality of life research of the department of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute.

References

1. HILGERS FJ, AARONSON NK, SCHOUWENBURG PF, ZANDWIJK N. The influence of a heat and moisture exchanger (HME) on the respiratory symptoms after total laryngectomy. *Clin Otolaryngol.* 1991;16(2):152-156.
2. HILGERS FJ, ACKERSTAFF AH, AARONSON NK, SCHOUWENBURG PF, ZANDWIJK N. Physical and psychosocial consequences of total laryngectomy. *Clin Otolaryngol.* 1990;15(5):421-425.
3. van der Molen L, Kornman AF, Latenstein MN, van den Brekel MW, Hilgers FJ. Practice of laryngectomy rehabilitation interventions: a perspective from Europe/the Netherlands. *Curr Opin Otolaryngol Head Neck Surg.* 2013;21(3):230-238.
4. Zuur J, Muller S, de Jongh FH, Van Zandwijk N, Hilgers F. The physiological rationale of heat and moisture exchangers in post-laryngectomy pulmonary rehabilitation: a review. *Eur Arch Otorhinolaryngol.* 2006;263(1):1-8.
5. Ackerstaff A, Hilgers F, Aaronson N, Schouwenburg P. Physical and psychosocial sequelae of total larynx extirpation and the use of a heat and moisture exchanger. *Ned Tijdschr Geneeskd.* 1990;134(50):2438-2442.
6. Lansaat L, van den Boer C, Muller SH, van der Noort V, van den Brekel MW, Hilgers FJ. Ex vivo humidifying capacity and patient acceptability of stoma cloths in laryngectomized individuals. *Head Neck.* 2017;39(5):921-931.
7. van den Boer C, Vas Nunes JH, Muller SH, van der Noort V, van den Brekel MW, Hilgers FJ. Water uptake performance of hygroscopic heat and moisture exchangers after 24-hour tracheostoma application. *Otolaryngology--Head Neck Surgery.* 2014;150(6):999-1004.
8. van den Boer C, Muller 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. In: Respiratory Care; 2014.
9. Jones AS, Young PE, Hanafi ZB, Makura ZGG, 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):361-367.
10. Mérol JC, Charpiot A, Langagne T, Hémar 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):275-281.
11. Dassonville O, Mérol JC, Bozec A, et al. Randomised, multi-centre study of the usefulness of the heat and moisture exchanger (Provox HME®) in laryngectomised patients. *Eur Arch Otorhinolaryngol.* 2011;268(11):1647-1654.
12. van den Boer C, Muller SH, van der Noort V, 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):3439-3450.

13. Griffith TE, Friedberg SA. LXXII Histologic Changes in the Trachea following Laryngectomy. *Ann Otol Rhinol Laryngol.* 1964;73(4):883-892.
14. 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):20-23.
15. van den Boer C, van Harten MC, Hilgers FJ, van den Brekel MW, Retèl 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):3297-3303.
16. Foreman A, De Santis R, Sultanov F, Enepekides D, Higgins K. 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.
17. Bie- S, Okła 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):429-435.
18. Lorenz K, Maier H. Pulmonary Rehabilitation after Total Laryngectomy using a Heat and Moisture Exchanger (HME). *Laryngorhinootologie.* 2007;1(8):513-521.
19. 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):358-363.
20. Ackerstaff AH, Hilgers FJ, Balm AJ, Aaronson NK, van Zandwuk N. Improvements in respiratory and psychosocial functioning following total laryngectomy by the use of a heat and moisture exchanger. *Annals of Otology, Rhinology & Laryngology.* 1993;102(11):878-883.
21. Ackerstaff A, Hilgers F, Aaronson N, Balm A. Communication, functional disorders and lifestyle changes after total laryngectomy. *Clin Otolaryngol.* 1994;19(4):295-300.
22. Parrilla C, Minni A, Bogaardt H, et al. Pulmonary rehabilitation after Total Laryngectomy: a multicenter time-series clinical trial evaluating the Provox XtraHME in HME-Naïve patients. *Ann Otol Rhinol Laryngol.* 2015;124(9):706-713.
23. 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):705-712.
24. Beck A, Retèl V, van den Brekel M, van Harten W. Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries. *Oral Oncol.* 2019;91:56-64.
25. Retèl VP, van den Boer C, Steuten LM, Okła 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):2381-2388.
26. Massa ST, Osazuwa-Peters N, Boakye EA, Walker RJ, Ward GM. Comparison of the financial burden of survivors of head and neck cancer with other cancer survivors. *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):239-249.

27. Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding JJViH. Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: A Societal Perspective: The ISPOR Drug Cost Task Force Report—Part II. 2010;13(1):8-13.
28. REDCap. Last accessed: 29-4-2019.; https://www.project-redcap.org/.
29. Szende A, Oppe M, Devlin N. *EQ-5D value sets: inventory, comparative review and user guide.* Vol 2: Springer Science & Business Media; 2007.
30. Timmermans AJ, van Dijk BA, Overbeek LI, et al. Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. *Head Neck.* 2016;38(S1):E1247-E1255.
31. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Arch Otolaryngol Head Neck Surg.* 2004;130(7):875-879.
32. Xu X, Nardini HKG, Ruger JP. Micro-costing studies in the health and medical literature: protocol for a systematic review. *Systematic reviews.* 2014;3(1):47.
33. CMS Physician Fee Schedule 2019. Last accessed: 29-4-2019.; https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/index.html.
34. CMS Acute Inpatient PPS 2019. Last accessed: 29-4-2019.; https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/index.html.
35. IBM Micromedex RED BOOK. Last accessed: 29-4-2019.; https://www.ibm.com/us-en/marketplace/micromedex-red-book.
36. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA.* 1996;276(15):1253-1258.
37. Valenstein M, Vijan S, Zeber JE, Boehm K, Buttar A. The cost–utility of screening for depression in primary care. *Ann Intern Med.* 2001;134(5):345-360.
38. Antonuccio DO, Thomas M, Danton WG. A cost-effectiveness analysis of cognitive behavior therapy and fluoxetine (Prozac) in the treatment of depression. *Behav Ther.* 1997;28(2):187-210.
39. Krol M, Papenburg J, Koopmanschap M, Brouwer W. Do productivity costs matter? *Pharmacoeconomics.* 2011;29(7):601-619.
40. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316(10):1093-1103.
41. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.
42. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ.* 2001;10(8):779-787.
43. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation.* OUP Oxford; 2006.
44. Brandstorp-Boesen J, Falk RS, Boysen M, Brøndbo K. Impact of stage, management and recurrence on survival rates in laryngeal cancer. *PLoS One.* 2017;12(7):e0179371.

45. Ritoe SC, Bergman H, Krabbe PF, et al. Cancer recurrence after total laryngectomy: treatment options, survival, and complications. *Head Neck.* 2006;28(5):383-388.
46. Paracha N, Abdulla A, MacGilchrist KS. Systematic review of health state utility values in metastatic non-small cell lung cancer with a focus on previously treated patients. *Health quality of life outcomes.* 2018;16(1):179.
47. Solem CT, Sun SX, Sudharshan L, Macahilig C, Katyal M, Gao X. Exacerbation-related impairment of quality of life and work productivity in severe and very severe chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2013;8:641.
48. Simons PA, Ramaekers B, Hoebers F, et al. Cost-Effectiveness of Reduced Waiting Time for Head and Neck Cancer Patients due to a Lean Process Redesign. *Value Health.* 2015;18(5):587-596.
49. InHealth Technologies. . Last accessed: 8-1-2020.; https://www.inhealth.com/.
50. Atos Medical. Last accessed: 8-1-2020.; https://www.atosmedical.us/.
51. ADDvox. Last accessed: 8-1-2020.; https://www.addvox.com.
52. Romet. Last accessed: 8-1-2020.; https://www.romet.us/.
53. Kapitex Healthcare Limited. Last accessed: 8-1-2020.; https://www.kapitex.com/.
54. Bruce Medical Supply. Last accessed: 8-1-2020.; https://www.brucemedical.com.
55. Lauder Enterprises. Last accessed: 8-1-2020.; https://www.electrolarynx.com/#/.
56. DeVilbiss Healthcare. Last accessed: 8-1-2020.; http://www.devilbisshealthcare.com.
57. Philips healthcare. Last accessed: 8-1-2020. ; https://www.philips.co.uk/healthcare.
58. Vios Aerosol Delivery System. Last accessed: 8-1-2020.; https://www.pari.com/us-en/products/products/.
59. Andreas Fahl Medizintechnik. Last accessed: 8-1-2020.; https://www.fahl-medizintechnik.de/en/products/hospital-products/.
60. CMS Clinical Laboratory Fee Schedule. Last accessed: 29-4-2019.; https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html?redirect=/clinicallabfeesched/.
61. May 2018 National Occupational Employment and Wage Estimates United States. Last accessed: 29-4-2019.; https://www.bls.gov/oes/current/oes_nat.htm#00-0000.
62. Isaksson J, Wilms T, Laurell G, Fransson P, Ehrsson YT. Meaning of work and the process of returning after head and neck cancer. *Supportive Care in Cancer.* 2016;24(1):205-213.
63. Verdonck-de Leeuw IM, van Bleek W-J, Leemans CR, de Bree R. Employment and return to work in head and neck cancer survivors. *Oral Oncol.* 2010;46(1):56-60.
64. Costa JM, López M, García J, León X, Quer M. Impact of total laryngectomy on return to work. *Acta Otorrinolaringol Esp.* 2018;69(2):74-79.
65. Beck A-JC, Kieffer JM, Retèl VP, et al. Mapping the EORTC QLQ-C30 and QLQ-H&N35 to the EQ-5D for head and neck cancer: Can disease-specific utilities be obtained? *PLoS One.* 2019;14(12).
66. Zafar SY, Peppercorn JM, Schrag D, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *The oncologist.* 2013;18(4):381.

67. Mady LJ, Lyu L, Owoc MS, et al. Understanding financial toxicity in head and neck cancer survivors. *Oral Oncol.* 2019;95:187-193.
68. Deschler DG. Head and Neck Cancer Compared With Other Cancers—Does the Great Equalizer Equalize Equally? *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):249-250.

Chapter 8

Mapping the EORTC QLQ-C30 and QLQH&N35 to the EQ-5D for head and neck cancer: Can disease-specific utilities be obtained?

Ann-Jean C.C. Beck
Jacobien M. Kieffer
Valesca P. Retèl
Lydia F.J. van Overveld
Robert P. Takes
Michiel W.M. van den Brekel
Wim H. van Harten
Martijn M. Stuiver

PLoS One. 2019 Dec 13;14(12):e0226077.
doi: 10.1371/journal.pone.0226077.

Abstract

Introduction

Innovations in head and neck cancer (HNC) treatment are often subject to economic evaluation prior to their reimbursement and subsequent access for patients. Mapping functions facilitate economic evaluation of new treatments when the required utility data is absent, but quality of life data is available. The objective of this study is to develop a mapping function translating the EORTC QLQ-C30 to EQ-5D-derived utilities for HNC through regression modeling, and to explore the added value of disease-specific EORTC QLQ-H&N35 scales to the model.

Methods

Data was obtained on patients with primary HNC treated with curative intent derived from two hospitals. Model development was conducted in two phases: 1. Predictor selection based on theory- and data-driven methods, resulting in three sets of potential predictors from the quality of life questionnaires; 2. Selection of the best out of four methods: ordinary least squares, mixed-effects linear, Cox and beta regression, using the first set of predictors from EORTC QLQ-C30 scales with most correspondence to EQ-5D dimensions. Using a stepwise approach, we assessed added values of predictors in the other two sets. Model fit was assessed using Akaike and Bayesian Information Criterion (AIC and BIC) and model performance was evaluated by MAE, RMSE and limits of agreement (LOA).

Results

The beta regression model showed best model fit, with global health status, physical-, role and emotional functioning and pain scales as predictors. Adding HNC-specific scales did not improve the model. Model performance was reasonable; R2 = 0.39, MAE = 0.0949, RMSE = 0.1209, 95% LOA of -0.243 to 0.231 (bias -0.01), with an error correlation of 0.32. The estimated shrinkage factor was 0.90.

Conclusions

Selected scales from the EORTC QLQ-C30 can be used to estimate utilities for HNC using beta regression. Including EORTC QLQ-H&N35 scales does not improve the mapping function. The mapping model may serve as a tool to enable cost-effectiveness analyses of innovative HNC treatments, for example for reimbursement issues. Further research should assess the robustness and generalizability of the function by validating the model in an external cohort of HNC patients.

Introduction

Over the years, new treatment regimens, including innovative medical devices, have been emerging in the field of head and neck cancer (HNC) to improve quality of life of patients. In the process of securing access to these innovations for HNC patients, reimbursement plays a key role. Before reimbursement of clinical innovations is considered by governing bodies, an economic evaluation is often required.

This evaluation can be performed when data regarding costs of the treatment and quality of life of patients are available, provided that quality of life is expressed in quality-adjusted life years (QALYs). To calculate QALYs, utilities are necessary and these can be derived from preference- based measures (PBMs), such as the EuroQol five-dimensional questionnaire (EQ-5D) [1]. In clinical practice, however, utility data are not routinely collected by means of PBMs. The resulting unavailability of QALYs hinders the cost-effectiveness evaluation that is needed for clinical implementation of innovative treatments and to inform healthcare providers on the cost-effectiveness of existing treatment options.

While often not using PBMs, studies evaluating the effectiveness of head and neck cancer (HNC) treatments or devices frequently do use health-related quality of life (HRQoL) instruments, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the disease-specific EORTC QLQ module for HNC (QLQ-H&N35) [2, 3]. Such (disease-specific) HRQoL measures could be used to estimate utilities, by making use of a 'mapping model' [4,5]. For this purpose, several types of regression models can be employed, each with their own advantages and disadvantages [6].

The most commonly used regression method in the mapping literature is the ordinary least squares (OLS) linear regression [7,8]. The linear regression is a simplistic model, which is easily applicable in practice. However, the model may over- or undershoot the utility interval [0 to 1]. Also, assumptions related to the regression are often violated, e.g. homoscedasticity and normal distribution of residuals. To deal with the often skewed distribution and ceiling effects of HRQoL scores, the Tobit model has been suggested as an alternative model for mapping functions [9,10]. This model however, assumes an underlying (but unobserved) normal distribution of the data. The comparable semiparametric Cox proportional hazards model shares the advantages of the Tobit model for dealing with non-normal data, but without the undesirable parametric assumption [11]. Even so, it is less straightforward to interpret and has not been frequently used for mapping purposes. Finally, beta regression uses a beta distribution, which can shape according to the skewness of the data often seen in PBM data. The regression model accommodates a dependent variable that is limited to an interval of 0 to 1, but cannot handle the extreme values (0

and 1) on the boundaries of this interval [6,12]. Currently, there is no consensus on which statistical method to use in the development of mapping models.

Previous studies have concluded that estimating EQ-5D utilities using outcomes of the EORTC QLQ-C30 is feasible for several forms of cancer [4,5,7,8,13]. To the best of our knowledge, no mapping model based on the EORTC QLQ-C30 has been developed to date for use in a HNC population. Therefore, the primary objective of the current study was to develop an optimal mapping model to estimate utilities, required for economic evaluation, by translating the generic EORTC QLQ-C30 outcomes to EQ-5D utilities for HNC patients, comparing different statistical approaches.

HNC-specific symptoms have a substantial influence on the HRQoL of patients, but are not all addressed in the EORTC QLQ-C30. Adding (parts of) the EORTC QLQ-HN35 module to the mapping model might further improve utility estimations, but current evidence about the value of using cancer type-specific QLQ scales for mapping models is scarce [4,5]. Hence, the secondary objective of the study was to explore the added value of the EORTC QLQ-H&N35 scales to the mapping model.

Ultimately, the aim of this study is to facilitate economic evaluation of health care innovations for patients with HNC, in case of absence of utility data, and thereby support the implementation of such innovations in clinical practice.

Material and methods

Data source

Data used for the purpose of the current study were collected for the Dutch Head and Neck Audit (DHNA). The purpose of the audit is to measure and monitor the quality of care in the Dutch HNC centers using a set of quality indicators. The quality indicators have been described in detail elsewhere [14]. This audit collects data prospectively by means of an online survey completed by HNC patients. Patients diagnosed with primary HNC (head and neck squamous cell carcinoma (HNSCC) and salivary gland malignancies) and treated with curative intent are included in the audit. Exclusion criteria for the DHNA are: patients with other types of head and neck malignancies (e.g. skin cancer, sarcomas and esthesioneuroblastoma), a second primary tumor or with recurrent disease.

In the DHNA, quality of life is measured routinely using the EORTC QLQ-C30, EORTC QLQ-H&N35 and three-level EQ-5D (EQ-5D-3L) at diagnosis (baseline) and 3, 6 12 and 24 months after end of treatment. The register also incorporates patient and clinical characteristics, including age, sex, tumor site, treatment and TNM stage. For the current study, datasets were available

from patients treated in the Netherlands Cancer Institute (NKI) and Radboud University Medical Center (Radboudumc) between November 2014 and February 2017. Only cases with complete quality of life data (i.e. no missing scale scores on the QOL questionnaires) were included in the study. The data was de-identified to ensure the anonymity of the patients. The procedures were in accordance with the ethical standards of the ethics committee of the Radboudumc (registration number: 2014/070). Approval for this study was obtained by the ethics committee of the Netherlands Cancer Institute (NKI) (registration number: METC16.0502). The participating hospitals are: the NKI, Amsterdam and Radboudumc, Nijmegen. A written informed consent was obtained from all participants upon participation.

Instruments

The EORTC QLQ-C30 is a generic instrument that is developed to assess HRQoL in cancer patients. The EORTC QLQ-C30 consists of 30 questions, resulting in a two-item global health status/QoL scale, five multi-item functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting and pain) and six single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) [2].

The HNC-specific EORTC QLQ-H&N35 module is a supplement, containing seven multi-item scales (pain, swallowing, senses problems, speech problems, trouble with social eating and social contact, and less sexuality) and eleven single-item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, weight gain) [3]. Both the EORTC QLQ-C30 and QLQ-H&N35 scales employ a 4-point response format (''not at all" to ''very much"), with the exception of the global QoL scale, which has a 7-point response format. Scale scores are transformed to a scale from 0 to 100 according to the EORTC scoring algorithm [15]. For the functioning and the global QoL scale, a higher score indicates better health. For the symptoms scales, a higher score indicates a higher level of symptom burden [3,15].

The EQ-5D-3L is a generic preference-based instrument that functions as a health state classifier and consist of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D has three levels of functioning: no problems, some problems, and extreme problems. It provides 243 health profiles in total, which are often reported as vectors ranging from 11111 (full health) to 33333 (worst health). Health profiles can be converted into a utility index score by applying the EQ-5D scoring algorithm [1]. The utility index score, a number from 0 to 1, reflects the HRQoL, and is used for cost-effectiveness purposes. Utility values are adjusted for the respective country by means of a tariff applied in the mapping methods. In this study, the Dutch tariff was used.

Model development

Development of the best fitting mapping model was conducted in two phases. In the first phase, QLQ scales were preselected as potential predictors, resulting in three predictor sets based on theory (Set 1) and combined theory- and data-driven considerations (Set 2 and 3). This was done to retain parsimony of the model. In the second phase, statistical analyses were performed in three consecutive steps in order to select a model with the best fit, considering the different predictor sets. A schematic overview is given in Fig 1.

In this Methods section, both phases are described separately.

Preselection of QLQ scales.

Three sets of HRQoL outcomes were selected as potential predictors to map onto the EQ-5D. The first set of predictors was selected from EORTC QLQ-C30 scales based on the correspondence of these scales with the EQ-5D dimensions and its underlying construct. Correspondence was evaluated by matching EORTC QLQ-C30 scales to EQ-5D dimensions based on degree of overlap in content between items in both questionnaires. This predictor set functioned as a base for the model, and was retained in the model throughout the predictor selection from Set 2 and Set 3.

The second set of predictors included a number of the remaining EORTC QLQ-C30 scales, which were selected based on their ability to reflect on changes over time (a.k.a. responsiveness). A literature search was conducted to estimate the responsiveness of the scales. Studies were considered eligible when HNC patients had undergone a surgical and/or organ sparing intervention, the EORTC QLQ-C30 was completed at least twice by these patients at various time points within a timeframe of at least three months in which responsiveness of QoL was expected based on the treatment, and the sample size was ≥100. The search was restricted to studies published between January 2012 and July 2017. From the included studies, effect sizes (ES) were calculated for each EORTC QLQ-C30 scale, by dividing the mean difference of the score by the pooled standard deviation, and compared with the average ES of the EQ-5D calculated with the data used in this study [16].

A third set containing individual predictors consisting of EORTC QLQ-H&N35 scales was developed to explore whether use of HNC-specific HRQoL outcomes could improve the fit of the mapping model. Scales were assessed on intercorrelation, to limit overfitting as well as prevent multicollinearity. If a Pearson correlation coefficient of ≥0.7 between two individual EORTC QLQ-H&N35 scales was present, one of the scales was excluded based on theoretical considerations. Of the remaining EORTC QLQ-H&N35 scales, those that correlated with the dependent outcome (Pearson correlation coefficient ≥ 0.3) were included in the third set

of predictors. The data showed no outliers, but were not entirely normally distributed. For completeness, we re-ran the analyses on the basis of Spearman's correlation results.

