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Cost-utility and cost-effectiveness of a guided self-help head and neck exercise program for patients treated with total laryngectomy: Results of a multi-center randomized controlled trial

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ABSTRACT

Objectives: The guided self-help exercise program called In Tune without Cords (ITwC) is effective in improving swallowing problems and communication among patients treated with a total laryngectomy (TL). This study investigated the cost-utility and cost-effectiveness of ITwC.
Materials and methods: Patients within 5 years after TL were included in this randomized controlled trial. Patients in the intervention group (n = 46) received access to the self-help exercise program with flexibility, range-of-motion and lymphedema exercises, and a self-care education program. Patients in the control group (n = 46) received access to the self-care education program only. Healthcare utilization (iMCQ), productivity losses (iPCQ), health status (EQ-5D-3L, EORTC QLU-C10D) and swallowing problems (SwalQol) were measured at baseline, 3- and 6-months follow-up. Hospital costs were extracted from medical files. Mean total costs and effects (quality-adjusted life-years (QALYs) or SwalQol score) were compared with regression analyses using bias-corrected accelerated bootstrapping.
Results: Mean total costs were non-significantly lower (-€685) and QALYs were significantly higher (+0.06) in the intervention compared to the control group. The probability that the intervention is less costly and more effective was 73%. Sensitivity analyses with adjustment for baseline costs and EQ-5D scores showed non-significantly higher costs (+€119 to +€364) and QALYs (+0.02 to +0.03). A sensitivity analysis using the QLU-C10D to calculate QALYs showed higher costs (+€741) and lower QALYs (-0.01) and an analysis that used the SwalQol showed higher costs (+€232) and higher effects (improvement of 6 points on a 0–100 scale).
Conclusion: ITwC is likely to be effective, but possibly at higher expenses.
Trial Registration: NTR5255.

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Introduction

Head and neck cancer (HNC) patients often experience HNC-specific symptoms such as speech, swallowing and shoulder problems [1,2]. In the last decade, several supportive care interventions, have been developed targeting speech, swallowing and shoulder problems among HNC patients [3–16]. These interventions have, in general, been shown to be effective [4–14,16]. Besides evidence of the effectiveness, however, information about the cost-utility or cost-effectiveness (costs per unit of effect) of such interventions is needed, as economic resources are limited and decisions have to be made about which interventions are implemented and reimbursed in daily clinical practice.

So far, four studies focused on the cost-utility of interventions targeting swallowing problems or voice problems among HNC patients. Rétel et al. (2011) [17] showed that a preventive swallowing exercise program for advanced HNC patients treated with chemoradiotherapy was more effective in terms of quality-adjusted life-years (QALYs), but more costly from a healthcare perspective compared to a group that did not receive preventive exercises. Another study by Rétel et al. (2016) [18] showed that device-based exercises (TheraBite) targeting swallowing problems among advanced HNC patients treated with chemoradiotherapy was more effective in terms of QALYs, while total healthcare costs were lower compared to a group with protocol-guided swallowing exercises provided by a speech therapist. Wall et al. (2019) [19] found that an intensive prophylactic swallowing intervention performed at home via a telepractice application called SwallowIT for oropharyngeal cancer patients during (chemo)radiotherapy shows comparable effects and lower societal costs compared to face-to-face therapy by a speech therapist, while higher effects and higher costs were found when compared to independent patient-directed therapy. Finally, Johansson et al. (2020) [20] reported that a rehabilitation program provided by speech therapists targeting voice problems among laryngeal cancer patients treated with (chemo)radiotherapy was more effective in terms of QALYs, compared to a group that received general vocal hygiene advice. Total costs were higher from a healthcare perspective, but lower when all societal costs (including healthcare costs) were taken into account.

Studies thus far have shown that interventions targeting swallowing or voice problems have the potential to be effective at additional costs or even lower costs. No such study have targeted the combination of speech, swallowing and shoulder problems. Nor have any studies targeted HNC patients treated with major surgery such as a total laryngectomy (TL), while speech, swallowing and shoulder problems are frequently reported among such patients [21–25].