The predictors were tested one by one for their additional value to the model.

Statistical analysis.

The statistical analysis was conducted in three steps (Fig 1). The first step consisted of selecting the best fitting regression method using only the first set of predictors as input for the models. We considered four commonly used regression models:

1. Regression analysis using an OLS estimator (Model 1a);
2. Mixed-effects modeling approach (Model 1b) using a maximum likelihood solution, with a random intercept to take into account mutual correlation within repeated measurements present in our data;
3. Cox regression (Model 1c) with 'censoring' of all EQ-5D utility index scores <1.
4. Classical beta regression (Model 1d) modeling the dependent variable y in a unit interval $0 < y < 1$. In order to include the full health (utility value of 1) in this interval, a transformation of y was applied [17,18]:

$$(y \cdot (n - 1) + 0.5) /n$$

in which y is the utility and n is the sample size. To create a generalized linear model, we applied the logit link function [17].

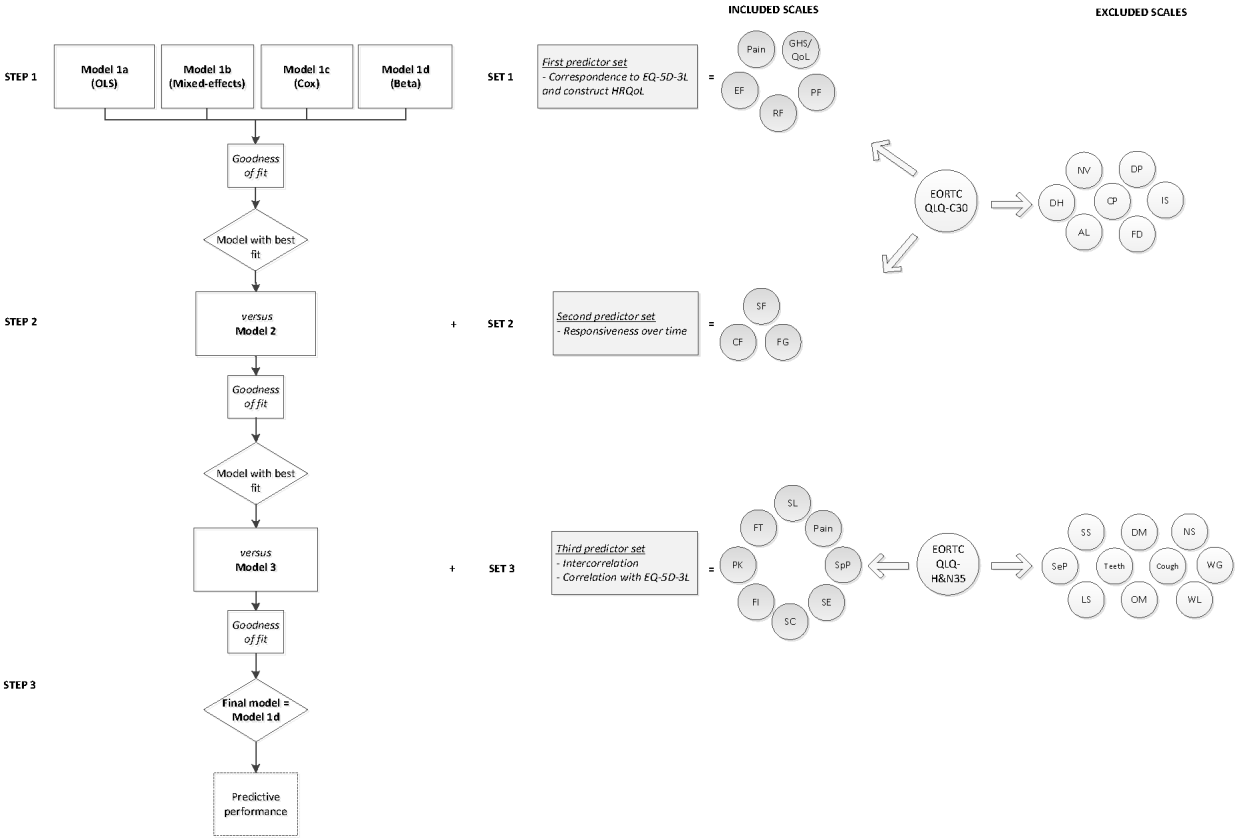

Figure 1. Flowchart of model development. The grey rectangles display the three predictor sets with their criteria; the white rectangles the different models. The squares indicate the assessment of the models during model comparison; the rhombuses indicate the decision-making in the process. Assessment of the model performance is displayed with a dotted line. The EORTC QLQ-C30 and QLQ-H&N35 scales included in the predictor sets are highlighted in grey circles. The scales that were excluded are colored white.

Abbreviations: AL, appetite loss; Cough, coughing; CF, cognitive functioning; CP, constipation; DH, diarrhea; DP, dyspnea; DM, dry mouth; EF, emotional functioning; EORTC, European Organization for Research and Treatment of Cancer ;EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; FD, financial difficulties; FG, fatigue; FI, felt ill; FT, feeding tube; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; IS, insomnia; LS, less sexuality; NT, nutritional supplements; NV, nausea and vomiting; OLS, ordinary least-squares, OM, opening mouth; PF, physical functioning; PK, pain killers; Quality of Life Questionnaire-Core 30; QLQ-H&N35, Quality of Life Questionnaire-Head and Neck35; RF, role functioning; SC, trouble with social contact; SE, trouble with social eating; SpP, speech problems; SeP, senses problems; SL, swallowing; SF, social functioning; SS, sticky saliva; WG, weight gain; WL, weight loss.

To select the overall best statistical approach, we compared the four models using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) [19,20]. The AIC and BIC can be used to compare non-nested models and reflect the relative quality of the models by assessing the goodness of fit while penalizing the number of model parameters. Models with lower BIC or AIC values are considered to be better fitting models, although there is much debate about how to interpret the numerical differences in outcomes between models. Published rules of thumb are: a between model difference in the AIC or BIC of 0 to 2 is considered to be weak, 2 to 6 to be positive, 6 to 10 to be strong and above 10 to be very strong [20,21]. In this study, we considered the regression method with the lowest AIC and BIC to be the most appropriate base model to use for the subsequent statistical steps.

In the second step, we extended the base model selected in step 1 with the second set of predictors containing all responsive EORTC QLQ-C30 scales (Model 2). The added value of these predictors was assessed using the AIC, BIC and likelihood-ratio (LR) test with a cutoff p-value of 0.05. In case of significant outcome ($p<0.05$) of the LR test and lower AIC and BIC values, we used manual stepwise backward elimination of predictors of the second set, for parsimony of the model. Backward elimination was based on the p-value of the coefficients (using a cutoff of 0.1).

In step 3, we explored the added value of the selected EORTC QLQ-H&N35 predictors (third set) for each variable separately (Model 3). Each of these models was compared to the model with the best fit so far obtained after step 2. The same model fit statistics were used as described in step 2.

Assessment of predictive performance and validation of final model

Predictive performance of the final model was evaluated with the R squared (R2), the mean absolute error (MAE) and root mean square error (RMSE). In addition, the 95% limits of agreement (LOA) of observed and predicted EQ-5D utilities and the correlation coefficient of the error were determined by means of a Bland-Altman analysis [13,22].

The estimated shrinkage factor (s) of the coefficients of the final model was calculated to adjust for inflated regression coefficients, and thus improve generalizability of the model to the target population. A heuristic formula was used:

$$s = (\text{model } \chi^2 - df) / \text{model } \chi^2$$

in which model χ^2 indicates the likelihood ratio χ^2 of the model, and df stands for the degrees of freedom of the candidate predictors involved in the model [23].

We cross-validated the model fit by calculating MAE and RMSE of models fitted in 1000 bootstrap samples (with replacement) as applied to the original data as a means to assess the robustness of the predictive performance and internal validation.

Statistical analyses were performed in R version 3.4.3. (2017-11-30).

Results

Descriptive analyses

Details on patient, tumor and treatment characteristics, including the response rate to the EORTC QLQ-C30 and QLQ-H&N35, are listed in Table 1.

In total, 361 measurements of 236 patients were included in this study. Only complete cases were included in the study. Of the 236 patients, 73% were male with a mean age of 63 years. The majority of carcinomas were situated in the oropharynx (27%), oral cavity (23%) and larynx (19%). Almost 30 percent of the patients had an advanced (T3 or T4) tumor. Most common treatment modalities were surgery (20%), surgery with postoperative RT (17%), RT alone (34%) and chemoradiation (CRT, 23%). The response rate to the questionnaires in the data used in this study varied from 6% to 32% at the different time points.

The mean utility value of the study population was estimated at 0.83 (range 0.11–1.00; SD 0.18) (Table 2). In total, 33 unique health states were observed. Optimal health (utility = 1) was observed 123 times (34%). Worst HRQoL scores were found on the EORTC QLQ-C30 global health status/QoL (functional) scale (mean 73.87; SD 18.42) and fatigue (symptom) scale (mean 26.72; SD 22.87), and of the EORTC QLQ-H&N35 scales on the pain killers scale (38.50; SD 48.73).

Table 1. Patient, tumor and treatment characteristics. Tumors were staged according to cTNM clinical classification of the Union for International Cancer Control (UICC) (2009, 7th edition) [24].

Characteristics	Total no. (%)
Mean age, y (range)	63.0 (30.3-90.6)
Median age, y (range)	62.4 (30.3-90.6)
Sex	
Male	172 (72.9)
Female	64 (27.1)
Smoking	
Never	49 (20.8)
Stopped	106 (44.9)
Current	77 (32.6)
Missing	4 (1.7)
Alcohol	
Never	60 (25.4)
Stopped	21 (8.9)
Current	153 (64.8)
Missing	2 (0.8)
Subsite	
Hypopharynx	18 (7.6)
Larynx	46 (19.5)
Nasopharynx	8 (3.4)
Oral cavity	55 (23.3)
Oropharynx	64 (27.1)
Sinonasal malignancies	15 (6.4)
Salivary glands	16 (6.8)
Unknown primary	14 (5.9)
cT classification	
T0	14 (5.9)
Tis	5 (2.1)
T1	69 (29.2)
T2	79 (33.5)
T3	35 (14.8)
T4	34 (14.3)
cN classification	
N0	121 (51.3)
N1	32 (13.6)
N2	81 (34.4)
N3	2 (0.8)

Table 1. Continued

cM classification	
Mx	15 (6.4)
M0	221 (93.6)
Treatment	
Surgery	48 (20.3)
Surgery + RT	42 (17.8)
Surgery + CRT	5 (2.1)
RT	79 (33.5)
CRT	54 (22.9)
BRT	8 (3.4)
Response rate*	
Baseline	117 (32.4)
3 months FU	84 (23.3)
6 months FU	91 (25.2
12 months FU	49 (13.6)
24 months FU	20 (5.5)
Total	361 (100)
Completed questionnaires per patient	
1 questionnaire	236 (100)
2 questionnaires	89 (38)
3 questionnaires	32 (14)
4 questionnaires	4 (2)
5 (all) questionnaires	0 (0)

*Time since diagnosis can be calculated 7 to 9 weeks prior to end of treatment.

Abbreviations: BRT, bioradiation; CRT, chemoradiotherapy; FU, follow-up; RT, radiotherapy.

Table 2. Summary results of HRQoL data derived from 361 observations.

EORTC QLQ-C30 scores	Mean (range)	SD
Functional scales		
Global health status/QoL	73.87 (16.67-100.00)	18.42
Physical functioning	87.37 (26.67-100.00)	16.27
Role functioning	79.13 (0.00-100.00)	24.53
Emotional functioning	80.06 (0.00-100.00)	20.86
Cognitive functioning	87.35 (33.33-100.00)	16.99
Social functioning	84.11 (0.00-100.00)	21.05
Symptom scales		
Fatigue	26.72 (0.00-100.00)	22.87
Nausea and vomiting	4.76 (0.00-100.00)	13.31
Pain	20.18 (0.00-100.00)	24.75
Dyspnea	10.25 (0.00-100.00)	20.10
Insomnia	23.00 (0.00-100.00)	27.06
Appetite loss	17.17 (0.00-100.00)	26.77
Constipation	8.77 (0.00-100.00)	19.72
Diarrhea	6.37 (0.00-100.00)	16.27
Financial difficulties	11.08 (0.00-100.00)	22.64
EORTC QLQ-H&N35 scores		
Symptom scales		
Pain	22.32 (0.00-100.00)	24.35
Swallowing	17.04 (0.00-100.00)	21.98
Senses problems	16.02 (0.00-100.00)	21.36
Speech problems	18.25 (0.00-100.00)	22.32
Trouble with social eating	19.34 (0.00-100.00)	20.66
Trouble with social contact	7.09 (0.00-100.00)	13.41
Less sexuality	21.56 (0.00-100.00)	30.13
Teeth	14.50 (0.00-100.00)	27.26
Opening mouth	6.65 (0.00-100.00)	19.53
Dry mouth	11.73 (0.00-100.00)	23.85
Sticky saliva	21.79 (0.00-100.00)	30.52
Coughing	20.31 (0.00-100.00)	26.17
Felt ill	5.36 (0.00-00.00)	15.78
Pain killers	38.50 (0.00-100.00)	48.73
Nutritional supplements	21.88 (0.00-100.00)	41.40
Feeding tube	4.16 (0.00-100.00)	19.98
Weight loss	24.93 (0.00-100.00)	43.32
Weight gain	19.67 (0.00-100.00)	39.80
EQ-5D-3L score		
Utility value	0.83 (0.11-1.00)	0.18

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer ; EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-H&N35, Quality of Life Questionnaire-Head and Neck35; SD, standard deviation.

Model development

Preselected QLQ scales.

For the first set of predictors, we selected physical functioning, role functioning, emotional functioning and pain, as these scales corresponded best to the EQ- 5D dimensions mobility, daily activities, anxiety/depression and pain/discomfort respectively. No overlapping item was found for the self-care dimension of the EQ-5D. Global health status/ QoL scale was also included in the first predictor set to reflect the broader construct of HRQoL. These five EORTC QLQ-C30 scales were considered the basic scales of the mapping model.

Out of the five eligible articles derived from the literature search, the social functioning, cognitive functioning and fatigue scales were found sufficiently responsive as the ES was ≥ 0.3, corresponding to the calculated average ES of the EQ-5D in this study. Consequently, these EORTC QLQ-C30 scales selected for the second set of predictors [25–29].

For the third set, the opening mouth, dry mouth and sticky saliva scales were excluded because they had a correlation of ≥ 0.7 with the social eating scale. This correlation was also observed between the scales felt ill and social contact. However, as these scales clearly cover different clinical aspects, both scales were considered for the third set. Eventually, eight EORTC QLQ-H&N35 scales were included in the third set of predictors based on their correlation (Pearson correlation coefficient ≥ 0.3) with the EQ 5D outcome: pain, swallowing, speech problems, trouble with social eating and social contact, felt ill, pain killers and feeding tube. We found similar results based on Spearman correlations, except for a lower correlation between the "feeding tube dependency" scale and the EQ-5D ($r < 0.3$), and less indications for collinearity between subscales "opening mouth" and "dry mouth " with "trouble with social eating" and "felt ill" with "trouble with social contact". Re-running the analyses based on these correlations did not change the final results and conclusions.

Selection of statistical method.

Based on the AIC and BIC, the beta regression method (Model 1d) showed the best relative goodness of fit and was therefore considered as the base model including the first predictor set for subsequent steps.

Supplementation of the base model with the second predictor set (Model 2) did not provide a better fit. In addition, the LR test was not significant ($p = 0.55$). Therefore, after step 2, the base model (Model 1d) was retained as the model with best fit.

In the third step, Models 3a to 3h were generated by adding HNC-specific scales individually to the base model. The addition of HNC-specific scales pain (Model 3b), pain killers (Model 3g) and feeding tube (Model 3h) resulted in a lower AIC compared to Model 1d. The BIC of these models

however, were higher than the BIC of Model 1d. The LR test was significant only for Model 3b and Model 3g ($p = 0.05$ and $p = 0.02$ respectively). Based on parsimony and because of the ambiguity of the above results—none of the models including HNC-specific scales satisfied all three criteria for improved model fit—Model 1d was considered as the final model. Details on model fit statistics for all models are reported in Table 3. The parameter estimates of the final model are listed in Table 4.

Table 3. Summary results of the regression models.

	AIC	BIC	RMSE	MAE	LR test p-value
Model 1a (OLS)	-486.04	-458.81	0.1211	0.0915	
Model 1b (mixed-effects model)	-486.64	-455.53	0.1042	0.0784	
Model 1c (Cox regression)	2381.50	2400.94	1.5225	1.3241	
Model 1d (beta regression)	-1029.93	-1002.71	0.1209	0.0949	
Model 2	-1026.04	-987.15	0.1209	0.0952	0.55
Model 3*					
Model 3a	-1029.43	-998.321	0.1211	0.0949	0.22
Model 3b	-1031.78	-1000.67	0.1214	0.0955	0.05
Model 3c	-1027.93	-996.82	0.1209	0.0949	1.00
Model 3d	-1028.03	-996.91	0.1209	0.0948	0.76
Model 3e	-1028.55	-997.44	0.1207	0.0946	0.43
Model 3f	-1027.97	-996.86	0.1209	0.0949	0.84
Model 3g	-1033.60	-1002.49	0.1208	0.0945	0.02
Model 3h	-1030.88	-999.77	0.1196	0.0939	0.09

***Model 1d supplemented with eight EORTC QLQ-H&N35 scales individually: swallowing (3a), pain (3b), speech problems (3c), social eating (3d), social contact (3e), felt ill (3f), pain killers (g), feeding tube (h)
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; EORTC, European Organization for Research and Treatment of Cancer ; LR, likelihood-ratio; MAE, mean absolute error; OLS, ordinary least-squares; QLQ-H&N35, Quality of Life Questionnaire-Head and Neck35; RMSE, root mean square error.

Table 4. Characteristics of the final model (Model 1d) without shrinkage.

EORTC QLQ-C30 scales	Coefficient	SE
Intercept	-1.0169	0.3721
Global health status/QoL	0.0210	0.0037
Physical functioning	0.0101	0.0038
Role functioning	0.0043	0.0027
Emotional functioning	0.0047	0.0026
Pain	-0.0126	0.0025

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire-Core 30; QoL, quality of life; SE, standard error.

Predictive performance and validation of final model

The final model had an R2 of 0.3884. The MAE was 0.0949 and RMSE was 0.1209 (Table 3). The 95% limits of agreement were estimated at -0.243 to 0.231 (mean -0.006) (Fig 2). The Bland-Altman plot indicates that especially the utility values of patients with lower utility scores (mean <0.65) tend to be overestimated, reflected in a small positive error correlation of 0.32. Fig 3 shows histograms of the data for observed and predicted EQ-5D utility values, which also displays the overestimation in the lower values. The shrinkage factor of the coefficients using the heuristic formula was 0.90, indicating that minimal shrinkage of the coefficients is necessary for future predictions in new patients.

In assessing the strength of the predictive performance and internal validation of our model, the bootstrapping procedure of the fit indices indicated that the estimates of model fit were robust (bias MAE: 0.001; bias RMSE: 0.002).

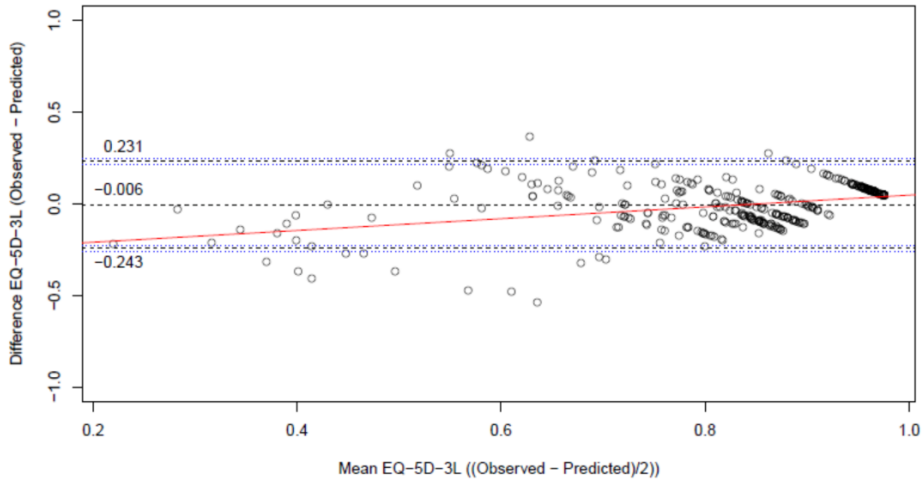

Figure 2. Bland-Altman plot of the final model with observed and predicted EQ-5D-3L values.

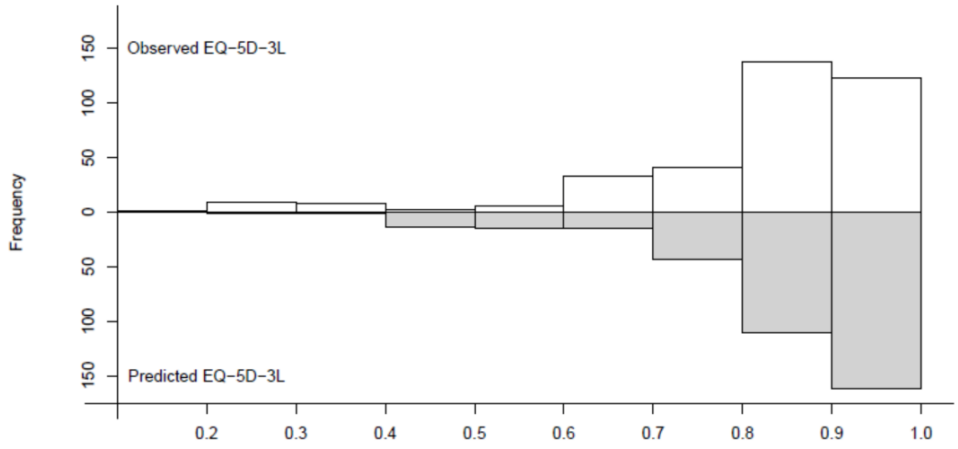

Figure 3. Mirrored histogram of observed and predicted EQ-5D-3L values.

Discussion

In this study, we mapped the EORTC QLQ-C30 scales onto the EQ-5D-derived utility values using data from a Dutch cohort of 236 HNC patients. The beta regression model including the physical functioning, role functioning, emotional functioning, pain and global health status/ QoL scales (Model 1d) was considered robust in terms of predictive performance. Taking into account dependency between repeated measurements by means of the multilevel approach (Model 1b) did not improve the model fit. The model had reasonable performance when comparing the MAE and RMSE to previously published models mapping the C30-scales onto the EQ-5D [4,5,7,13 30,31]. Adding additional EORTC QLQ-C30 scales did not contribute to a better fit of the model. Contrary to our expectation, adding HNC-specific scales to the model led to inconsistent results in the model based on our criteria, whereas the improvements observed in MAE and/or RMSE of the models with EORTC QLQ-H&N35 scales were found negligible. Similar to our findings, Rogers et al., investigated the relationship between the EQ- 5D domains and the domains of the University of Washington quality of life questionnaire (UW-QOL), and found that the generic domains of the UW-QOL (including pain, activity, recreation, mood and anxiety) showed strong correlations with the EQ-5D domains, whereas the HNC-specific domains did not [32,33].

In literature, most studies mapping the EORTC QLQ-C30 to the EQ-5D used linear regression models [4,5,7,8,13,30,31]. In our study, the beta regression method showed the best fit compared to the other modeling approaches (step 1). This was also observed in the study of Kahn et al. in which the beta regression model outperformed the linear and Tobit models for lung cancer patients [34]. Although recent guidelines for mapping models also advise applying beta-based regression [6],

few studies to date have employed the beta regression method [12,34] and further research on the usefulness of this approach is desirable.

Although our results are largely consistent with those of previous studies using disease-specific QLQ scales [4,5], our study provides no conclusive evidence on the value of adding disease-specific scales to mapping models in HNC patients. However, HNC-specific symptoms are very likely to have an important impact on HRQoL and we argue that they should therefore be of importance in calculating utility values to be used in cost-effectiveness analyses (CEAs). Therefore, development of a preference-based questionnaire that includes HNC-specific items may ultimately be a more efficient approach for generating disease-specific utilities for this population.

Designing and conducting prospective studies to collect PBM data for economic evaluation is time- and resource consuming. Applying a mapping model on readily available retrospective data can be advantageous, as it enables the conduct of CEAs even in the absence of utility data. However, the use of a mapping model inevitably introduces some uncertainty in the outcomes due to prediction error. In this study, the MAE was estimated at 0.0949. This seems acceptable, although it just exceeds the previously reported minimal important difference (MID) for EQ5D utilities of 0.08 [35]. There are no generally accepted cutoff values available to assess whether a model is suitable to apply in practice. The wide LOA in the Bland-Altman analysis indicates that our mapping model is less suitable for estimating utility levels of individual patients, but this is, of course, rarely done. However, the bias was close to 0 (mean -0.006), and the larger differences most often occurred in the lower and less common utility values. The QoL outcome for the HNC sample (Table 2) is rather good and – as this is a representative sample obtained from a national population database, the problem of the bias will be limited in clinical practice. Also, as the mean bias is very small, this model is likely well suited for use at a group level, as is usually the case in CEAs, and could therefore be a relevant tool to use to assess the cost-effectiveness in the clinic. As a cautionary note, the average overestimation of utility for patients with lower valued health states may impact the estimation of difference in utilities when comparing a group with high utility values to a group with low values, diluting the contrast.

Because predicting utilities will always be associated with uncertainty, mapping models should be seen as a second best solution, and we believe that ensuring availability of direct utilities should be promoted for all future research. As long as a HNC-specific PBM has not yet been developed, this should be done by using the generic EQ-5D-5L, in prospective studies.

To our knowledge, this is the first study to develop a mapping model, using the EORTC QLQ-C30 as well as EORTC QLQ-H&N35 scores as input data. Some limitations of this study need to be taken into consideration. Our sample size was limited due to the relatively low incidence

of HNC and the amount of (complete) data available. The degree of variation of utility values below one was limited in our sample, which may have impacted precision of the estimates in low values (Fig 2). The clinical consequences of this may be limited, as such low values may not occur frequently among HNC patients. Subtypes of HNC included in this study were assumed to have similar patterns in QoL response to treatment and disease. Because of this, and with the objective to reduce the risk of overfitting, the prediction models did not include tumor diagnosis or stage. Finally, the model was tested on internal validity, but external validation in a new cohort of patients is needed to confirm the robustness of the model, before it can be used with confidence. Strengths of this study include: the robust approach used in developing the mapping model, including preselecting covariates based largely on theoretical considerations, comparison of four different statistical methods, and the exploration of the added value of disease-specific scales.

The fact that there is no gold standard for developing mapping models is reflected in the various methods and model fit statistics applied in literature. This makes it difficult to compare our study with other studies [10,12,13,36]. Reaching international consensus on the preferred approach to modeling method(s) would enhance comparability across different mapping studies. Until such consensus has been reached, we would recommend adopting a similar strategy to modeling and reporting as applied in the current study, for future research.

Conclusions

In this study, we were able to develop a model that maps the EORTC QLQ-C30 scales to the EQ-5D-derived utility values for patients with HNC. The added value of EORTC QLQ-H&N35 scales to the model remains ambiguous. The final model, using the beta regression method, includes five EORTC QLQ-C30 scales: global health status/QoL, physical functioning, role functioning, emotional functioning and pain. This model can be used cautiously to obtain utilities of HNC patients in situations where direct utilities are not available, to support economic evaluation and thus facilitate the implementation of innovative treatments and devices for HNC in clinical practice. Further research should assess the robustness and generalizability of the mapping model by validating the model in an external cohort of HNC patients.

References

1. Szende A, Oppe M, Devlin N. EQ-5D value sets: inventory, comparative review and user guide: Springer Science & Business Media; 2007.
2. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute. 1993; 85(5):365–76. https://doi.org/10.1093/jnci/85.5.365 PMID: 8433390
3. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck module (QLQ-H&N35). Archives of otolaryngology—head & neck surgery. 2000; 126(4):459–67.
4. Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health and quality of life outcomes. 2014;12(1):35.
5. Kim E-j, Ko S-K, Kang H-Y. Mapping the cancer-specific EORTC QLQ-C30 and EORTC QLQ-BR23 to the generic EQ-5D in metastatic breast cancer patients. Quality of Life Research. 2012; 21(7):1193–203. https://doi.org/10.1007/s11136-011-0037-y PMID: 22012023
6. Wailoo AJ, Hernandez-Alava M, Manca A, Mejia A, Ray J, Crawford B, et al. Mapping to Estimate Health-State Utility from Non–Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. Value in Health. 2017; 20(1):18–27. https://doi.org/10.1016/j.jval.2016.11.006 PMID: 28212961
7. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. The European journal of health economics. 2010; 11(4):427–34. https://doi.org/10.1007/s10198-010-0233-7 PMID: 20473703
8. McKenzie L, Van Der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. Value in Health. 2009; 12(1):167–71. https://doi.org/10.1111/j.1524-4733.2008.00405.x PMID: 18637140
9. Sullivan PW, Ghushchyan V. Mapping the EQ-5D index from the SF-12: US general population preferences in a nationally representative sample. Medical Decision Making. 2006; 26(4):401–9. https://doi.org/10.1177/0272989X06290496 PMID: 16855128
10. Alava MH, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. Value in Health. 2012; 15(3):550–61. https://doi.org/10.1016/j.jval.2011.12.014 PMID: 22583466
11. Tobin J. Estimation of relationships for limited dependent variables. Econometrica: journal of the Econometric Society. 1958:24–36.
12. Hunger M, Baumert J, Holle R. Analysis of SF-6D index data: is beta regression appropriate? Value in Health. 2011; 14(5):759–67. https://doi.org/10.1016/j.jval.2010.12.009 PMID: 21839416
13. Longworth L, Yang Y, Young T, Hernandez Alva M, Mukuria C, Rowen D, et al. Use of generic and condition- specific measures of health-related quality of life in NICE decision-making: systematic review, statistical modelling and survey. 2014.

14. van Overveld LF, Braspenning JC, Hermens RP. Quality indicators of integrated care for patients with head and neck cancer. Clinical otolaryngology: official journal of ENT-UK; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2017; 42(2):322–9.

15. Fayers PM, Aaronson NK, Bjordal K, Grønvold M, Curran D, Bottomley A. EORTC QLQ-C30 scoring manual. 2001.

16. Cohen J. Statistical power analysis for the behavioral sciences (revised ed.). New York: Academic Press; 1977.

17. Cribari-Neto F, Zeileis A. Beta Regression in R. 2010. 2010; 34(2):24.

18. Smithson M, Verkuilen J. A better lemon squeezer? Maximum-likelihood regression with beta-distributed dependent variables. Psychological methods. 2006; 11(1):54. https://doi.org/10.1037/1082-989X.11.1.54 PMID: 16594767

19. Akaike H. Information theory and an extension of the maximum likelihood principle. Selected papers of hirotugu akaike: Springer; 1998. p. 199–213.

20. Raftery A. bayesian model selection in social research. Sociological Methodology. 1995; 25:111–63.

21. Schwarz G. Estimating the dimension of a model. The annals of statistics. 1978; 6(2):461–4.

22. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. The lancet. 1986; 327(8476):307–10.

23. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating: Springer Science & Business Media; 2008.

24. Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours: John Wiley & Sons; 2011.

25. Tsai WL, Chien CY, Huang HY, Liao KC, Fang FM. Prognostic value of quality of life measured after treatment on subsequent survival in patients with nasopharyngeal carcinoma. Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation. 2013; 22(4):715– 23.

26. Zmijewska-Tomczak M, Milecki P, Olek-Hrab K, Hojan K, Golusinski W, Rucinska A, et al. Factors influencing quality of life in patients during radiotherapy for head and neck cancer. Archives of medical science: AMS. 2014; 10(6):1153–9. https://doi.org/10.5114/aoms.2013.34317 PMID: 25624853

27. Tribius S, Raguse M, Voigt C, Munscher A, Grobe A, Petersen C, et al. Residual deficits in quality of life one year after intensity-modulated radiotherapy for patients with locally advanced head and neck cancer: Results of a prospective study. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al]. 2015; 191(6):501–10.

28. Hoxbroe Michaelsen S, Gronhoj C, Hoxbroe Michaelsen J, Friborg J, von Buchwald C. Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. European journal of cancer (Oxford, England: 1990). 2017; 78:91–102.

29. Bozec A, Schultz P, Gal J, Chamorey E, Chateau Y, Dassonville O, et al. Evaluation of the information given to patients undergoing head and neck cancer surgery using the EORTC QLQ-INFO25 questionnaire: A prospective multicentric study. European journal of cancer (Oxford, England: 1990). 2016; 67:73–82.

30. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQC30 to the preference-based EQ-5D, SF-6D, and 15D instruments. Value in Health. 2009; 12(8):1151– 7. https://doi.org/10.1111/j.1524-4733.2009.00569.x PMID: 19558372

31. Kim SH, Jo M-W, Kim H-J, Ahn J-H. Mapping EORTC QLQ-C30 onto EQ-5D for the assessment of cancer patients. Health and quality of life outcomes. 2012; 10(1):151.

32. Rogers S, Miller R, Ali K, Minhas A, Williams H, Lowe DJIjoo, et al. Patients' perceived health status following primary surgery for oral and oropharyngeal cancer. 2006; 35(10):913–9.

33. Kanatas A, Rogers SJBJoO, Surgery M. A systematic review of patient self-completed questionnaires suitable for oral and maxillofacial surgery. 2010; 48(8):579–90.

34. Khan I, Morris S. A non-linear beta-binomial regression model for mapping EORTC QLQ-C30 to the EQ-5D-3L in lung cancer patients: a comparison with existing approaches. Health and quality of life outcomes. 2014; 12(1):163.

35. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health and quality of life outcomes. 2007; 5(1):70.

36. McTaggart-Cowan H, Teckle P, Peacock S. Mapping utilities from cancer-specific health-related quality of life instruments: a review of the literature. Expert review of pharmacoeconomics & outcomes research. 2013; 13(6):753–65.

Abbreviations

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CEA	Costeffectiveness analysis
DHNA	Dutch Head and Neck Audit
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and neck cancer-35
EQ-5D	EuroQol five-dimensional questionnaire
ES	Effect size
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HRQoL	Health-related quality of life
LOA	Limits of agreement
LR	Likelihood-ratio
MAE	Mean absolute error
MID	Minimal important difference
NKI	Netherlands Cancer Institute
OLS	Ordinary least squares
PBM	Preference-based measures
QALY	Quality-adjusted life years
Radboudumc	Radboud University Medical Center
RMSE	Root mean square error

Acknowledgments

We would like to thank R.J.J.H. van Son, PhD, for his practical support with the statistical analyses.

Author Contributions

Conceptualization: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Valesca P. Retèl, Michiel W. M. van den Brekel, Wim H. van Harten, Martijn M. Stuiver.
Data curation: Ann-Jean C. C. Beck, Lydia F. J. van Overveld, Robert P. Takes.
Formal analysis: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Martijn M. Stuiver.
Investigation: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Valesca P. Retèl, Lydia F. J. van Overveld,
Robert P. Takes, Michiel W. M. van den Brekel, Wim H. van Harten, Martijn M.
Stuiver.
Methodology: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Valesca P. Retèl, Lydia F. J. van Overveld,
Robert P. Takes, Michiel W. M. van den Brekel, Wim H. van Harten, Martijn M.
Stuiver.
Supervision: Michiel W. M. van den Brekel, Wim H. van Harten, Martijn M. Stuiver.
Visualization: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Martijn M. Stuiver.
Writing – original draft: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Valesca P. Retèl, Michiel W. M. van den Brekel, Wim H. van Harten, Martijn M. Stuiver.
Writing – review & editing: Ann-Jean C. C. Beck, Jacobien M. Kieffer, Valesca P. Retèl, Lydia F. J. van Overveld, Robert P. Takes, Michiel W. M. van den Brekel, Wim H. van Harten,
Martijn M. Stuiver

Competing interests

The authors have read the journal's policy and the authors of this manuscript have the following competing interests: AB and MS are supported by a non-restricted research grant from ATOS Medical Sweden contributing to the existing infrastructure for health-related quality of life research of the department of Head and Neck Oncology and Surgery. ATOS Medical Sweden had no involvement in the development and conduction of the study.

Data Availability Statement

The minimal data setis uploaded to Dryad (citation: Beck, Ann-Jean (2019), Minimal data set mapping study_PLOSONE, v2, Dryad, Dataset, https://doi.org/10.5061/dryad.qbzkh18cz).

Funding

AB and MS are supported by a non-restricted research grant from ATOS Medical Sweden contributing to the existing infrastructure for health-related quality of life research of the department of Head and Neck Oncology and Surgery. The funder provided support in the form of salaries for authors AB and MS, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Part IV

Key points for optimization of patient access

Chapter 9

General discussion, future perspectives and conclusion

Aim

The aim of this dissertation was to obtain more knowledge on the (cost-)effectiveness of innovations in head and neck cancer (HNC) treatment and rehabilitation to facilitate clinical and policy decision-making with this knowledge in order to optimize access to innovation and rehabilitation for HNC patients at an international level. This discussion comprises five sections: 1) Main findings; 2) Methodological consideration and key points for future research; 3) Key points for policy decision-making in head and neck cancer treatment and rehabilitation; 4) Key points for clinical decision-making in head and neck cancer treatment and rehabilitation and 5) Concluding remarks. In the Main findings section, the chapters of the dissertation are briefly outlined including addressing the aspects of the HTA framework: legal/administrative, physician-related, organizational, hospital, economic and patient-related. Subsequently, key points for optimization of implementing innovation and rehabilitation, that come forth from this dissertation, are given. Each key point addresses both improvements for implementation of innovation (Part 1 of the dissertation) and rehabilitation (Part 2), and is divided into three paragraphs: 1) a summary of the key point in one sentence; 2) a discussion of the results of this dissertation and 3) recommendations related to the key point that come forth from these findings. Finally, a summary of key aspects is provided in the Concluding remarks.

Main findings

In **Chapter 2**, the *legal/administrative* aspects on effective patient access to innovative medical devices were investigated. In the process towards access to innovative medical devices, several procedures and practices related to market approval and reimbursement have to be undertaken which are not transparent in European countries. Therefore, we performed a systematic literature review to provide insight in the country-specific procedures involved in obtaining effective patient access to innovative medical devices in Europe. In addition, from literature we identified barriers and facilitators related to time to access. Forty publications were included concerning eight countries: France, Germany, Italy, Spain, the United Kingdom, the Netherlands, Sweden and Poland. Market approval procedures (Conformité Européenne (CE) mark assignment) were uniformly described across European countries, whereas reimbursement procedures were heterogeneous and little information was available with the exception of France and Germany. The reimbursement procedures were an important factor in the time until access. Important barriers to early effective patient access were: unclear European legislation, complex market approval procedures, requirements for a particular level of evidence, evidence collection during reimbursement procedures, and regional reimbursement and provision of medical devices. Important facilitators were: sufficient evidence collection, implementation of a diagnosis-related group (DRG)-based system, additional payment methods and research programs. Prescription

practices were influenced by the waiting times, costs of device types and hospital-physician relationships. There were no studies in literature on the patient's role in early effective patient access.

Chapter 3 was a follow-up study of Chapter 2 examining the *social (physician-related)* aspects with special attention to the role of the head and neck surgeon as a prescriber of the voice prosthesis and heat and moisture exchanger (HME). In this study, we evaluated factors influencing prescription and reimbursement of voice prostheses and HMEs. In addition, we identified barriers to and facilitators of effective patient access in the Europe. We conducted a mixed-methods study in which head and neck surgeons and managers of the device industry in several countries completed an online survey on prescription practices and reimbursement procedures respectively. Of the 36 participating head and neck surgeons of 30 hospitals in Belgium, France, Germany, Italy, the Netherlands, Poland, Spain and the United Kingdom, all surgeons prescribed voice prostheses. Four surgeons in Poland (n=3) and Italy (n=1) did not prescribe HMEs in practice. Factors impacting non-prescription were: lack of reimbursement, lack of training/experience and feeling uncomfortable with device use. Other restrictive factors to device access, occurring in Poland and countries with decentralized systems such as Spain and Italy, were increased workload and insufficient number of staff. Most mentioned barriers were: restrictions to reimbursement (e.g. fixed lump sum), lack of physicians' and patients' education, increased physicians' workload and complications after device use. Most common facilitators were: education for healthcare professionals and patients, and device support from healthcare professionals.

The *organizational* aspects of head and neck cancer (HNC) rehabilitation care in the Netherlands were addressed in **Chapter 4**. From practice, it was known that the rehabilitation differed among HNC centers. However, an overview of the exact organizational structure, content and financing was lacking. We conducted a survey study to evaluate the organizational structure, rehabilitation modules, financial matters, barriers and facilitators, and satisfaction and future improvements from the healthcare providers' perspective with regard to HNC rehabilitation among the 14 Dutch HNC centers. The aim was to evaluate guideline implementation and adherence in all centers, and explore factors influencing rehabilitation provision. We developed an online survey that included nine criteria based on the framework of the national cancer rehabilitation guideline [1,2]. All centers provided HNC rehabilitation. Most centers (86%) applied a rehabilitation protocol, of which four centers (29%) reported to have implemented the national cancer rehabilitation guideline. Of these, two centers met all criteria based on the guideline. The SLP, physiotherapist and dietician were included in the dedicated rehabilitation team in all centers, whereas the other healthcare professionals were present in less than 60% of the centers. There was sustainable funding by means of a rehabilitation-specific DRG available in only one center. In the other centers, various other (combined) sources were applied. Most facilitators of rehabilitation

provision were: attitude, motivation and expertise/knowledge of health care professionals with regard to HNC rehabilitation, availability of a contact person and patient information. Most barriers were: patient's medical history, transport (time), health literacy, financial capacity, motivation/ compliance, and coverage. Of the centers that implemented the national guideline, items were scored more often as a facilitator in the two centers that fully adhered compared to the two that only partially adhered. There were no clear associations observed between the barriers and facilitators and the extent to which the guideline was adhered to.