This study, therefore, aimed to investigate the cost-utility and cost-effectiveness of a guided self-help exercise program aiming to prevent or diminish speech, swallowing and neck and shoulder problems in patients treated with TL from both a societal and healthcare perspective. This intervention was developed for TL patients specifically and is built into the (online) application In Tune without Cords (ITwC) [16,26–28]. This guided self-help exercise program has previously been found to be effective in improving patient-reported swallowing problems and communication [16].

Methods

Design, study population and randomization

The design of the study has been described previously [16,28]. In short, this multi-center randomized controlled trial was conducted in five HNC centers throughout the Netherlands. From June 2015 to January 2018 patients were approached to participate. Inclusion criteria were TL within the past five years. Exclusion criteria were treatment with TL combined with total glossectomy, treatment with a partial laryngectomy, age <18 years, having cognitive impairments, and/or being unable to understand the Dutch language. Patients were asked to participate by their treating head and neck surgeon, speech therapist or nurse specialist/practitioner.

After signing informed consent, patients were randomized (1:1) to the intervention or control group by an independent person in blocks of two and four using an automatically created randomization list. Randomization was stratified for time since TL (≤6 months vs. >6 months), neck dissection (treated vs. not), and primary or salvage TL indication. Patients randomized to the intervention group received access to the guided self-help exercise program and the self-care education program. Patients randomized to the control group received care as usual and had access to the self-care education program.

All patients provided written informed consent. The study is registered in the Dutch Clinical Trial register (NTR5255) and was approved by the Medical Ethics Committee of the VU University Medical Center (2014.514).

Self-help exercise program

The guided self-help exercise program consists of flexibility and range-of-motion exercises for head, neck, shoulders, tongue, lips, and jaw. In addition, for patients with facial lymphedema, five additional exercises were provided targeting facial lymphedema. At the start of the intervention, patients randomized to the intervention group were invited to the hospital for an instruction session in which the prescribed exercises were explained. At the end of the session patients were instructed to perform the exercises at home, three times a day for 12 weeks, using the written instructions, images and videos of the online application or booklet with DVD version of ITwC. Patients were coached by their speech therapist or nurse practitioner/specialist via e-mail or telephone on a weekly basis. For more information see the previous publication [28].

Self-care education program

The self-care education program of ITwC provides information and advice on self-care for TL patients via written information, photos and videos. Topics discussed are stoma care, voice prosthesis care, speech, smell, nutrition and mobility. More information can be found in previous publications [27,28].

Outcome assessment

To investigate the cost-utility and cost-effectiveness of the guided self-help exercise program, patient-reported outcome measures were collected before randomization, immediately after the intervention or control period (at three months follow-up) and at six months follow-up. In addition, healthcare utilization data was extracted from medical files.

The EQ-5D-3L and the EORTC QLU-C10D were used to measure patient's health status. The EQ-5D-3L contains five items measuring problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression [29]. Patients can answer they have no problems, some problems or extreme problems. The EORTC QLU-C10D consists of 13 items covering 10 domains of the EORTC QLQ-C30 [30], namely physical functioning, emotional functioning, social functioning, role functioning, pain, fatigue, sleep problems, appetite loss, nausea, and bowel problems [31]. On each of these domains, patients can get a score ranging from level 1 (no impairments in functioning or no symptoms) to level 4 (very much impaired in functioning or many symptoms). The resulting profile of answers on the EQ-5D-3L and the EORTC QLU-C10D can be transformed to a utility score given by the general public using Dutch utility weights [29,32]. QALYs are calculated by multiplying the length of time spend in a particular health state by the corresponding utility score.

The SwalQoL was used to measure swallowing problems [33]. Based on 23-items of the domains on food selection, eating duration, eating desire, fear, burden, mental health and social functioning a total

SwalQoL score can be calculated ranging from 0 to 100 (no to severe swallowing problems).