At a *hospital* level, in **Chapter 5,** we evaluate the (cost-)effectiveness of an interdisciplinary head and neck rehabilitation (IHNR) program compared to usual supportive care (USC) by means of a prospective controlled study. The Netherlands Cancer Institute (NKI-AVL) offers an IHNR which is covered by health insurers since 2011 [3]. The hypothesis is that because HNC patients' symptoms are often complex and interrelated, an interdisciplinary approach will be more effective in the (time to) recovery of these patients than USC. The goal of the program is to preserve or restore patients' functioning, and to optimize health-related quality of life (HRQoL), with the ultimate goal to retain participation in society. The aim of this study was to investigate the effectiveness and cost-effectiveness of IHNR (intervention group) compared to USC (control group) in advanced HNC patients treated with concomitant chemoradiation (CRT) or bioradiotherapy (BRT) in a prospective controlled clinical study. Six centers (three academic and three non-academic centers) were included in the control group, which made this a heterogeneous group. The primary outcome comprises of the HRQoL represented in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) summary score [4]. Secondary outcomes are: functional HRQoL, societal participation, utility values, return to work (RTW), unmet needs (UN), patient satisfaction and clinical outcomes. Both groups complete study-specific questionnaires at: diagnosis (baseline; T0), 3 months (T1), 6 months (T2), 9 months (T3) and 12 months (T4) after start of medical treatment. Both groups have reached a sample size of at least 83 (required 64 + accounting for 30% dropout rate) and the follow-up period of one year will be finished in the second quarter of 2021. We will apply a mixed effects model and Markov decision model to assess the effectiveness and cost-effectiveness of IHNR respectively.

Two cost-effectiveness analyses were undertaken in **Chapter 6** and **Chapter 7** to compare the survival, QoL and *economic* aspects between two regimes. In Chapter 6, the aim was to evaluate the cost-effectiveness of surgery, comprising of total laryngectomy with(out) postoperative RT , compared to organ preservation (OP), consisting of RT, CRT (Cisplatin) and BRT (Cetuximab) in advanced (stage 3 and 4) laryngeal cancer from a healthcare perspective. In the analysis, short- and long-term adverse events were included. It is known that the decision on whether to choose a surgical or organ preserving treatment in advanced laryngeal cancer is often a trade-off between survival and QoL after treatment. For policy decision-making regarding coverage and guideline

implementation, costs come in addition to this equation. Our cost-effectiveness analysis showed that total laryngectomy with(out) adjuvant RT is cost-effective compared to organ preservation. The surgical approach was more costly but provided more QALYs. The information on QALYs could serve as input for the decision aid in the shared decision-making process. Additionally, the cost-effectiveness results support reimbursement decision-making internationally.

In Chapter 7 we zoomed in on a specific device used during the pulmonary rehabilitation of laryngectomy patients: the heat and moisture exchanger (HME). This study also arose from a clinical issue; the HMEs are often not reimbursed for HNC patients in the United States. Evidence on the cost-effectiveness to support reimbursement decision-making was lacking. Therefore, the aim of this study was to assess the cost-utility the cost-effectiveness of the HME compared to alternative stoma covers in total laryngectomy patients. Patient-level data was gathered regarding pulmonary rehabilitation, QoL, productivity loss, pulmonary events and medical consumption related to pulmonary symptoms. Results showed that the HME use was cost-effective compared to alternative stoma covers in the US healthcare and societal setting. Use of the HME resulted in fewer occurrences of pulmonary events, fewer complaints of mucus production and extensive coughing, and less productivity loss. QoL differences between both groups were not clearly observed by means of generic utility outcomes. The annual hospital budget savings were up to $40,183,593 in the societal setting.

Based on the results of Chapter 6 and 7, we observed that the use of the generic EuroQol five-dimensional questionnaire (EQ-5D) is not suitable to reflect HNC complaints into an utility. Besides, ample studies are performed including HRQoL measurements but without use of the EQ-5D. That is why, in this thesis, *social (patient-related)* aspects were addressed by aiming to improve existing methods regarding mapping the patient-reported outcome measurements into preference-based measurements for cost-effectiveness purposes in **Chapter 8**. In cost-effectiveness analyses, utility measures represent the preferences of patients and are often measured by the generic EQ-5D. However, EQ-5D data is often lacking whereas QoL outcomes measured by the EORTC QLQ-C30 and the disease-specific EORTC QLQ module for HNC (QLQ-H&N35) are available. Furthermore, HNC-specific symptoms have a substantial impact on patients' QoL but are not questioned with the EQ-5D tool. In this way, we developed an optimal mapping model to estimate utilities, required for economic evaluation, by translating the generic EORTC QLQ-C30 outcomes to EQ-5D utilities for HNC patients. This was done by applying different statistical approaches. Secondarily, we explored the added value of the EORTC QLQ-H&N35 scales to the mapping model. From our study, the best performing model (final model) was developed using a beta regression method, which included five EORTC QLQ-C30 scales: global health status/QoL, physical functioning, role functioning, emotional functioning and pain. Adding the EORTC QLQ-H&N35 scales to the model did not improve the model's performance and therefore the role of disease-specific scales remains ambiguous. This model could be of use

cautiously to obtain utilities of HNC patients in situations where direct utilities are not available, to facilitate economic evaluation and thus achieve implementation of innovative treatments and devices for HNC in clinical practice.

Methodological considerations and key points for future research

An overview of the methodological considerations and key points for future research that come forth from this dissertation are:

1. Data collection
    a. Conducting (cost-)effectiveness analyses in an early phase
    b. Aligning prospective clinical trials for the collection of cost-effectiveness data
2. Research design
    a. Conducting qualitative studies with all relevant stakeholders
    b. Head and neck cancer rehabilitation: analyzing from a societal perspective
3. Patients' outcome assessment
    a. Studying patients' use and experiences
    b. Developing a head and neck cancer-specific utility

1. Data collection

1a. Conducting (cost-)effectiveness analyses in an early phase

To facilitate (and anticipate) funding of innovation and rehabilitation, we stimulate to conduct (cost-) effectiveness analyses in an early phase of development.

The results in several of our chapters highlight issues with regard to timely evidence collection in current practice. The results of Chapter 2 show that the requirements with regard to generating evidence – that can be used to file for reimbursement – is one of the most important barriers. In addition, early patient access is often hampered due to lack of amount and quality of evidence. Available clinical evidence on a device was mentioned as a facilitator to access in the Netherlands and France in Chapter 3. In addition, proving cost-effectiveness information of a medical device is required for reimbursement in countries such as the Netherlands, United Kingdom and Germany [5-7]. Until recently, information on device's safety and performance were only necessary evidence to obtain market approval [7-9]. With the Medical Device Regulation (MDR 2017/745), which came into effect in 2017 (due date probably May 26th 2021), stricter evidence requirements will be needed before market approval will be realized including more often the requirement of

a clinical trial [10-12]. Whereas these MDR-related requirements are meant to improve patients' safety, one could speculate that this approach will delay patient access to medical devices [12,13]; on the other hand generating evidence in an early as possible stage is an improvement to the present situation and contributes to acceptance and implementation by physicians Chapter 7 is an example of a clinical case in which evidence on cost-effectiveness data in early phase was lacking. As a result, patient access is hindered due to reimbursement issues. That was our motivation to assess the cost-effectiveness of the HME compared to alternative stoma covers in laryngectomized patients in the United States.

Therefore, in anticipation to the recent changes of the MDR, we recommend evidence collection – data on effectiveness as well as cost-effectiveness of the innovation and rehabilitation – in an early phase of development. For innovative medical devices, this means data collection prior to the application for market approval. In this way, the applicant will meet the new requirements for market approval and also possess sufficient evidence to facilitate reimbursement. An example of assessing cost-effectiveness of a rehabilitation program in an early phase is Chapter 5, parallel to the assessment of the effectiveness of the program. In this prospective trial, the (cost-)effectiveness of IHNR is assessed, which is the first study to assess the effectiveness of an interdisciplinary program in the HNC rehabilitation field. If this proves effective, the cost-effectiveness analysis will support reimbursement decisions of the program at a national level.

1b. Aligning of prospective clinical trials for the collection of cost-effectiveness data

An overview of the data collection necessary for cost-effectiveness evaluation is advised to be incorporated within the protocol of prospective trials in the HNC field.

Because no prospective studies were available which took into account the right data for the assessment of cost-effectiveness in Chapter 6, the cost-effectiveness analysis had to be conducted based on data obtained from available studies in literature, From this study, one of the limitations included the lack of data specific to laryngeal cancer patients, regarding adverse events and QoL. Subsequently, this caused considerable uncertainty in the outcomes, resulting in more uncertainty for policy and clinical decision-making. Also, in Chapter 6 and Chapter 7, there were issues related to low sample size in the conduction of the studies, which is more common in this low incidence disease, and causes substantial uncertainty in one of the most important outcomes, the quality-adjusted life years (QALYs). Another point is that, as we discussed in Chapter 8, patient-reported outcome measures (PROMS) such EORTC QLQ-C30 and HNC-specific module QLQ-H&N35 are often included in trials but preference-based measures such as the very concise EQ-5D are not, while the latter is needed to calculate utilities [14-16].

These issues related to data availability could be solved by assessing relevant parameters in clinical trials needed to conduct proper cost-effectiveness analysis such as survival analysis

(mean progression-free survival, probability of progression and disease-specific death), QoL data and data on (long and short term) adverse events specific to the tumor group (e.g. laryngeal cancer patients) and stage (e.g. stage 3 and stage 4 separately). It should be noted that often this information may be available but not reported in the publication (e.g. data on advanced laryngeal cancer patients but the numbers are not separately mentioned for stage 3 and stage 4 disease). In these cases, public accessibility of study databases would enhance the quality of input data in cost-effectiveness analyses for other than the original clinical issue, e.g. by means of a publicly accessible repository such as Dryad. Once the information is available, this will result in more precision of the estimates and less uncertainty during the cost-effectiveness analyses. In addition, this could also prevent issues related to low sample size [17]. According to the ISPOR Task Force on Good Research Practices, it is recommended to fully integrate data necessary for cost-effectiveness analysis in clinical trials, preferably a (randomized) controlled trial [18]. In addition, as the mapping model that resulted from Chapter 8 is considered second best, we recommend to standardize the use of a preference-based measurement tool, e.g. the EQ-5D in prospective trials to enhance accessibility on utility data. Moreover, the development and use of a HNC-specific utility measurement would be preferable in future research whenever available (see key point 3b).

2. Research design

2a. Conducting qualitative studies with all relevant stakeholders

To provide insight into the process towards effective patient access, it is recommended to conduct qualitative studies with all relevant stakeholders to obtain more in-depth information.

As we concluded from Chapter 2 and Chapter 3, little is currently reported in literature in a transparent manner on the general procedures and practices regarding patient access to innovations in European countries, and the factors influencing the process. In addition, even less is known specifically to the HNC field [7,9,19-29]. In the introduction of Chapter 4 we described that few studies are available on the practices regarding (inter-/multidisciplinary) HNC rehabilitation provision and implementation including influencing factors in European countries as well as the Netherlands specifically.

In our studies, we (partially) contributed in closing this gap in literature. In addition to our results, more in-depth information on the: 1) causal relationship between implementation and influencing factors (barriers and facilitators) and 2) possible solutions for barriers is necessary. In this way, it would be helpful to perform future in-depth studies with relevant stakeholders. For legal procedures related to access of innovation, studies should focus on health policy decision-makers and the device industry. Physicians and patients could serve as stakeholders

in studies regarding the practices of access to innovation and rehabilitation. In studies related to the organization of rehabilitation, dedicated/relevant healthcare professionals should be involved, but also cooperation with policy makers in order to discuss what evidence is needed in health policy in order to improve access and to evaluate whether current study designs meet the criteria to obtain the right evidence for policy decision-making. Methodologically, semi-structured interviews with the stakeholders could be of value to clarify and deepen the process of implementation in current practice and to explore possible links with barriers and facilitators [30,31]. This was partly conducted in Chapter 3 by interviewing managers of a medical device company to deepen the barriers and facilitators in accessing voice prostheses and heat and moisture exchangers (HMEs). To overcome barriers, focus discussion groups could be formed [30]. Especially in the implementation of inter-/multidisciplinary rehabilitation, various healthcare professionals are involved. In this way, focus group discussions could discuss and align provision of rehabilitation. Other methodological alternatives that can be considered are structured interviews – for interviews at a greater scale such as an European study – and reports of individual cases requiring special attention regarding the process of medical devices towards patient access or rehabilitation care for patients [31,32].

2b. Head and neck cancer rehabilitation: analyzing from a societal perspective

It is recommended to conduct studies regarding rehabilitation of HNC patients from a societal perspective, taking into account relevant societal aspects that are hypothesized to have an impact on the (cost-)effectiveness outcome.

Nowadays, rehabilitation of HNC patients continues once the patient has left the hospital. Return to work and participation in society are examples of important outcomes in rehabilitation research [2,33]. In the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices, three main groups are defined by the Panel on Cost-Effectiveness in Health and Medicine (PCEHM) for cost-effectiveness analyses from a societal perspective [34]. The three groups comprise of indirect costs related to productivity (e.g. productivity loss) and opportunity costs, and community values. Productivity costs are work-related costs, e.g. related to absenteeism, presenteeism (reduced performance at work) and early retirement, due to consequences of treatment and/or disease. Opportunity costs are the benefits (not only financial) earned if one would choose the other alternative, e.g. decreased hospital stay [35]. Community utilities are obtained by using community preferences [36]. Taking all these aspects into account can lead to complex analyses. The analysis is highly dependent on the healthcare system of the respective country and involvement of costs from multiple parties, e.g. the hospital as well as primary care, make this challenging [36]. Furthermore, it can be hard to define an endpoint for the outcome because these are not as clear as oncologic and survival outcomes. Relevant aspects which could be included in the evaluation of HNC rehabilitation are productivity loss and community preferences to estimate the utility of health states. Intuitively, one

would hypothesize that productivity loss would not be relevant as a great portion of HNC patients are retired at diagnosis of disease [33]. However, the study of Verdonck et al. showed that the majority of patients under 65 years at diagnosis, return to work within six months after treatment [37]. In addition, the evaluation of productivity loss has shown to be of importance in the evaluation of the cost-effectiveness of HME use in Chapter 7. The analysis resulted in more convincing evidence when analyzed from a societal perspective, because (costs related to) productivity loss were significantly higher for the alternative stoma cover group compared to the HME group. In Chapter 5, we also included return to work and societal participation in the study as secondary outcomes and input for the cost-effectiveness analyses. Applying community values provides a representative outcome on patients' QoL which is necessary for reimbursement decision-making and clinical decision-making regarding guideline implementation.

As a consequence, aspects of social functioning such as return to work (productivity loss) and participation in society, and the use of community preferences are necessary in analyzing the (cost-) effectiveness of HNC rehabilitation to obtain a complete overview of relevant costs and outcomes. For cost-effectiveness evaluation within the Dutch perspective, the friction cost method is to be preferred above the human capital approach to calculate the costs resulting from productivity loss [38-40].

3. Patients' outcome assessment

3a. Studying patients' use and experiences

It is advised to conduct future studies in which patients' use of HNC innovations and related barriers and facilitators are evaluated by involving patients as respondents.

In this dissertation, we evaluated the process towards access of patients to innovation and rehabilitation. Results from Chapter 2 and Chapter 3 showed that there are few studies in literature on the evaluation of the use of medical devices by the patient, and no studies in the HNC field specifically. In addition, from Chapter 4 we observed differences in responses between physicians and healthcare professionals (e.g. SLPs) on the barriers and facilitators related to the patient. Actual patient-related barriers and facilitators will only be identified when involving the patient itself.

As our approach in this dissertation was 'top-down' by first investigating legalization, the physician as a prescriber, organizational and hospital aspects, it would additionally be interesting to initiate a study investigating the use of HNC innovations and related barriers and facilitators in which the patients are the respondents of the study, Methodologically, a mixed-methods study taking into account a structured survey – as guidance – and semi-structured interviews – to provide

detailed information on barriers and facilitators until saturation is achieved – would be preferable. For countries with decentralized systems, patients of various regions should be included because, from the results of Chapter 3, we observed that HNC care can vary significantly among the regions. In evaluating patients' experiences in literature, the framework of the Institute of Medicine and the Picker principles were most common applied [41,42]. In addition, the National Health Service (NHS) in the United Kingdom has described a suitable framework to evaluate the patient-related aspects, comprising eight dimensions considered of importance in patient-centered care, based on the framework of Gerteis et al. and the Picker principles: 1) respect for patient-centered values, preferences, and expressed needs; 2) coordination and integration of care; 3) information, communication and education; 4) physical comfort; 5) emotional support' 6) welcoming the involvement of family and friends; 7) transition and continuity and 8) access to care [42-44]. Results from a study including patients' responses could provide new insights on barriers and facilitators at a patient level (e.g. related to patient's travel time, health literacy, social safety net), and could therefore lead to possible solutions for optimization of implementation of innovation and rehabilitation for patients. Chapter 5 is an example of a study in which patients' outcomes and experiences are investigated by means of PROMS. Subsequently, the results of this could serve as a starting point for further studies.

3b. Developing a head and neck cancer-specific utility

From our study results, it can be advised to develop a HNC-specific utility which could improve QoL assessment of HNC patients.

Despite the fact that there is strong evidence on the positive impact of HME use on patients' QoL, we did not observe this improvement in Chapter 7, based on a generic instrument [45-50]. Also, laryngectomy patients who completed the survey in this study often noted that HNC-specific symptoms they experienced and the improvements that the HME caused in their life were not clearly represented in the preference-based measurements of the EQ-5D. The study of Noel et al. showed that use of indirect questionnaires such as the EQ-5D reflect QoL of HNC patients better than direct methods such as visual analog scale (VAS), standard gamble and time tradeoff (TTO). In addition, the results of the most optimal mapping model in Chapter 8 did of include HNC-specific scales. However, we do believe that by means of using a generic measurement tool, the differences in QoL could have been diluted [51]. This could also have occurred in the analysis of Chapter 6, in which studies were used that assessed QoL of patients treated with either surgery or organ preservation with the EQ-5D.

Therefore, a HNC-specific utility could be a solution to enhance precision and sensitivity of QoL estimates in HNC patients which would lead to reduced uncertainty of the cost-effectiveness outcomes.

No HNC-specific utility is currently available. However, as it is also still important to compare utility outcomes among different diseases, a balance should be found between the generic utility aspects and the disease-specific elements. The Health Utilities Index Mark 3 (HUI 3) is an example of an utility instrument – comprising of eight attributes (vision, hearing, speech, ambulation, dexterity, emotion , cognition and pain and/or discomfort) – more specifically focused on HNC-related complaints [51]. Also, efforts have being undertaken to develop a cancer-specific utility: the QLU-C10D comprising 10 dimensions [52,53]. The QLU-C10D is derived from the EORTC QLQ-C30 and is being developed to apply in health economic evaluations. The instrument is still under development, but could solve some of the issues mentioned above. We therefore recommend future studies evaluating the applicability of the tool in HNC research and as a possible consecutive step, the development of a HNC-specific utility derived from the EORTC H&N-35.

Key points for policy decision-making in head and neck cancer treatment and rehabilitation

An overview of the key points for policy decision-making that come forth from this dissertation are:

4. Legal policy
    a. Centralizing legal/administrative procedures to enhance timely access
    b. Improving guideline implementation: specific, transparent, uniform
5. Strengthening financial support

4. Legal policy

4a. Centralizing legal/administrative procedures to enhance timely access

At an European level, time to access of innovations in Chapter 2 was hampered by decentralized reimbursement procedures and practices, whereas the market approval procedures were more efficient [54]. From the survey results of Chapter 3, we observed more variation in HNC device provision within countries with decentralized systems such as Spain and Italy.

It is recommended to centralize legal procedures for reimbursement and provision of innovation at a European level but also within countries. This would result in uniform European requirements for reimbursement of innovation instead of assessing at each country separately, which would therefore accelerate the time to access. Within countries, this would mean that only approval

at a national level would be necessary instead of separately for all country regions, leading to nationwide access to HNC devices instead of only the large scaled influential regions[19,55].

4b. Improving guideline implementation: specific, transparent, uniform

It is recommended for guidelines on HNC treatment and rehabilitation to be specific, transparent and uniform, in order to improve and speed up the implementation and diffusion of innovation and comprehensive rehabilitation programs.

At all levels of the pathway towards effective access, we observed room for improvement with regard to guideline implementation. In Chapter 2, results showed that guidelines on market approval were often complex and not clear to the users [7,8]. These were important barriers to market access of innovative medical devices. With the MDR emerging in May 2021, changes will occur in the medical device regulations. The MDR and its procedures have been described as more complex. The MDR results in a hundred additional provisions compared to the Directive 93/42/EEC and an increase in the number of annexes [12]. Therefore, it can be questioned whether this regulation will be more clear for the applicant. With regard to reimbursement, issues arose from heterogeneous procedures within and between EU countries and non-transparency [56]. At a physician level, poor or no guideline implementation for the voice prosthesis and HME use was reported in France, Germany, Italy and Spain. This was also described in literature for cardiac device implementation [57]. At an organizational level, the assessment of the implementation of the national cancer rehabilitation guideline among Dutch HNC centers showed that this was limited in Chapter 4. Most centers did apply (various) guideline(s), which led to substantial practice variation. Also, implementation and adherence could of the national guideline could be hindered as no specific direction were provided on HNC rehabilitation.

Uniformity in access of innovation and rehabilitation could be realized by implementation of feasible – by which we mean specific, uniform and transparent – (inter)national guidelines. This would support the device industry in obtaining timely market and reimbursement access, and would support the physician in effectively implementing best practice, especially in countries such as France and Italy where esophageal speech is sometimes still the standard of care. In addition, guideline implementation could also convince physicians e.g. in Poland who are often not trained and experienced with HME use. Specific guideline directions for rehabilitation care in the Netherlands could enhance guideline adherence and implementation of multidisciplinary rehabilitation for HNC patients.

5. Strengthening financial support

Sustainable reimbursement of innovation and rehabilitation is recommended to facilitate the implementation.

Lack of reimbursement was one of the most important barriers to timely access of innovative medical devices in Chapter 2. In addition, absence of reimbursement of the HME was one of the factors associated with non-prescription in Chapter 3. In the United States, non-reimbursement of the HME led to out-of-pocket payments, reuse of HMEs and involuntarily discontinuation of HME use by respondents of Chapter 7. In addition, in our benchmark study (Chapter 4) we noted little infrastructure for funding of HNC rehabilitation at a national level leading to lacunar- and significant differences in reimbursement in the Netherlands. In addition, most frequent barriers to provision of rehabilitation in this study were, aside from the lack of reimbursement, patient-related and included financial capacity and transport (costs). From Chapter 2, we also concluded that the implementation of a diagnosis-related group (DRG)-system showed to be a sustainable reimbursement method to secure access [58,59]. From this study, results showed that the DRG-based system has been applied by France, Germany, United Kingdom and the Netherlands, and could improve care implementation in countries such as Italy, Poland and Spain. One center that had implemented and fully adhered to the national cancer rehabilitation guideline, applied a rehabilitation-specific DRG as a reimbursement method for the care provided by all healthcare professionals within the dedicated team. This center had the highest percentage of facilitators reported at an economic level.

From our findings of the literature review (Chapter 2), temporary reimbursement methods are recommended to guarantee timely implementation of innovation such coverage with evidence development (CED), already applied in countries such as the Netherlands, United Kingdom and France, and other research programs such as the program for medical economic research (PRME) in France [26,27]. For the reimbursement of rehabilitation care and innovations that already have a role in standard care in some centers or countries, we recommend to improve reimbursement methods with focus on facilitating implementation at an international level by means of countries learning from one another, and at a national level by increasing the use of a rehabilitation-specific DRG for rehabilitation care. At a patient level, it is important to provide financial support for this vulnerable group who suffer from financial toxicity and often have to deal with great financial burden [60]. Unrestricted reimbursement of devices e.g. voice prostheses and HMEs including accessories, increasingly prescribed by the physician for certain indications (e.g. complications such as fistula formation), and reimbursement of travel costs to the hospital would facilitate 'the patient as a user' of innovation and rehabilitation.

Key points for clinical decision-making in head and neck cancer treatment and rehabilitation

An overview of the key points for clinical decision-making that come forth from this dissertation are:

6. Strengthening clinical support
7. Integrating quality of life scores in practice: the trade-off between survival and QoL

6. Strengthening clinical support

In the review of Chapter 2, little was reported on the physician as a prescriber. Aside from the barriers reported in literature such as waiting times and costs of the device, the hospital-physician relationship was solely reported and analyzed as a facilitator. The results of the semi-structured interviews in Chapter 3 showed suggestions for implementation of the voice prostheses and HMEs by educating physicians to overcome barriers related to physicians who have had a lack of training and experience during their residency. Multidisciplinary teamwork and collaborations were reported as an important facilitator in multiple studies, by means of a rehabilitation team (Chapter 3), multidisciplinary team meetings (Chapter 4) and interhospital collaborations in providing rehabilitation (Chapter 7). From a patient's point of view, the process could be improved by educating patients on device use (Chapter 3) and providing patient guidance during the rehabilitation phase (Chapter 4).

Possible solutions to improve the knowledge on voice prosthesis and HME use is by introducing device use in their residency, providing continuous education by competent healthcare providers (e.g. physicians, SLPs) and manufacturers for physicians as well as patients. For physicians this could be done by hands-on courses or online e-learning modules [61]. The presence of a (dedicated) rehabilitation team is advised to reduce the work load of physicians during the follow-up period and provide the care needed to regain patients' participation in society [33,62-64]. We recommend standardization of multidisciplinary team meetings for resetting patients' goals and for effect evaluation. Interhospital collaborations through teleconsultation and/or telehealth will expand knowledge on the provision of rehabilitation among hospitals [65]. This is especially of value in countries such as the US, where few hospitals provide HNC rehabilitation and physical distances to specialized HNC centers are challenging for the patient. Related to the individual patient, providing support such as self-management training or a contact person such as a case manager or nurse specialist who can provide tailored guidance during rehabilitation could overcome barriers regarding motivation and compliance.

7. Integrating quality of life scores: the trade-off between survival and QoL

Aside from the treatment survival outcomes, there is growing attention towards QoL outcomes after treatment. Information on QALYs showed to be useful for the evaluation of various treatment strategies in which survival outcome and consequences of toxicity differ (Chapter 6). In addition, QoL assessment by means of validated instruments is useful for the purpose of effect evaluation (Chapter 4).

Implementation of the QALY in clinical practice could provide more objective information on the trade-off between survival and QoL, e.g. by application in a decision aid [66,67]. In addition, standardized use of PROMs to assess QoL has proven to be valuable in the effect evaluation of the patient's individual course during and after treatment and in the shared decision-making process, but also at greater scale to evaluate hospital's performance in an audit based on real-world data with the aim to improve patient care [68]. The development of a e-health platform, e.g. patient completion in the waiting room by means of a tablet computer and evaluation of results incorporated in the medical records system would be efficient and user friendly, thereby achieving optimal adherence of both the physician and patient [67].

Concluding remarks

In this dissertation, the aim was to provide more evidence regarding the (cost-)effectiveness of innovations in HNC treatment and rehabilitation as support to improve patient access. Our review results showed ample literature on market approval of innovations, which was uniform across Europe, in contrast to the few publications regarding reimbursement procedures, which were heterogeneous among the European countries and had a great impact on timely access. Also, little information was available in literature on this topic specifically to the HNC field, including on prescription practices. We provided insight in the reimbursement and prescription related to voice prostheses and HMEs in European countries, and evaluated what is needed for healthcare professionals to provide patient access to these medical devices including guideline implementation, sufficient reimbursement and a supporting rehabilitation team. At a national level, we evaluated guideline implementation and adherence for HNC rehabilitation, and gave insight into the organization and financing of among the Dutch centers. Although all centers applied some kind of rehabilitation protocol, only four centers implemented the national cancer rehabilitation guideline. Information on themes such as barriers and facilitators, and future improvements can be used in order for centers to learn from each other and to improve HNC rehabilitation care in the Netherlands. Most barriers were economic and patient-related. Our design paper on prospective study describes the structure and content of our IHNR program. The results of this study will reveal whether interdisciplinary rehabilitation is effective and/or cost-effective and could therefore be beneficial in HNC care. Our economic evaluation

of the HME provided evidence on the cost-effectiveness of the HME in the US and showed potential annual budget savings in applying the device, which can be used in strengthening the evidence for reimbursement of the HME in the US. The results of the economic evaluation of treatment modalities in advanced laryngeal cancer not only provides evidence for guideline improvement and reimbursement decisions, but also provides more attention to QoL in the equation with survival outcome. In this way, we added more information on the QoL outcome by means of QALYs to improve shared decision-making in clinical practice. In addition, both evaluations resulted in recommendations to improve the conduction of economic evaluation in future research by means of better (access to) clinical data as input for the model and improving evaluation of health effects (QoL). The latter was also investigated in Chapter 8, in which we came forth with a mapping model which should be further validated, and also led to alternative suggestions for future research such as the development of a HNC-specific utility.

Overall, by means of evaluating procedures and practices, related barriers and facilitators to patient access and obtaining (cost-)effectiveness data regarding HNC treatment and rehabilitation, we presented the current infrastructure regarding access to HNC innovation and rehabilitation at an international level. Important findings from this dissertation to achieve better access include uniform and feasible guidelines at an (inter)national level; centralizing procedures and practices nationally; focus on solving reimbursement barriers by means of providing cost-effectiveness data, prospective healthcare systems and temporary payments for innovations; integration of cost-effectiveness data collection in trials; involvement of patients in research on utilization of innovations; continuing the growing attention to QoL in research and decision-making; and supporting healthcare providers as well as patients financially but also clinically by means of a supporting team, training and education.

The recommendations that come forth from the dissertation will hopefully contribute to a more structured and integrated infrastructure for innovation and rehabilitation in the pathway towards accessing HNC care within the healthcare system with the ultimate goal to *optimize implementation of innovation and rehabilitation* for the patient.

References

1. Netherlands Comprehensive Cancer Organisation. Cancer Guideline (2011). Last accessed: 12-2-2020.; http://www.oncoline.nl/cancer-rehabilitation.
2. Van den Berg J, Velthuis M, Gijsen B, Lindeman E, van der Pol M, Hillen H. Guideline" Cancer rehabilitation". *Nederlands tijdschrift voor geneeskunde.* 2011;155(51):A4104-A4104.
3. Netherlands Cancer Institute. HNR 2.0 (version 2006). . Last accessed: 12-2-2020.; https://www.avl.nl/flipbooks/HHR-HNR%202.0/index.html#p=1. .
4. Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *Journal of clinical epidemiology.* 2016;69:79-88.
5. Seidel D, Brass P, Sehnke N, Jakob V, Eglmeier W, Neugebauer EA. [Assessment of the benefit of medical devices in surgical practice. Problems and possible solutions]. *Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen.* 2014;85(5):407-415.
6. Cohen D. Devices and desires: Industry fights toughening of medical device regulation in Europe (BMJ (Online) (2013) 347, (f6204) DOI:10.1136/bmj.f6204). 2013;347.
7. Boudard A, Martelli N, Prognon P, Pineau J. Clinical studies of innovative medical devices: What level of evidence for hospital-based health technology assessment? *Journal of Evaluation in Clinical Practice.* 2013;19(4):697-702.
8. Guillou J. Medical device reimbursement in France process of decision. [French, English] Remboursement des dispositifs medicaux en France processus de decision. *STP.* 2011;Pharma Pratiques. 21(5):425-432.
9. Parquin F, Audry A. Clinical evaluation of medical devices: Main constraints and specificities. *Therapie.* 2012;67(4):311-318.
10. Migliore A. On the new regulation of medical devices in Europe. In: Taylor & Francis; 2017.
11. Medical Device Regulation 2017/745. Last accessed: 3-3-2020.; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745.
12. Zenner HP, Boži- M. Clinical Evaluation of Medical Devices in Europe. In: *Personalized Medicine in Healthcare Systems.* Springer; 2019:21-32.
13. ZonMw: Meer onderzoek naar medische hulpmiddelen door nieuwe wetgeving. . Last accessed: 3-3-2020. ; https://publicaties.zonmw.nl/meer-onderzoek-naar-medische-hulpmiddelen-door-nieuwe-wetgeving/.
14. Szende A, Oppe M, Devlin N. *EQ-5D value sets: inventory, comparative review and user guide.* Vol 2: Springer Science & Business Media; 2007.
15. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck module (QLQ-H&N35). *Archives of otolaryngology--head & neck surgery.* 2000;126(4):459-467.
16. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute.* 1993;85(5):365-376.

17. Hunink MG, Bult JR, De Vries J, Weinstein MC. Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. *Medical Decision Making.* 1998;18(3):337-346.

18. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value in health.* 2005;8(5):521-533.

19. Cappellaro G, Fattore G, Torbica A. Funding health technologies in decentralized systems: A comparison between Italy and Spain. *Health Policy.* 2009;92(2-3):313-321.

20. van der Molen L, Kornman AF, Latenstein MN, van den Brekel MW, Hilgers FJ. Practice of laryngectomy rehabilitation interventions: a perspective from Europe/the Netherlands. *Current opinion in otolaryngology & head and neck surgery.* 2013;21(3):230-238.

21. Betlejewski S, Ossowski R, Sinkiewicz A. [Rehabilitation after total laryngectomy--vision and realization]. *Otolaryngologia polska = The Polish otolaryngology.* 2007;61(3):344-348.

22. Ten Hallers EJ, Marres HA, Rakhorst G, et al. Difficulties in the fixation of prostheses for voice rehabilitation after laryngectomy. *Acta oto-laryngologica.* 2005;125(8):804-813.

23. 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. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2011;36(3):235-241.

24. Wierzchowska M, Burduk PK. [Early and late complications after implantation of the Provox 2 voice prosthesis in patients after total laryngectomy]. *Otolaryngologia polska = The Polish otolaryngology.* 2011;65(3):184-187.

25. Zimmer-Nowicka J, Morawiec-Sztandera A. [Causes and indwelling times of multiple voice prosthesis replacements in patients after total laryngectomy--analysis of 184 replacements in 42 patients]. *Otolaryngologia polska = The Polish otolaryngology.* 2012;66(5):322-327.

26. Olberg B, Perleth M, Busse R. The new regulation to investigate potentially beneficial diagnostic and therapeutic methods in Germany: Up to international standard? *Health Policy.* 2014;117(2):135-145.

27. Martelli N, van den Brink H. Special funding schemes for innovative medical devices in French hospitals: The pros and cons of two different approaches. *Health Policy.* 2014;117(1):1-5.

28. Loge P, Delalande F, Reymond MC, Germain S. FACTORS INFLUENCING REIMBURSEMENT OF MEDICAL DEVICES IN FRANCE. *International journal of technology assessment in health care.* 2015;31(6):399-406.

29. Schwander B, Krone FA, Walzer S. Clinical and health economic evidence requirements for obtaining health insurance coverage for innovative medical devices in Germany. *Value in Health.* 2013;16 (7):A474.

30. Gill P, Stewart K, Treasure E, Chadwick B. Methods of data collection in qualitative research: interviews and focus groups. *British dental journal.* 2008;204(6):291-295.

31. Murphy E. *Qualitative methods and health policy research.* Routledge; 2017.

32. Hutchinson A, Coster J, Cooper K, et al. Comparison of case note review methods for evaluating quality and safety in health care. *Health Technology Assessment.* 2010;14(10):1-170.

33. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of

life in advanced head and neck cancer patients. *European Archives of Oto-Rhino-Laryngology.* 2016;273(6):1577-1587.

34. Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding JJViH. Good Research Practices for Measuring Drug Costs in Cost-Effectiveness Analyses: A Societal Perspective: The ISPOR Drug Cost Task Force Report—Part II. 2010;13(1):8-13.
35. Buchanan JM. Opportunity cost. In: *The world of economics.* Springer; 1991:520-525.
36. Garrison LP, Mansley EC, Abbott TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report—part II. *Value in Health.* 2010;13(1):8-13.
37. Verdonck-de Leeuw IM, van Bleek W-J, Leemans CR, de Bree R. Employment and return to work in head and neck cancer survivors. *Oral oncology.* 2010;46(1):56-60.
38. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *Jama.* 1996;276(15):1253-1258.
39. Krol M, Papenburg J, Koopmanschap M, Brouwer W. Do productivity costs matter? *Pharmacoeconomics.* 2011;29(7):601-619.
40. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *Jama.* 2016;316(10):1093-1103.
41. Wolfe A. Institute of Medicine Report: crossing the quality chasm: a new health care system for the 21st century. *Policy, Politics, Nursing Practice.* 2001;2(3):233-235.
42. Shaller D. *Patient-centered care: What does it take?* : Commonwealth Fund New York; 2007.
43. National CGCU. Patient Experience in Adult NHS Services: Improving the Experience of Care for People Using Adult NHS Services: Patient Experience in Generic Terms. 2012.
44. Gerteis M. Through the patient's eyes: understanding and promoting patient-centered care. 1993.
45. Ackerstaff A, Hilgers F, Aaronson N, Schouwenburg P. Physical and psychosocial sequelae of total larynx extirpation and the use of a heat and moisture exchanger. *Nederlands tijdschrift voor geneeskunde.* 1990;134(50):2438-2442.
46. Jones AS, Young PE, Hanafi ZB, Makura ZGG, 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):361-367.
47. Brook I, Bogaardt H, van As-Brooks C. Long-term use of heat and moisture exchangers among laryngectomees: medical, social, and psychological patterns. *Annals of Otology, Rhinology & Laryngology.* 2013;122(6):358-363.
48. Ackerstaff AH, Hilgers FJ, Balm AJ, Aaronson NK, van Zandwuk N. Improvements in respiratory and psychosocial functioning following total laryngectomy by the use of a heat and moisture exchanger. *Annals of Otology, Rhinology & Laryngology.* 1993;102(11):878-883.
49. Ackerstaff A, Hilgers F, Aaronson N, Balm A. Communication, functional disorders and lifestyle changes after total laryngectomy. *Clinical Otolaryngology.* 1994;19(4):295-300.

50. 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. *Otolaryngology and Head and Neck Surgery.* 2003;129(6):705-712.

51. Noel CW, Lee DJ, Kong Q, et al. Comparison of health state utility measures in patients with head and neck cancer. *JAMA Otolaryngology–Head Neck Surgery.* 2015;141(8):696-703.

52. Utility Weights for QLU-C10D. Last accessed: 3-3-2020.; https://qol.eortc.org/projectqol/utility-weights-for-qlu-c10d/.

53. King MT, Costa D, Aaronson N, et al. QLU-C10D: a health state classification system for a multi-attribute utility measure based on the EORTC QLQ-C30. *Quality of Life Research.* 2016;25(3):625-636.

54. Basu S, Hassenplug JC. Patient access to medical devices--a comparison of U.S. and European review processes. *The New England journal of medicine.* 2012;367(6):485-488.

55. Schafer E, Schnell G, Bobakova T. Diabetes device reimbursement in the EU-5. *Journal of diabetes science and technology.* 2013;7(4):1084-1092.

56. Altenstetter C. EU and member state medical devices regulation. *International Journal of Technology Assessment in Health Care.* 2003;19(1):228-248.

57. Boriani G, Burri H, Mantovani LG, et al. Device therapy and hospital reimbursement practices across European countries: a heterogeneous scenario. *Europace.* 2011;13(suppl_2):ii59-ii65.

58. Finocchiaro Castro M, Guccio C, Pignataro G, Rizzo I. The effects of reimbursement mechanisms on medical technology diffusion in the hospital sector in the Italian NHS. *Health policy (Amsterdam, Netherlands).* 2014;115(2-3):215-229.

59. Hertz D, Marcarelli AD, Patel L, Garfield S. Adoption of new technologies in twenty established and emerging markets. *Value in Health.* 2012;15 (7):A323-A324.

60. Massa ST, Osazuwa-Peters N, Boakye EA, Walker RJ, Ward G. Comparison of the financial burden of survivors of head and neck cancer with other cancer survivors. *JAMA Otolaryngology–Head Neck Surgery.* 2019;145(3):239-249.

61. Tarpada SP, Hsueh WD, Gibber MJ. Resident and student education in otolaryngology: A 10-year update on e-learning. *The Laryngoscope.* 2017;127(7):E219-E224.

62. van Weert E, Hoekstra-Weebers J, Grol B, et al. A multidimensional cancer rehabilitation program for cancer survivors: effectiveness on health-related quality of life. *Journal of Psychosomatic Research.* 2005;58(6):485-496.

63. King G, Lemon J, Martin J. Multidisciplinary teamwork in the treatment and rehabilitation of the head and neck cancer patient. *Texas dental journal.* 1992;109(6):9-12.

64. Licitra L, Keilholz U, Tahara M, et al. Evaluation of the benefit and use of multidisciplinary teams in the treatment of head and neck cancer. *Oral oncology.* 2016;59:73-79.

65. Beswick DM, Vashi A, Song Y, et al. Consultation via telemedicine and access to operative care for patients with head and neck cancer in a Veterans Health Administration population. *Head neck.* 2016;38(6):925-929.

66. Petersen JF, Berlanga A, Stuiver MM, et al. Improving decision making in larynx cancer by developing a decision aid: A mixed methods approach. *The Laryngoscope.* 2019.