Healthcare usage and received informal care was measured using the medical consumption questionnaire (iMCQ) [34] and by extracting data from medical files using a study-specific form. The iMCQ contains questions on visits to different care providers, received personal care by a visiting nurse or nurse assistant, received home care, received informal care, participation in support groups and used medication in the last 3 months. The study-specific form contained items on HNC-related visits to the medical specialist, HNC-related day treatment and hospitalization and was completed by extracting data from medical files. Costs of healthcare and costs of received informal care were calculated as units of resource use multiplied by the integral cost price per unit [35]. Costs of travelling to healthcare services were calculated as number of visits multiplied by the average distance to the location multiplied by €0.19 per kilometer. All prices were adjusted to 2017 prices using the consumer price index.

Productivity losses in the last 3 months were measured using the productivity costs questionnaire (iPCQ) [36]. This instrument measures productivity losses from formal work due to absenteeism and presenteeism. Absenteeism was measured as the number of days absent from work. Presenteeism was measured as the number of days with less productivity at work (while being at work) multiplied by the perceived amount of lost quantity of work on a 11-point scale. Total absenteeism and presenteeism costs were calculated by multiplying both productivity losses by the price of one hour paid work adjusted to 2017 prices (i.e. €36.38) using the friction cost approach [35].

Intervention costs consisted of the costs of one visit to a speech therapist (€31 per visit) for instructions on the exercise program summed with the costs of 15 min for coaching by telephone or e-mail per week (valued as 0.5 visit) for 12 weeks. For usage of the intervention €250 was added (total costs for ICT, hosting services, maintenance of the program, printing costs and taxes estimated at €12,500 per year divided by 50 users per year). This equals to €467 per patient.

Sociodemographic characteristics (age, gender, education and living situation) were collected using questionnaires and clinical characteristics (cancer stage, cancer treatment, time since TL and co-morbidity) were collected from medical files using a study-specific form. Comorbidity was measured using the Adult Comorbidity Evaluation 27 (ACE-27) [37].

Statistical analyses

All analyses were performed using the IBM Statistical package for the Social Science (SPSS) version 26 (IBM Corp., Armonk, NY USA) and STATA version 14.1 (StataCorp LP, Texas, USA). Descriptive statistics were generated for all socio-demographic and clinical characteristics, utility measures, SwalQol total score and cost categories. Chi-square tests and independent t-tests were used to analyze whether randomization resulted in comparable patient groups.

To measure the cost-utility of the guided self-help exercise intervention, first a base case cost-utility analysis was performed in agreement with the intention-to-treat principle using regression analyses with bias-accelerated bootstrapping and multiple imputation for missing data (for more details, see below). We did not adjust for baseline variables in this base case analysis. Total costs were measured from a societal perspective, including intervention costs, costs of healthcare, cost for patients and their families (e.g. informal care costs or travelling costs) and productivity losses. QALYs were measured using the EQ-5D-3L. Incremental costs were calculated as (C_{int} − C_{con}) and incremental QALYs as ($QALY_{int}$ − $QALY_{con}$). To study the uncertainty surrounding the incremental cost and QALY estimate, we used bootstrapping with 5000 replications. Results were projected on a cost-utility plane. In addition, a cost-utility acceptability curve was plotted, which presents the probability that the intervention is cost-effective compared to the control group for different willingness-to-pay thresholds for one QALY.

Table 1
Baseline sociodemographic and clinical characteristics.