67. Duman-Lubberding S, van Uden-Kraan C, Jansen F, et al. Durable usage of patient-reported outcome measures in clinical practice to monitor health-related quality of life in head and neck cancer patients. *Supportive Care in Cancer.* 2017;25(12):3775-3783.

68. van Overveld LF, Braspenning JC, Hermens RP. Quality indicators of integrated care for patients with head and neck cancer. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery.* 2017;42(2):322-329.

Chapter 10

Summary

Summary

In this dissertation, we aimed to obtain more knowledge on the (cost-)effectiveness of innovations in head and neck cancer (HNC) treatment and rehabilitation. With this knowledge, we came up with recommendations for clinical and policy decision-making to optimize access to innovation and rehabilitation for HNC patients internationally.

In **Chapter 1**, background information is provided on HNC disease, treatment and rehabilitation, and the procedures and practices towards patient access to innovations. Also, the reason behind conducting the research provided within this chapter is explained. The number of HNC survivors is increasing worldwide and quality of life (QoL) is becoming a more important topic in HNC care [1]. After disease and treatment, rehabilitation care is essential for patients who often suffer from physical an psychosocial problems which impact their functioning, QoL and participation in society [2,3]. Innovations are regularly used in HNC treatment and rehabilitation, including medical devices (e.g. voice prosthesis and heat and moisture exchanger (HME) in laryngectomy rehabilitation) and medicines (e.g. immunotherapy). However, at an international level, these innovations are not always accessed by HNC patients. Restriction to access is often multifactorial and caused by barriers in the procedures and practices towards effective patient access which were not yet all identified. Therefore, we conducted a broad health technology assessment (HTA) including cost-effectiveness analyses and identification of barriers to and facilitators of patient access. Each chapter discusses one of the aspects of the HTA framework including legal/administrative, social (physician- and patient-related), organizational, hospital and economic aspects as guidance for the chapters.

Chapter 2 is a systematic literature review on legal procedures of market approval and reimbursement of medical devices in eight countries, and on identified barriers of and facilitators to early patient access to innovative medical devices. In the review, we included forty publications concerning eight countries: France, Germany, Italy, Spain, the United Kingdom (UK), the Netherlands, Sweden and Poland. Market approval procedures (Conformité Européenne (CE) mark assignment) were uniformly described across countries. Reimbursement procedures were heterogeneous and very few articles were available in literature except for France and Germany. Time until access was mainly dependent on the reimbursement procedures. Important barriers to early effective patient access were unclear European legislation, complex market approval procedures, requirements for a particular level of evidence, evidence collection during reimbursement procedures, and regional reimbursement and provision of medical devices. Important facilitators were sufficient evidence collection, implementation of a system based on diagnosis-related groups (DRGs), additional payment methods and research programs. Waiting times, costs of device types and hospital-physician relationships were influential on the prescription practices. No studies in literature were found regarding the patient's role in early effective patient access.

Chapter 3 was conducted as a follow-up study of Chapter 2. In this chapter, factors influencing the physicians' prescription practices and reimbursement of the voice prosthesis and HME were evaluated in eight countries. In addition, barriers of and facilitators to effective patient access were identified. A mixed-methods study was conducted with head and neck surgeons and representatives of a device industry by means of an online survey. In addition, semi-structured interviews were performed with the representatives. In total, 36 head and neck surgeons participated employed at 30 hospitals in Belgium, France, Germany, Italy, the Netherlands, Poland, Spain and the UK. All surgeons prescribed voice prostheses. Four surgeons in Poland and Italy did not prescribe HMEs in practice, which was impacted by a lack of reimbursement, lack of training/experience and feeling uncomfortable with device use. Other restrictive factors to device access reported in Poland, Spain and Italy, were increased workload and insufficient number of staff. Most barriers reported were restrictions to reimbursement (e.g. fixed lump sum), lack of physicians' and patients' education, increased physicians' workload and complications after device use. Most common reported facilitators were education for healthcare professionals and patients, and device support from healthcare professionals.

In **Chapter 4**, we provide an overview of the organization, content and funding of the practice variation with regard to HNC rehabilitation among the 14 Dutch center. The aim was to evaluate guideline implementation and adherence in all centers, and explore factors influencing rehabilitation provision. An online survey was completed by a representative of each discipline within the dedication HNC rehabilitation team and of the Financial Department. The survey included five themes: the organizational structure, rehabilitation modules, financial matters, barriers and facilitators, and satisfaction and future improvements. The first theme included nine criteria based on the framework of the national cancer rehabilitation guideline [4,5]. In addition, the barriers and facilitators were based on the six domains of the Institute of Medicine (IOM) [6]. The results showed that all centers provided HNC rehabilitation. Most centers (86%) applied some type of rehabilitation protocol. Four centers (29%) reported to have implemented the national cancer rehabilitation guideline, of which two centers met all criteria based on the national guideline. The speech-language pathologist, physiotherapist and dietician were involved in all dedicated rehabilitation teams, whereas the other healthcare professionals were present in less than 60% of the centers. One center had sustainable funding by means of a rehabilitation-specific DRG. In the other centers, various other (combined) funding method were sourced. Most frequent facilitators of rehabilitation provision were attitude, motivation and expertise/knowledge of health care professionals with regard to HNC rehabilitation, availability of a contact person and patient information. Most frequent barriers were patient's medical history, transport (time), health literacy, financial capacity, motivation/compliance, and coverage. Of the centers that implemented the national guideline, items were scored more often as a facilitator in the two centers that fully adhered compared to the two centers that only partially adhered. There were no clear associations observed between the barriers and facilitators and guideline adherence.

Chapter 5 focuses on HNC rehabilitation at a hospital level. Since 2011, the Netherlands Cancer Institute (NKI-AVL) offers an interdisciplinary head and neck rehabilitation (IHNR) program which is covered for HNC patients [7]. We hypothesize that an interdisciplinary approach will be more effective in the (time to) recovery of these patients than usual supportive care (USC) because patients' symptoms are often complex and interrelated. Therefore, we initiated an ongoing prospective controlled study in which the (cost-)effectiveness of IHNR is compared to USC in advanced HNC patients treated with concomitant chemoradiation (CRT) or bioradiotherapy (BRT). The intervention group comprises of the NKI-AVL. For the control group, six centers (three academic and three non-academic centers) were included, which made this an heterogeneous group. To obtain our results, a study-specific questionnaire including patient-reported outcome measures (PROMS) are completed by the patients at diagnosis (baseline; T0), 3 months (T1), 6 months (T2), 9 months (T3) and 12 months (T4) after start of medical treatment. The primary outcome comprises of the health-related quality of life (HRQoL) represented in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) summary score [8]. Secondary outcomes are: functional HRQoL, societal participation, utility values, return to work (RTW), unmet needs (UN), patient satisfaction and clinical outcomes. A mixed effects model and Markov decision model[1] will be performed to assess the effectiveness and cost-effectiveness of IHNR respectively.

In **Chapter 6**, a cost-effectiveness analysis using a Markov decision model was performed of surgery versus organ preservation in advanced stage laryngeal cancer from a healthcare perspective. This was conducted in order to compare the impact of both regimens on the survival, short- and long-term adverse events, QoL and costs. Results showed that total laryngectomy with(out) adjuvant radiotherapy is cost-effective compared to organ preservation. The surgical approach was more costly but provided more quality-adjusted life years (QALYs). At an international level, the information on QALYs and costs could be helpful in the shared decision-making process and policy decision-making respectively.

The second cost-effectiveness analysis we performed is described in **Chapter 7**. The aim was to evaluate the cost-effectiveness of the HME compared to alternative stoma covers in the United States (US) from a healthcare and societal perspective. This was executed because the HME is not always accessed by HNC patients in the US and more cost-effectiveness evidence is needed on the HME in order to support reimbursement decisions. For the analysis, a Markov decision models was applied. Patient-level data was collected prospectively regarding pulmonary rehabilitation, QoL, productivity loss, pulmonary events and medical consumption related to pulmonary symptoms. We found that the HME use was cost-effective compared to alternative

1 A Markov model is a mathematical model in which two cohorts of patients are simulated to compare the quality of life and costs between the groups.

stoma covers in the US healthcare and societal setting. HME use led to fewer occurrences of pulmonary events, fewer complaints of mucus production and extensive coughing, and less productivity loss. QoL differences between both groups were not found by means of generic utility outcomes. With use of the HME, the annual hospital budget savings were up to $40,183,593 in the societal setting.

In cost-effectiveness analysis, preference-based measures such as the EuroQol five-dimensional questionnaire (EQ-5D) are necessary to obtain utilities, and HRQoL data assessed by PROMS cannot be used directly. To enable use of HRQoL results in a cost-effectiveness analysis, HRQoL outcomes can be converted into utilities (preference-based) by means of mapping. Therefore, in **Chapter 8**, we developed a mapping model which converts the EORTC QLQ-C30 outcomes into an EQ-5D utility by means of regression modeling. Also, the value of adding disease-specific EORTC QLQ module for HNC (EORTC QLQ-H&N35) scales to the mapping model was explored. Our results showed that the best performing model (final model) was developed using a beta regression method, which included five EORTC QLQ-C30 scales: global health status/QoL, physical functioning, role functioning, emotional functioning and pain. Adding the EORTC QLQ-H&N35 scales to the model did not improve the model's performance, and therefore the role of disease-specific scales remains ambiguous. This model could be of use cautiously to calculate utilities of HNC patients when direct utilities are not available, to facilitate economic evaluations and thus achieve implementation of innovative treatments and devices for HNC in clinical practice.

Finally, in **Chapter 9**, the main findings are discussed and key points for future research, policy decision-making and clinical decision-making in HNC treatment and rehabilitation are discussed. In literature, the evidence regarding procedures and practices, cost-effectiveness and implementation of rehabilitation within the HNC field proved to be scarce. There is more to explore and optimize in this field through future research. First, it is advised to conduct (cost-)effectiveness analyses in an early phase which means prior to the application for market approval for innovative medical devices and cost-effectiveness analyses parallel to investigating effectiveness of rehabilitation programs. Second, clinical trials should be aligned to the collection of cost-effectiveness data including tumor- and stage-specific data on survival, QoL and adverse events. Third, it is recommended to conduct in-depth (qualitative) studies on procedures and practices with policy decision-makers/device industry and healthcare providers/patients respectively. Fourth, it is advised to explore the societal perspective in HNC rehabilitation research taking into account aspects such as return to work and participation in society. Fifth, initiatives could be taken to develop a HNC-specific utility to improve QoL measurement in this specific population.

In practice, national and international efforts have been taken to promote implementation of innovation and rehabilitation for head and neck cancer patients. First, it is advised to centralize

legal procedures on access to innovations. Second, more specific, transparent and uniform guidelines is advised at an (inter)national level. Third, financial support should be strengthened through sustainable temporary (e.g. coverage with evidence (CED)) and permanent (e.g. DRG-based) reimbursement schemes. Fourth, clinical support could be improved by means of multidisciplinary teamwork, interhospital collaborations, (online) education and training. Fifth, use of QALYs in decision-aid tools and effect evaluation is highly recommended.

Future initiatives could focus on the 'patient as a user' as a starting point, by conducting studies regarding patient utilization and related barriers and facilitators, in which patients are involved as respondents. In addition, patients' support in HNC treatment and rehabilitation could be enhanced by means of financial support, education and tailored guidance.

In this dissertation, we provided insight in the current infrastructure of access to HNC innovation and rehabilitation internationally by means of evaluating procedures and practices, barriers and facilitators related to patient access and (cost-)effectiveness data. The recommendations that come forth from the dissertation will hopefully contribute to a more structured and integrated infrastructure for HNC innovation and rehabilitation within the healthcare system to optimize implementation of innovation and rehabilitation for the patient.

References

1. Overview of approach to long-term survivors of head and neck cancer. Last accessed: 26-2-2020.; https://www.uptodate.com/contents/overview-of-approach-to-long-term-survivors-of-head-and-neck-cancer.
2. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Archives of Otolaryngology - Head and Neck Surgery.* 2004;130(7):875-879.
3. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. *European Archives of Oto-Rhino-Laryngology.* 2016;273(6):1577-1587.
4. Netherlands Comprehensive Cancer Organisation. Cancer Guideline (2011). Last accessed: 12-2-2020.; http://www.oncoline.nl/cancer-rehabilitation.
5. Van den Berg J, Velthuis M, Gijsen B, Lindeman E, van der Pol M, Hillen H. Guideline" Cancer rehabilitation". *Nederlands tijdschrift voor geneeskunde.* 2011;155(51):A4104-A4104.
6. Wolfe A. Institute of Medicine Report: crossing the quality chasm: a new health care system for the 21st century. *Policy, Politics, Nursing Practice.* 2001;2(3):233-235.
7. Netherlands Cancer Institute. HNR 2.0 (version 2006). . Last accessed: 12-2-2020.; https://www.avl.nl/flipbooks/HHR-HNR%202.0/index.html#p=1. .
8. Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *Journal of clinical epidemiology.* 2016;69:79-88.

Samenvatting

In dit proefschrift wilden we meer kennis verwerven over de (kosten-)effectiviteit van innovaties in de behandeling en revalidatie van hoofd-halskanker (HHC). Met behulp van deze kennis kwamen we met aanbevelingen voor klinische en beleidsmatige besluitvorming om de toegang tot innovatie en revalidatie voor HHC patiënten internationaal te optimaliseren.

In **Hoofdstuk 1** wordt achtergrondinformatie gegeven over de ziekte HHC, behandeling en revalidatie, en de procedures en toepassingen in de praktijk gerelateerd aan toegang tot innovaties voor patiënten. Ook wordt de reden achter het uitvoeren van het onderzoek in dit hoofdstuk uitgelegd. Het aantal HHC overlevenden neemt wereldwijd toe en kwaliteit van leven (KvL) wordt een steeds belangrijker onderwerp binnen de HHC zorg [1]. Na ziekte en behandeling is revalidatiezorg essentieel voor patiënten omdat zij vaak lijden aan fysieke en psychosociale problemen die hun functioneren, KvL en participatie in de samenleving beïnvloeden [2,3]. Innovaties worden regelmatig toegepast bij HHC behandeling en revalidatie, waaronder medische hulpmiddelen (bijv. de stemprothese en warmte- en vochtwisselaar (HME) bij laryngectomie revalidatie) en medicijnen (bijv. immunotherapie). Op internationaal niveau zijn deze innovaties echter niet altijd toegankelijk voor HHC patiënten. Toegangsbeperking is vaak multifactorieel en wordt veroorzaakt door barrières in de procedures en praktijktoepassingen in het proces naar effectieve toegang voor patiënten, welke nog niet allemaal waren geïdentificeerd. Daarom hebben wij een uitgebreide beoordeling van gezondheidstechnologie (health technology assessment – HTA) uitgevoerd, inclusief kosteneffectiviteitsanalyses en identificatie van belemmerende en bevorderende factoren omtrent toegang tot zorg voor patiënten. Elk hoofdstuk bespreekt een van de aspecten van het HTA kader, waaronder juridische/administratieve, sociale (arts- en patiënt-gerelateerde), organisatorische, ziekenhuis- en economische aspecten als leidraad voor de hoofdstukken.

Hoofdstuk 2 is een systematisch literatuuronderzoek naar de juridische procedures voor marktgoedkeuring en vergoeding van medische hulpmiddelen in acht landen, en naar bevorderende en belemmerende factoren die werden geïdentificeerd met betrekking tot toegang tot innovatieve medische hulpmiddelen voor patiënten in een vroeg stadium. In de review hebben we 40 publicaties geïncludeerd die betrekking hadden op acht landen: Frankrijk, Duitsland, Italië, Spanje, het Verenigd Koninkrijk (VK), Nederland, Zweden en Polen. Marktgoedkeuringsprocedures (Conformité Européenne (CE)-markering) werden uniform beschreven in alle landen. De vergoedingsprocedures waren heterogeen en er waren zeer weinig artikelen beschikbaar in de literatuur, behalve voor Frankrijk en Duitsland. De tijd tot het verkrijgen van toegang tot innovatieve medische hulpmiddelen was voornamelijk afhankelijk van de vergoedingsprocedures. Belangrijke belemmerende factoren voor effectieve toegang voor patiënten in een vroeg stadium waren onduidelijke Europese wetgeving, complexe

marktgoedkeuringsprocedures, vereisten voor een bepaald niveau van wetenschappelijk bewijs, verzameling van wetenschappelijk bewijsmateriaal tijdens de vergoedingsprocedures en regionale vergoeding en verstrekking van medische hulpmiddelen. Belangrijke bevorderende factoren waren voldoende wetenschappelijke bewijsvoering, implementatie van een systeem gebaseerd op diagnose-gerelateerde groepen (DRGs), aanvullende financieringsmethoden en onderzoeksprogramma's. Wachttijden, kosten van verschillende typen hulpmiddelen en relaties tussen het ziekenhuis en de arts waren van invloed op het voorschrijven in de praktijk. Er zijn geen literatuurstudies gevonden over de rol van de patiënt bij effectieve toegang tot innovaties voor patiënten in een vroeg stadium.

Hoofdstuk 3 werd uitgevoerd als vervolgonderzoek op Hoofdstuk 2. In dit hoofdstuk werden factoren geëvalueerd die het voorschrijven in de praktijk van artsen en de vergoeding van de stemprothese en HME beïnvloeden in acht landen. Ook werden belemmerende en bevorderende factoren voor effectieve toegang voor patiënten geïdentificeerd. Door middel van een online enquête werd een mixed methods onderzoek uit gevoerd met hoofd-halschirurgen en vertegenwoordigers van de hulpmiddelen industrie. Daarnaast vonden semigestructureerde interviews plaats met de vertegenwoordigers. In totaal hebben 36 hoofd-halschirurgen deelgenomen, werkzaam bij 30 ziekenhuizen in België, Frankrijk, Duitsland, Italië, Nederland, Polen, Spanje en het VK. Alle chirurgen hebben stemprothesen voorgeschreven. Vier chirurgen in Polen en Italië schreven in de praktijk geen HME's voor, wat werd beïnvloed door een gebrek aan vergoeding, gebrek aan training/ervaring en zich niet op hun gemak voelen bij het gebruik van het medisch hulpmiddel. Andere beperkende factoren voor de toegang tot medische hulpmiddelen die in Polen, Spanje en Italië werden gemeld, waren een verhoogde werkdruk en onvoldoende personeel. De meeste belemmerende factoren die werden gemeld, waren beperkingen met betrekking tot vergoeding (bijv. een gefixeerd bedrag), gebrek aan opleiding van artsen en patiënten, hoge werkdruk voor artsen en complicaties na gebruik van het medisch hulpmiddel. De meest voorkomende bevorderende factoren waren onderwijs voor zorgverleners en patiënten en ondersteuning bij gebruik van het hulpmiddel door zorgverleners.

In **Hoofdstuk 4** geven we een overzicht van de organisatie, inhoud en financiering van de praktijkvariatie met betrekking tot HHC revalidatie in 14 Nederlandse centra. Het doel was om de implementatie en naleving van de nationale richtlijn voor oncologische revalidatie in alle centra te evalueren en factoren te onderzoeken die van invloed zijn op het verschaffen van revalidatiezorg. Een vertegenwoordiger van elke discipline binnen het toegewijde HHC revalidatieteam en van de financiële afdeling heeft de online enquête ingevuld. Het onderzoek omvatte vijf thema's: de organisatiestructuur, rehabilitatiemodules, financiële zaken, belemmerende en bevorderende factoren, en tevredenheid en toekomstige verbeteringen. Het eerste thema omvatte negen criteria die zijn gebaseerd op het kader van de nationale richtlijn voor oncologische revalidatie [4,5]. Daarnaast waren de barrières en facilitators gebaseerd op de zes domeinen van het Institute

of Medicine (IOM) [6]. De resultaten lieten zien dat alle centra HHC revalidatiezorg verleenden. De meeste centra (86%) pasten een revalidatieprotocol toe. Vier centra (29%) rapporteerden de nationale richtlijn voor oncologische revalidatie te hebben geïmplementeerd, waarvan twee centra voldeden aan alle criteria op basis van de nationale richtlijn. De logopedist, fysiotherapeut en diëtist waren betrokken bij alle toegewijde revalidatieteams, terwijl de overige zorgprofessionals aanwezig waren in minder dan 60% van de centra. Eén centrum ontving duurzame financiering door middel van een revalidatie-specifieke DRG. In de andere centra zijn diverse andere (gecombineerde) financieringsmethoden toegepast. De meest frequente bevorderende factoren van revalidatieverstrekking waren attitude, motivatie en expertise/kennis van zorgprofessionals met betrekking tot HHC revalidatie, beschikbaarheid van een contactpersoon, en patiëntinformatie. De meest voorkomende belemmerende factoren waren medische geschiedenis van de patiënt, vervoer (tijd), gezondheidsgeletterdheid, financiële draagkracht, motivatie/therapietrouw en financiële dekking. Van de centra die de landelijke richtlijn implementeerden, werden items vaker als bevorderend gescoord in de twee centra die volledig voldeden aan de criteria in vergelijking met de twee centra die gedeeltelijk voldeden. Er werden geen duidelijke verbanden waargenomen tussen de belemmerende en bevorderende factoren en de naleving van de richtlijnen.

Hoofdstuk 5 richt zich op HHC revalidatie op ziekenhuisniveau. Het Nederlands Kanker Instituut (NKI-AVL) biedt sinds 2011 een interdisciplinair hoofd-halsrevalidatieprogramma (IHHR) aan dat financieel gedekt is voor HNC-patiënten [7]. We veronderstellen dat een interdisciplinaire aanpak effectiever zal zijn in het herstel (en de tijd tot herstel) van patiënten dan de standaard ondersteunende zorg, omdat de symptomen van patiënten vaak complex en onderling gerelateerd zijn. Daarom zijn we een nog lopend prospectief gecontroleerd onderzoek gestart waarin de (kosten-)effectiviteit van IHHR wordt vergeleken met standaard ondersteunende zorg bij patiënten met een gevorderd stadium van HHC die worden behandeld met concomitante chemoradiatie (CRT) of bioradiotherapie (BRT). De interventiegroep bestaat uit de NKI-AVL. Voor de controlegroep nemen zes centra (drie academische en drie niet-academische centra) deel, waardoor dit een heterogene groep is geworden. Om onze resultaten te verkrijgen, wordt een studie-specifieke vragenlijst met door de patiënt-gerapporteerde uitkomstmaten (PROMS) ingevuld door de patiënten bij diagnose (baseline; T0), 3 maanden (T1), 6 maanden (T2), 9 maanden (T3) en 12 maanden (T4) na start van medische behandeling. De primaire uitkomst bestaat uit de gezondheidsgerelateerde kwaliteit van leven (GKvL) uitgedrukt in de European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) samenvattende score [8]. Secundaire uitkomsten zijn: functionele GKvL, maatschappelijke participatie, utiliteiten, werkhervatting, onvervulde behoeften, patiënttevredenheid en klinische resultaten. Er zal een “mixed effects-model” en Markov

beslissingsmodel[1] worden uitgevoerd om respectievelijk de effectiviteit en kosteneffectiviteit van IHHR te beoordelen.

In **Hoofdstuk 6** werd met behulp van een Markov beslissingsmodel een kosteneffectiviteitsanalyse verricht van chirurgische behandeling versus orgaanpreservatie bij larynxkanker in een vergevorderd stadium vanuit een gezondheidszorgperspectief. Dit werd uitgevoerd om de impact van beide regimes op de overleving, korte en lange termijn bijwerkingen, KvL en kosten te vergelijken. De resultaten toonden aan dat totale laryngectomie met of zonder adjuvante radiotherapie kosteneffectief is in vergelijking met orgaanpreservatie. De chirurgische aanpak was duurder, maar leverde meer gezonde levensjaren (quality-adjusted life years – QALY's) op. Op internationaal niveau kan de informatie over QALY's en kosten nuttig zijn bij respectievelijk het gezamenlijke besluitvormingsproces in de kliniek en de beleidsmatige besluitvorming.

De tweede kosteneffectiviteitsanalyse die we hebben uitgevoerd, wordt beschreven in **Hoofdstuk 7**. Het doel was om de kosteneffectiviteit van de HME te evalueren in vergelijking met alternatieve stoma-bedekkende materialen in de Verenigde Staten (VS) vanuit een gezondheidszorg- en maatschappelijk perspectief. Dit werd uitgevoerd omdat de HME niet altijd toegankelijk is voor HHC patiënten in de VS en er meer wetenschappelijk bewijs nodig is met betrekking tot de kosteneffectiviteit van de HME om beslissingen omtrent vergoeding te ondersteunen. Voor de analyse is gebruik gemaakt van een Markov beslissingsmodel. Gegevens met betrekking tot pulmonale revalidatie, KvL, afname van de arbeidsproductiviteit, longinfecties en medische consumptie gerelateerd aan pulmonale symptomen werden prospectief verzameld op patiëntniveau. We ontdekten dat het gebruik van HME kosteneffectief was in vergelijking met alternatieve stoma-bedekkende materialen vanuit de Amerikaanse gezondheidszorg- en de maatschappelijke setting. HME gebruik leidde tot minder longinfecties, minder klachten van slijmproductie en overmatig hoesten, en minder arbeidsproductiviteitsverlies. KvL verschillen tussen beide groepen werden niet gevonden door middel van generieke metingen (gebaseerd op preferentie). Met gebruik van de HME bedroegen de jaarlijkse besparingen op het ziekenhuisbudget tot $40.183.593 in de maatschappelijke setting.

Bij het uitvoeren van een kosteneffectiviteitsanalyse zijn preferentie-gebaseerde metingen zoals door de EuroQol five-dimensional questionnaire (EQ-5D) noodzakelijk om utiliteiten te verkrijgen, en GKvL gegevens die door PROMS worden gemeten, kunnen niet rechtstreeks worden toegepast. Om de toepassing van GKvL metingen mogelijk te maken in een kosteneffectiviteitsanalyse, kunnen GKvL metingen worden omgezet in (preferentie-gebaseerde) utiliteiten door middel van mapping. Daarom hebben we in **Hoofdstuk 8** een mappingmodel

1 Een Markov model is een wiskundig model waarin twee cohorten patiënten worden gesimuleerd om de kwaliteit van leven en kosten tussen de groepen te vergelijken.

ontwikkeld dat de EORTC QLQ-C30-resultaten omzet in een EQ-5D-utiliteiten door middel van regressiemodellering. Ook werd de waarde onderzocht van het toevoegen van de schalen van de ziekte-specifieke EORTC QLQ module voor HHC (EORTC QLQ-H&N35) aan het mappingmodel. Onze resultaten toonden aan dat het best presterende model (definitief model) is ontwikkeld met behulp van de bètaregressiemethode, waaronder vijf EORTC QLQ-C30-schalen: algemene gezondheidsstatus/KvL, fysiek functioneren, rol-functioneren, emotioneel functioneren en pijn. Het toevoegen van de EORTC QLQ-H&N35-schalen aan het model verbeterde de prestaties van het model niet, waardoor de rol van ziekte-specifieke schalen onduidelijk blijft. Dit model kan met enige voorzichtigheid worden gebruikt om de utiliteiten van HHC patiënten te berekenen wanneer er geen directe utiliteiten beschikbaar zijn, om op die manier economische analyses te vergemakkelijken en zo de implementatie van innovatieve behandelingen en hulpmiddelen voor HHC in de klinische praktijk te verwezenlijken.

Ten slotte worden in **Hoofdstuk 9** de belangrijkste bevindingen besproken en worden de belangrijkste punten voor toekomstig onderzoek, beleidsmatige en klinische besluitvorming omtrent HHC behandeling en revalidatie besproken. In de literatuur bleek het wetenschappelijk bewijs met betrekking tot procedures en toepassingen in de praktijk, kosteneffectiviteit en implementatie van revalidatie binnen het HNC onderzoeksveld schaars te zijn. Er valt meer te ontdekken en te optimaliseren op dit gebied door toekomstig onderzoek. Allereerst wordt geadviseerd om in een vroeg stadium (kosten-)effectiviteitsanalyses uit te voeren, dat wil zeggen voorafgaand aan de aanvraag voor marktgoedkeuring voor innovatieve medische hulpmiddelen, en kosteneffectiviteitsanalyses parallel aan het effectiviteitsonderzoeken van de van revalidatieprogramma's. Ten tweede dienen klinische onderzoeken worden afgestemd op het verzamelen van kosteneffectiviteitsgegevens, waaronder gegevens over de overleving gespecificeerd voor tumortype and stadium van de ziekte, KvL en bijwerkingen. Ten derde wordt aanbevolen om verdiepende (kwalitatieve) onderzoeken uit te voeren naar procedures en toepassingen in de praktijk met respectievelijk beleidsmakers/medische hulpmiddelenindustrie en zorgverleners/patiënten. Ten vierde wordt er geadviseerd om het maatschappelijke perspectief in HHC revalidatieonderzoek te verkennen, rekening houdend met aspecten als werkhervatting en participatie in de samenleving. Ten vijfde zouden er initiatieven kunnen worden genomen om een HHC-specifieke utiliteit te ontwikkelen om de KvL metingen in deze specifieke populatie te verbeteren.

In de praktijk zijn nationale en internationale inspanningen geleverd om de implementatie van innovatie en revalidatie voor hoofd-halskankerpatiënten te bevorderen. Ten eerste wordt geadviseerd om de juridische procedures voor toegang tot innovaties te centraliseren. Ten tweede worden er op (inter)nationaal niveau meer specifieke, transparante en uniforme richtlijnen geadviseerd. Ten derde moet financiële steun worden versterkt door middel van duurzame tijdelijke (bijv. voorwaardelijk toelatingstraject) en permanente (bijvoorbeeld op DRG-

gebaseerde) vergoedingsregelingen. Ten vierde zou de klinische ondersteuning kunnen worden verbeterd door middel van multidisciplinair teamwerk, samenwerking tussen ziekenhuizen, (online) onderwijs en training. Ten vijfde wordt het gebruik van QALY's in een keuzehulptool en effectevaluatie ten zeerste aanbevolen.

Toekomstige initiatieven zouden zich kunnen richten op de 'patiënt als gebruiker' als uitgangspunt, door studies uit te voeren naar zorggebruik van de patiënt en gerelateerde belemmerende en bevorderende factoren, waarbij patiënten betrokken worden als respondenten. Bovendien kan de ondersteuning van patiënten bij HHC behandeling en revalidatie worden verbeterd door middel van financiële ondersteuning, educatie en begeleiding op maat.

In dit proefschrift hebben we inzicht gegeven in de huidige infrastructuur van toegang tot HHC innovatie en revalidatie op internationaal niveau door middel van evaluatie van procedures en toepassingen in de praktijk, belemmerende en bevorderende factoren met betrekking tot toegang voor patiënten en (kosten-)effectiviteitsgegevens. De aanbevelingen die uit het proefschrift naar voren komen, zullen hopelijk bijdragen aan een meer gestructureerde en geïntegreerde infrastructuur voor HHC innovatie en revalidatie binnen de gezondheidszorg, om de implementatie van innovatie en revalidatie voor de patiënt te optimaliseren.

Referenties

1. Overview of approach to long-term survivors of head and neck cancer. Last accessed: 26-2-2020.; https://www.uptodate.com/contents/overview-of-approach-to-long-term-survivors-of-head-and-neck-cancer.
2. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. *Archives of Otolaryngology - Head and Neck Surgery.* 2004;130(7):875-879.
3. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. *European Archives of Oto-Rhino-Laryngology.* 2016;273(6):1577-1587.
4. Netherlands Comprehensive Cancer Organisation. Cancer Guideline (2011). Last accessed: 12-2-2020.; http://www.oncoline.nl/cancer-rehabilitation.
5. Van den Berg J, Velthuis M, Gijsen B, Lindeman E, van der Pol M, Hillen H. Guideline" Cancer rehabilitation". *Nederlands tijdschrift voor geneeskunde.* 2011;155(51):A4104-A4104.
6. Wolfe A. Institute of Medicine Report: crossing the quality chasm: a new health care system for the 21st century. *Policy, Politics, Nursing Practice.* 2001;2(3):233-235.
7. Netherlands Cancer Institute. HNR 2.0 (version 2006). . Last accessed: 12-2-2020.; https://www.avl.nl/flipbooks/HHR-HNR%202.0/index.html#p=1. .
8. Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *Journal of clinical epidemiology.* 2016;69:79-88.

Addendum

PhD portfolio
List of publications
Dankwoord
Curriculum Vitae

PhD portfolio

PhD student:	A.C.C. Beck
PhD period:	September 2015 – June 2020
PhD supervisors:	Prof. dr W.H. van Harten
	Prof. dr. M.W.M. van den Brekel
	Dr. V.P. Retèl

Courses	**Year**	**Location**
GPRA Postlaryngectomy Rehabilitation course – NKI-AVL	2015	Amsterdam
Introduction to Health Technology Assessment – ISPOR	2015	Milan, Italy
Transferability of Cost-effectiveness Data between Countries – ISPOR	2015	Milan, Italy
Reimbursement Systems for Pharmaceuticals in Europe – ISPOR	2015	Milan, Italy
Basic Medical Statistics – OOA	2015	Amsterdam
Kennissessie kosteneffectiviteit – NKI-AVL	2015	Amsterdam
Clinical Data Management – AMC Graduate School	2016	Amsterdam
Evaluation of Medical Tests – AMC Graduate School	2016	Amsterdam
Practical Biostatistics – AMC Graduate School	2016	Amsterdam
Medical Business Masterclass	2016	Amsterdam
Training in Scientific Data Visualizations – OOA	2016	Amsterdam
Cost-effectiveness Modeling Methods – Maastricht University	2016	Maastricht
Good Clinical Practice – Clinical Trial Service	2016	Amsterdam
Scientific Writing Course – AMC Graduate School	2016	Amsterdam
Value Based Healthcare Masterclass – Value in Care	2017	Amsterdam
Decision Analytic Modelling – University of York	2017	York, UK
Medical Business Masterclass	2017	Amsterdam
Scientific Writing – OOA	2017	Amsterdam
Scientific Integrity – ACTA	2018	Amsterdam
Statistical programming with R – Tridata	2019	Utrecht
Medical Business Masterclass	2019	Multiple
BROK specifieke bijeenkomst – OOA	2019	Amsterdam
Good Clinical Practice – OOA	2019	Amsterdam

Presentations	Year	Location
Study protocol of a prospective multicenter study comparing (cost-)effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo- or bioradiotherapy *Oral presentation – ECCO*	2016	Amsterdam
Study protocol of a prospective multicenter study comparing (cost-)effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo- or bioradiotherapy *Poster presentation – OOA Retreat*	2016	Renesse
Study protocol of a prospective multicenter study comparing (cost-)effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo- or bioradiotherapy *Poster presentation – NWHHT Jonge Onderzoekersdag*	2017	Rotterdam
Case presentation esthesioneuroblastoma treated with lutetium-dotatate *Oral presentation – Head and Neck Symposium NKI-AVL*	2017	Amsterdam
Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries *Oral presentation – OOA Retreat*	2017	Renesse
Mapping the EORTC QLQ-C30 and QLQH&N35 to the EQ-5D for head and neck cancer: Can disease-specific utilities be obtained? *Poster presentation – International PhD Student Cancer Conference*	2018	London, UK
Mapping the EORTC QLQ-C30 and QLQH&N35 to the EQ-5D for head and neck cancer: Can disease-specific utilities be obtained? *Oral presentation – SMDM*	2018	Leiden
Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries *Poster presentation – IFHNOS*	2018	Buenos Aires, Argentina

Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries *Poster presentation – ISPOR*	2019	New Orleans, US

Supervision of students	**Year**
Riin Ots, student Science and Business Management – Utrecht University	2017
Rosaly Meissner, student Health Economics – University of Twente	2018
Cheetel Algoe, student Medicine – AmsterdamUMC	2018
Mickey Leentjes, student Medicine AmsterdamUMC	2019

Other	**Year**
Founder and coordinator of weekly OIO overleg – NKI-AVL	2015 - 2019
Hostess GPRA course – NKI-AVL	2015 – 2020

List of publications

- **Beck ACC**, Kieffer JM, Retèl VP, van Overveld LFJ, Takes RP, van den Brekel MWM, van Harten WH, Stuiver MM. Mapping the EORTC QLQ-C30 and QLQ-H&N35 to the EQ-5D for head and neck cancer: can disease-specific utilities be obtained? *PLoS One. 2019 Dec 13;14(12):e0226077.*
- **Beck ACC**, Retèl VP, Bhairosing PA, van den Brekel MWM, van Harten WH. Patient access to medical devices in Europe: A systematic literature review. *Health Policy. 2019 Dec;123(12):1185-1198.*
- **Beck ACC**, Oomens MA. Een hobbelig palatum. *Quality Practice, 2019 Oct.*
- Klop WMC, Elshot YS, **Beck ACC**, Brandsen RE, Lohuis PJFM. Oncodermatology of the head and neck. *Facial Plast Surg. 2019 Aug;35(4):368-376*
- **Beck ACC**, Passchier E, Retèl VP, Stuiver MM, van der Molen L, Klop WMC, van Harten WH, van den Brekel MWM. Study protocol of a prospective multicenter study comparing (cost-) effectiveness of a tailored interdisciplinary head and neck rehabilitation program to usual supportive care for patients treated with concomitant chemo- or bioradiotherapy: A multicenter prospective observational study. *BMC Cancer. 2019 Jul 3;19(1):655*
- **Beck ACC**, Retèl VP, van den Brekel MWM, van Harten WH. Patient access to voice prostheses and heat and moisture exchangers: Factors influencing physician's prescription and reimbursement in eight European countries. *Oral Oncol. 2019 Apr;91:56-64.*
- **Beck ACC**, Lohuis PJFM, Al-Mamgani A, Smit LA, Klop WMC. Salivary duct carcinoma: evaluation of treatment and outcome in a tertiary referral institute. *Eur Arch Otorhinolaryngol. 2018 Jul;275(7):1885-1892.*
- Boogerd LSF, Boonstra MC, **Beck ACC**, Charehbili A, Hoogstins CES, Prevoo HAJM, Singhal S, Low PS, Van de Velde CJH, Vahrmeijer AL. Concordance of folate receptor-α expression between biopsy, primary tumor and metastasis in breast and lung cancer patients. *Oncotarget. 2016 Apr 5;7(14):17442-54.*
- **Beck ACC**, Hagemeijer A, Tortolani B, Birkhahn RH. Comparing an Unstructured Risk Stratification to Published Guidelines in Acute Coronary Syndromes. *West J Emerg Med. 2015 Sep;16(5):683-9*

Dankwoord

Het zit erop, mijn tijd in het **Antoni van Leeuwenhoek**. Het AVL is een organisatie met een warme sfeer, waar men vriendelijk tegen elkaar is, elkaar altijd gedag zegt op de gang, een ieder zichzelf kan zijn, en de patiënten zich thuis voelen – ik heb het als speciaal ervaren. Dat ik hier onderdeel van heb mogen zijn, vind ik erg bijzonder en deze ervaring heeft mij persoonlijk veel geleerd. Met plezier ging ik iedere dag naar het werk en ik kijk dan ook terug op een megaleuke tijd. Ik wil graag de organisatie en iedereen die zich binnen de organisatie inspant en bijdraagt om het AVL te maken tot wat het is, bedanken. In de periode dat ik hier heb mogen werken, heb ik met een aantal mensen in het bijzonder mogen samenwerken die ik graag persoonlijk zou willen bedanken.

Allereerst mijn **promotors en copromotor**. Je hoort regelmatig dat PhD studenten (te) weinig begeleiding krijgen en lang moeten wachten op respons. Ik heb mij tijdens mijn promotietijd vaak gerealiseerd dat ik niet tot deze groep behoor en daar ben ik mijn begeleiders dankbaar voor. Ik had de beschikking over feedback van een promotor met expertise van de hoofd-halskankerzorg, een tweede promotor die tevens de grote lijnen en de beleidsmatige kant aanstipte, en een copromotor die inhoudelijk detailgericht mee kon beoordelen: een Dreamteam, zoals Neil tijdens mijn OOA meeting zei. Ze hebben mij ook altijd de ruimte gegeven voor mijn eigen ideeën, projecten en manier van schrijven. Het werkte erg prettig en efficiënt. Ik wil mijn begeleiders heel hartelijk danken voor de kans die zij mij hebben geboden met dit traject en voor de fijne samenwerking.

Promotor prof. dr. W.H. van Harten, beste **Wim**. Toen ik in 2015 jouw cv doornam ter voorbereiding van mijn sollicitatie, werd ik ineens erg nerveus; zoveel functies vervuld door een persoon! Maar die zenuwen verdwenen al redelijk snel. Je prompte reacties met betrekking tot feedback en mails, je 'to the point' maar open houding en je nuchtere blik heb ik als zeer prettig ervaren. Jouw helikopterview hielp bij het overzichtelijk houden van de projecten en tijdsplanning. Ik vond het daarbij ook erg leuk om je algemene manier van werken mee te krijgen, en ik heb daar ook veel van kunnen leren. Los van deze zaken waren de meetings, met Michiel en Valesca samen, gezellig en hebben we regelmatig gelachen. Dank voor alles!

Promotor prof. dr. M.W.M. van den Brekel, beste **Michiel**. Je vliegt regelmatig door het AVL van afspraak naar afspraak. Toch verliep mijn promotie vlot o.a. doordat je je erg benaderbaar hebt opgesteld. Ik kon altijd tussendoor binnenlopen met een vraag. Je bent zelden niet vrolijk en hebt een positieve houding, wat niet alleen voor mij, maar ook voor assistenten en co-assistenten erg prettig werkt. Als afdelingshoofd geef je mensen de mogelijkheid om te doen wat ze leuk vinden en waar ze goed in zijn. 'Nee' is een woord wat je niet vaak gebruikt; je staat open voor eigen input. Ik heb gezien dat dat ruimte biedt om het beste in een ieder naar boven

te halen, en het stimuleert tot zelfontplooiing: 'yes is more'. Zelf heb ik het ook zo ervaren. Dank voor alles!

Copromotor dr. V.P. Retèl, beste **Valesca**, jij bent de 'key' in mijn promotie. Met jou sparde ik regelmatig over de inhoud en naast de werkinhoudelijke zaken kan ik het ook op persoonlijk vlak goed met je vinden. Ik heb bewondering voor je, het feit dat je als een duizendpoot alle specialismen in het AVL voorziet van adviezen en studies omtrent kostenanalysen, je daarnaast je PhDs begeleidt en moeder bent van twee jongens. Ondanks dit alles blijf je altijd bescheiden. Ik hoop je nog eens terug te zien in Den Hoorn ☺. Dank voor alles!

Geachte leden van de promotiecommissie: **prof. dr. M.G.W. Dijkgraaf**, **prof. dr. F.J.M. Hilgers**, **prof dr. M.A. Joore**, **prof. dr. H.A.M. Marres**, **prof. dr. C.R.N. Rasch** en **prof dr. Smeele**, hartelijk dank dat u in de commissie zitting wilt nemen, de tijd heeft genomen om mijn proefschrift kritisch te lezen en te beoordelen, en met mij van gedachte wilt wisselen tijdens de plechtigheid. Beste **Manuela**, in het begin van mijn promotietraject volgde ik jouw vak waardoor ik leerde modelleren. Ik vind het erg leuk dat we elkaar nu tijdens de plechtigheid weer zullen treffen.

Ik wil graag de **patiënten** bedanken die deel hebben genomen aan de P16HNR revalidatiestudie en de HME studie. Zij hebben ons middels vragenlijsten veel informatie verschaft omtrent de effectiviteit van hoofd-halsrevalidatie wat zal leiden tot optimalisatie van de revalidatiezorg. Graag bedank ik ook de patiënt die ter illustratie wilde poseren voor de Introductie van dit proefschrift.

Graag bedank ik alle **zorgverleners** en **medewerkers van de Financiële afdelingen** die meedachten en deelnamen aan de surveystudies. Dank aan de **voorzitters van de NWHHT** zonder wie we niet zo'm mooi overzicht van de nationale hoofd-hals revalidatie hadden kunnen maken. De inclusie van de P16HNR revalidatiestudie verliep vlot met veel dank aan **Bing**, **prof. dr. De Bree**, **mevr. Goossens**, **dr. Hoebers**, **dr. Speksnijder**, **dr. Verschuur** en – in het bijzonder – **dr. Bouman**, **Jacintha**, **Kim**, **Rody**, **dr. Wensing** en **Xbem**, die driewekelijks de tijd namen om contact met mij te onderhouden. Xbem, dank ook voor de 'meeloopdagen' en voor de altijd gezellige etentjes in Enschede en Amsterdam.

I would also very much like to thank my supervisors from Boston. Dear **dr. Deschler** and **dr. Bunting**, thank you very much for giving me the opportunity to perform the study at your Department. I really felt welcome and also very much felt part of the team. Thank you for the experience. Dear **staff of the Voice and Speech Lab**, thank you for welcoming me so kindly in your team and for helping me with the inclusion of the patients! I have learned a lot from you in practice and at your course, and I also had a very nice time. Dear **Ira**, **Liz** and **Stefani**, thank you for the great times in- and outside of the hospital and showing me around in Boston. That gave an extra spark to my research internship.

Dank aan alle co-auteurs voor hun input en feedback tijdens het uitvoeren van de studies en bij het schrijven van het manuscript. Beste **Martijn** en **Jacobien**, dank dat jullie het mapping avontuur met mij aan wilden gaan. Het was een lang proces maar we hebben er veel lol aan beleefd! Martijn, dank ook voor jouw betrokkenheid in andere studies. Ik streef nog altijd naar jouw volmaakte Engels en vlotte denkwijze. Beste **Liset**, je bent een van de oprichters van het hoofd-hals programma. Dank voor jouw waardevolle input in de studies en je kritische blik. Beste **Arash**, dank voor jouw expertise en hulp bij diverse studies. Beste **Ellen**, dank voor de samenwerking al die jaren. Je bent een warm persoon. Succes met de VS opleiding en we houden contact. Ik wil ook graag iedereen bedanken die ik in de Acknowledgements heb genoemd, waaronder **Rob**. Dank voor jouw hulp bij het programmeren in R, de vertaling van Duitse artikelen en de gezellige gesprekken. Studenten **Cheetel**, **Mickey**, **Riin** en **Rosaly**, dank voor jullie inzet en hulp tijdens het uitvoeren van de studies.

De **Afdeling Hoofd-Halschirurgie**. Toen ik op de afdeling kwam werken wist ik niet precies wat ik kon verwachten. In de eerste dagen dat ik aan deze baan begon kwam ik in ieder geval niet toe aan werken. Ik wist niet wat ik zag: heel veel vriendelijk en laagdrempelig contact tussen stafleden en assistenten. Mijn ogen klapperden toen een van de professoren mij naast mijn bureau gedag kwam zeggen. Ik belde die dag een van mijn vriendinnen op om te vertellen dat op de afdeling 'de professoren in het wild rondliepen'. Ik was dat totaal niet gewend vanuit mijn opleiding. De open en vriendelijke houding van niet alleen de stafleden maar ook de rest van het team van paramedici en arts-assistenten maakt het een superfijne afdeling om te werken.

Alle **(oud)stafleden** van de Hoofd-Halschirurgie, beste **prof. Balm, Baris, Bing, Frans, Klop, Lilly-Ann, Lohuis, Lot, Luc, Ludi, Pim en Richard,** dank voor jullie begeleiding en (laagdrempelig) contact in de kliniek en op onderzoeksgebied.
Beste **Baris**, de man zonder angst en goed met deeg! We hebben wat af geborreld. Dank voor de gezelligheid en het delen van jouw expertise op OBC. Beste **Frans**, je bent een voorbeeld voor velen. Jouw inzet en motivatie voor de hoofd-hals revalidatie heeft geleid tot o.a. een volledig hoofd-hals revalidatieprogramma, waar ik tijdens mijn promotie verder onderzoek naar heb mogen doen. Ik ben erg blij dat jij tot de promotiecommissie behoort. Beste **Klop** en **Lohuis**, ik vind jullie een leuk duo. Op het krukje hebben we veel hilarische gesprekken gevoerd, maar ook bespraken we serieuze levenslessen en hebben we zelfs een 'article of the month' eruit geperst. Dank voor jullie betrokkenheid, gezellige en persoonlijke gesprekken. Beste **Lilly-Ann** en **Lot**, dank voor de gezellige en persoonlijke gesprekken. Jullie zijn een voorbeeld voor de vrouwen! Beste **Luc** en **Richard**, van fellows tot bazen. Van jullie leerde ik respectievelijk biopteren en scopiëren! Dank voor jullie onderwijs en gezelligheid op de afdeling. Beste **Ludi**, we troffen elkaar vaak op de poli. Bedankt voor de begeleiding en heel fijn dat je in mijn commissie wilt plaatsnemen. Beste **Pim**, paradijsvogelen kan ik met jou als de beste! Hoogtepuntje was toch wel de cocktails op het dakterras. Dank voor de (poli)begeleiding en de gezelligheid.

(Fellow) Marjolijn, dank voor de gezellige gesprekken en erg leuk dat we samen nog een stukje konden schrijven.

Anne, onze trouwe onderzoekster, van wc politie tot kakhiel; ik kon echt niet ophouden met lachen met jou! **Merel**, ik heb erg genoten van de tijd met jou in de feestcommissie! Dank dames! **Robert** en **Renske**, dank voor de gezellige koffiegesprekken in het U-gebouw. **Hannah** en **Marene**, dank voor de gezelligheid op de poli's en daarbuiten. **Marion** en **Henny**, bedankt voor jullie ondersteuning bij de projecten en gezellige gesprekken over bakken. Dank aan iedereen van **polikliniek 1D** en de **backoffice**.

Werken wordt pas echt leuk als je leuke **onderzoekscollega's** hebt. Wij als hoofd-hals onderzoekers hadden de luxe om grotendeels vanuit het U-gebouw onderzoek te doen. Dit werd niet alleen snel omgetoverd tot vrijmibo hotspot op de vrijdagmiddag maar ook het startpunt van late avondjes in o.a. de Ebeling, Waterkant en Kopstootbar. Op maandag was dit het epicentrum voor achterklap van het weekend. Ik heb zo hard gelachen en houd hier mooie herinneringen aan over. **Rebelse**, wij lieten het vanaf moment een niet alleen bij werk. Het begon bij een middagje shoppen bij de Bijenkorf, en veeeel avondjes in de Pijp, festivals, rodelavonturen, surfvakantie, en diners volgden, tot aan kerst toe. Ik heb een waanzinnige tijd met je gehad! Daarbij in het team hoort ook **Jootje**, eindelijk een man op de afdeling, en wel een met upskear die de datingsapps en Wikipedia pagina's domineert. Eindeloze koffies met z'n drieën in de pantry. Hoogtepuntje met Jootje was wel ' the day after' mijn verjaardag, toen jij mij geholpen hebt met de kratten, buikpijn van het lachen. **Marij**, jij nam mij op sleeptouw op de afdeling en was behulpzaam in de beginfase van mijn PhD, inclusief de kadavervoorbereidingen tijdens de GPRA cursus. En samen op skiles. We hebben veel gelachen. Jij bent een ideale klant voor mijn taarten, zeker vanwege jouw genetische (slanke) bouw! **Klassie**, we lopen parallel met ons PhD avontuur en vele gezellige koffietjes later komt dat nu ten einde. Het avontuur in Zweden hebben we overleefd en is uiteindelijk een zeer gezellige trip geworden. Je citroenmerengue is verrukkelijk. Ik hoop dat we nog een keer samen bakken! **Maartje** en **Coralie**, onze gedeelde office was van korte duur maar wel gezellig. Succes met jullie PhDs! **Alejandra**, **Charlotte**, **Dannie**, **Jaqueline**, **Jos**, **Liset**, **Luuk**, **Kilian**, **Maarten**, **Martijn**, **Michel**, **Nes**, **Sophie**, **Tessa**, bedankt voor de gezellige en fijne tijden!

De **Afdeling PSOE**. Hoewel ik fysiek minder vaak aanwezig was, houd ik mooie herinneringen over aan de afdeling, zoals mijn tijd in de feestcommissie, de PSOE uitjes en natuurlijk de gezellige jaarlijkse kerstdiners. Ik wil graag **iedereen op de PSOE** bedanken voor jullie gezelligheid en feedback tijdens de PSOE meetings.
Beste **Floor,** dank voor jouw steun vanuit de afdeling en voor jouw grappige en authentieke speeches en mails tijdens kerst en quarantainetijd. **Jacqueline**, onze PhD en feestcommissie tijd was gezellig! **Daniëlle**, **Karin**, **Marion** en **Jorrita**, dank voor jullie ondersteuning in de planning van mijn PhD.

A special thanks to the **Van Harten group**. Dear **Anke**, **Bruno**, **Danalyn, Hester**, **Inge**, **Joost**, **Laura**, **Nora**, **Willeke**, **Wim Groen**. The group is diverse, everyone studies his/her own field and that is what I think was fun and educational during the monthly meetings. We had a lot of fun during the Van Harten group outings. Hope to see you soon in a non-Zoom environment ;).

En dan natuurlijk onze trouwe **O-gebouw collega's**. Jullie leken zo ver weg maar aan het eind waren jullie middels de verplichte verhuizing toch weer dichtbij. Samen met de hoofdhals collega's hebben we fantastische tijden beleefd, inclusief vrijmibo's, koningsdagen, boottochten, festivals, zelfs skivakanties begon ik leuk te vinden. Al deze avonturen hebben mijn kwaliteit van leven tijdens het PhD leven aanzienlijk verhoogd. Dank aan de oude en nieuwe garde – **Arthuro**, **Brigit**, **Elies**, **Eva**, **Hester**, **Joost**, **Lisette**, **Marieke, Mathilde**, **Max**, **Nick**, **Ravi**, **Rosa**, **Ruud**, **Sophie**, **Vera** en **Willem**! Special shout out to de collega vriendinnen **Char**, **Hannie**, **MaritMarit**, **Saar**, **Sim** en **Viool**. Ik hoop jullie snel weer te treffen voor een lekker diner ergens in Amsterdam!

Mijn lieve **vrienden**, min of meer in chronologische volgorde: Lieve **ketenleden** – **Juul**, **Lys, Mai**, **Nadien** en **Suus** – we worden oud geloof ik. Kijk naar de stappen die we allen zetten; en ook de eerste ketenbaby is een feit! Onze hilarische apps, uitjes door heel de Benelux en tegenwoordig ook de gezellige quarantaine borrels! Na al die jaren still going strong, ik ben heel erg blij met onze vriendschap. Lieve **Haag** en **Pad**, ik vind onze band erg speciaal. We delen lief en leed, etentjes gaan door tot sluitingstijd en dan zijn we nog niet uitgepraat! Een oprechte vriendschap. Ik ben trots op jullie beiden, jullie zijn me erg dierbaar! Lieve **Ais**, ik houd van je oprechtheid, je inspireert me vaak – niet alleen maar in de gym haha – op naar een levenslange vriendschap. Lieve **meiden van Gewaagd** – **Fien**, **Heems, Ing**, **Lau**, **L-J**, **Lyts**, **Roos**, **San**, **Siem**, **Suus**, **Taar** en **Yaar** – ook al zien we elkaar niet zo vaak, we houden frequent contact. De vakantie naar Madagaskar is tijdens mijn PhD een echt hoogtepunt geweest. Ik ben blij dat iedereen het goed maakt. In het bijzonder lieve Siem, het is altijd fijn en gezellig om jou te spreken, je bent me erg dierbaar. Lieve **Marrie** en **As**, ik blijf het zeggen; ik ben zo blij dat we nog steeds vriendinnen zijn ;). Een trouwe en openhartige vriendschap! Dank voor jullie aanmoediging all times! Lieve **Flo**, ik geniet van onze dates, jij bent een heerlijk persoon! Lieve **Plink**, op pad met jou is altijd een feestje! Lieve **An**, mijn BovenlJ maatje, ik houd van onze gesprekken, je bent een toppertje! Lieve **An**, **Floor** en **Lies**, elke date is weer lachen gieren brullen. Van NYC tot aan elke zondagavond met BZV voor de buis. Ik ben blij dat ik jullie op de hockey heb ontmoet. Op naar veel meer tripjes en culinaire eetdates met giermomenten! Lieve **Lazin** en **Allardo**, zo leuk dat ik jullie in Boston heb ontmoet en we nog steeds contact hebben. Jullie hebben veel talent en jullie gezelschap vind ik altijd genieten!

Ramon, wat maak jij supertoffe kunstwerken en wat was het een feestje om mijn omslag met jou te ontwerpen. Hartelijk dank voor dit leuke proces, jouw geduld en het mooie resultaat! **Bregje**,

dank voor al jouw hulp in het ontwerpen van het boekje! **Willemijn**, dank voor je gesprekken en je advies, ik heb er zoveel aan gehad niet alleen op carrièregebied maar ook privé!

Mijn **paranimfen**! Lieve **Lot**, tijdens mijn keuzecoschap in Suriname hebben we elkaar ontmoet en sindsdien hebben we zoveel leuke dingen samen beleefd. Feestjes, sporten met een 'afterworkout biertje' in de Pijp, en we gaan nog steeds talloze keren uiteten. We hebben samen het 'carrièrepad' bewandeld en daarbij lief en leed met elkaar gedeeld. Heerlijk om met jou over promotietaferelen te kletsen. Ik had de eer om jouw paranimf te zijn en nu vind ik het superleuk dat jij de mijne bent. Lieve **Melania**, tijdens het PSOE uitje van 2015 leerden wij elkaar kennen en kort daarna gingen we samen naar ISPOR Milaan. Ondanks dat we van elkaar verschilden hadden we meteen een klik. We hebben veel lol beleefd op werk en congressen. Het is een verademing om met jou over kostenanalysen te kletsen, jij snapt meteen wat ik bedoel. Buiten het werk om ben je een vriendin geworden, ik verheug me nu al op onze B&B date!

Lieve **Gerda**, **Frans**, **Anke**, **Marc**, **Baukje**, **Nick**, **Rens** en **Cas**. Het voelde bij jullie meteen als een warm bad. Dank daarvoor en hopelijk zien we elkaar weer snel na de quarantaine tijd!

Lieve **Ria**, je kent me al van jongs af aan en we zijn praktisch familie. Samen met Annelies ben jij op alle belangrijke momenten erbij geweest. Ik vind het erg leuk dat ik mijn boekje aan jou kan overhandigen en je hopelijk op mijn promotie aanwezig kunt zijn. Annelies is er in gedachten bij, dat weet ik zeker.

Lieve **Guy**, daar waar ik in deze quarantainetijd onderzoek zit te doen, sta jij aan de frontlinie voor de COVID-patiënten. Ik ben altijd trots op je broeder! Je betekent veel voor me, jouw support is voor mij waardevol. Ik kijk ernaar uit dat we elkaar weer uitgebreid kunnen zien na quarantainetijd. Lieve **Jannie**, ik hoop weer snel bij jou in de stoel te mogen zitten voor een van jouw vele talenten. Of samen in de tuin bij m'n ouders, dat is altijd gezellig! Dank voor jullie support en onvoorwaardelijke liefde. <3

Lieve **ouders**, ik draag dit proefschrift graag aan jullie op. Ik zeg dit eigenlijk niet vaak maar ik ben jullie enorm dankbaar dat jullie Guy en mij altijd steunen, in elk opzicht. Naarmate ik ouder ben geworden heb ik geleerd dat dat niet altijd vanzelfsprekend is. Wij mogen ons als kinderen echt gelukkig prijzen. Jullie zijn zulke warme, leuke, lieve en gezellige mensen! Met het hart op de goede plek. Waren er maar meer exemplaren van jullie, daar zou de wereld ongetwijfeld baat bij hebben. Lieve mam, je vindt het vast onzin maar je bent toch wel een beetje een 'powervrouw' in mijn ogen; een harde werkster, oprecht, lief voor de kids en je kan echt als de beste koken! De grote lijnen van mijn promotie hield je in de gaten, de journals met mijn artikelen verzamelde je trots, en je wees me er vooral ook op dat er andere belangrijke dingen in het leven zijn naast werk. Lieve pap, je bent een echte nurd. Niemand was zo enthousiast over mijn promotie als jij:

manuscripten gingen mee op vakantie, talloze vragen over het begrip ‘utility’, en als ik langskwam wilde je graag met me zitten om het model te snappen en me ‘het hemd van het lijf te vragen’. Ik zat – met name in de weekenden – er niet altijd op te wachten maar uiteindelijk ben ik het toch erg gaan waarderen. Jouw interesse, steun en aanmoediging als het even niet mee zat, was en is voor mij enorm waardevol. Daarnaast kan ik met jou als de beste lachen en taarten bakken! Lieve ouders, dank voor jullie support en voor jullie onvoorwaardelijke liefde. <3

Lieve **Harmen**, nooit gedacht dat ik zo’n leuke vent in Amsterdam zou ontmoeten als jij. Een verhuizing, afronding van mijn promotie – het was soms een hectische tijd waar jij middenin belandde. Dank voor je geduld en vooral voor de persoon die je bent. We vormen een goed team en we genieten. Nu al een persoonlijk recordje, op naar jaren en jaren. <3

Curriculum Vitae

Ann-Jean Chavelli Carla Beck was born on July 30, 1989, in Leiden, the Netherlands. She grew up in Delft with her parents and her older brother Guyon, and attended primary school at the Delftsche Schoolvereeniging and secondary school (Gymnasium) at the Sint Stanislas College in Delft. After graduating Cum Laude in 2007, she started studying Medicine at the Leiden University Medical Center (LUMC). During her study, she completed a clinical internship at the Department of General Surgery and the Department of Emergency Medicine of the Academic Hospital Paramaribo in Paramaribo, Surinam. Together with her close friend Anouk Hagemeijer, she went to New York City, the United States, for a research internship at the Department of Emergency Medicine of New York-Presbyterian Brooklyn Methodist Hospital and Cornell University under the supervision of prof. dr. R.H. Birkhahn and drs. B.A. Byrd. Her first job was working as a resident not in training at the Department of General Surgery of the BovenIJ Hospital in Amsterdam. At the end of 2015, she started working as a PhD student at the Department of Head and Neck Surgery and Department of Psychosocial Research and Epidemiology in the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL). Her supervisors were prof. W.H. van Harten, prof M.W.M. van den Brekel and dr. V.R. Retèl. Her PhD was partially conducted at the Department of Head and Neck Surgery of the Massachussetts Eye and Ear Infirmary and Harvard Medical School in Boston, United States, in 2018 under the supervision of prof. dr. D.G. Deschler and G. Bunting, MS CCC-SLP. Parallel to her thesis she worked as a resident not in training at the outpatient clinic of the Department of Head and Neck Surgery.