	Control group (n = 46)		Intervention group (n = 46)		
	Number	%	Number	%	P-value
Age (years)					0.58
mean (SD)	64 (9)		65 (7)		
Gender					0.16
– men	41	89.1%	36	78.3%	
– women	5	10.9%	10	21.7%	
Living situation[1]					0.20
– living alone	7	15.6%	12	26.7%	
– living together (with partner and/or children)	38	84.4%	33	73.3%	
Education level[1]					0.41
– elementary	5	11.1%	4	8.9%	
– lower	22	48.9%	16	35.6%	
– secondary	7	15.6%	13	28.9%	
– higher	11	24.4%	12	26.7%	
Employment status					0.36
– employed in paid work	5	10.9%	10	21.7%	
– not employed or not able to work	17	37.0%	14	30.4%	
– retired	24	52.2%	22	47.8%	
Time since total laryngectomy (months)					
Mean (SD)	19 (15)		24 (18)		0.11
– < 6 months	10	21.7%	10	21.7%	1.00
– 6 months–5 years	36	78.3%	36	78.3%	
Type of total laryngectomy					1.00
– primary	21	45.7%	22	47.8%	
– salvage	25	54.3%	24	52.2%	
Treated with a neck dissection					1.00
– yes	31	67.4%	31	67.4%	
– no	15	32.6%	15	32.6%	
Surgery prior to total laryngectomy					0.40
– yes	9	19.6%	6	13.0%	
– no	37	80.4%	40	87.0%	
Treatment with (chemo) radiation before or after total laryngectomy					0.56
– yes	38	82.6%	40	87.0%	
– no	8	17.4%	6	13.0%	
Comorbidity[2]					0.64
– none	11	23.9%	13	26.4%	
– mild	25	54.3%	20	44.4%	
– moderate/severe	10	21.7%	12	26.7%	

Abbreviations: NA, not assessed due to small number.
[1] Missing in two patients.
[2] Missing in one patient.

To investigate the robustness of this base case cost-utility analysis, six sensitivity analyses were performed: (a) an analysis in which only patients with complete data were included; (b) an analysis with adjustment for total costs and EQ-5D utility score at baseline; (c) an analysis from a healthcare perspective; (d) an analysis in which a cheaper version of ITwC (without a personal account) is evaluated (€317 in total); (e) an analysis in which QALYs were measured using the EORTC QLU-C10D; and (f) a cost-effectiveness analysis in which incremental costs were compared to incremental effects on swallowing problems (SwalQol) at 6 months follow-up.

Missing data on item level (e.g. a patient reported to have visited a physiotherapist, but did not report the number of visits) was resolved by making assumptions based on means per group and time point. In case data was missing on questionnaire level, total costs or utility outcomes at that specific timepoint were imputed per study arm using multiple imputation by chained equations (predictive mean matching). Variables associated with costs (gender, work, time since TL and EORTC QLQ-C30 sum score [38] for societal costs and gender, education and EORTC QLQ-

Table 2
Mean costs per time point of patients with complete data.

	Reference price per unit (€)	Control group				Intervention group			
		Baseline[1] n = 46 Mean (SD)	3 months follow-up[1] n = 44 Mean (SD)	6 months follow-up[1] n = 40 Mean (SD)	From t0 to t2[2] n = 46 Mean (SD)	Baseline[1] n = 46 Mean (SD)	3 months follow-up[1] n = 35 Mean (SD)	6 months follow-up[1] n = 34 Mean (SD)	From t0 to t2[2] n = 46 Mean (SD)
Costs of healthcare		1006 (1466)	1181 (1897)	1134 (1601)		706 (1083)	473 (785)	591 (1154)	
General practitioner	17, 34, 51[3]	118 (214)	116 (206)	81 (106)		49 (56)	38 (55)	35 (46)	
Occupational physician	70	21 (61)	18 (48)	9 (36)		9 (38)	10 (42)	6 (27)	
Social worker	67	52 (296)	15 (54)	10 (29)		3 (14)	0 (–)	22 (115)	
Physiotherapist	34	149 (256)	147 (238)	170 (315)		70 (157)	113 (258)	107 (201)	
Occupational therapist	34	4 (30)	25 (123)	0 (–)		0 (–)	6 (29)	0 (–)	
Dietitian	30	11 (21)	5 (15)	9 (31)		11 (32)	5 (19)	4 (10)	
Speech therapist	31	78 (129)	51 (121)	71 (175)		34 (74)	52 (100)	26 (62)	
Oral hygienist	26	11 (17)	12 (24)	8 (13)		8 (15)	6 (11)	3 (9)	
Psychological help	96	29 (92)	109 (423)	23 (104)		13 (60)	6 (33)	17 (60)	
Spiritual care	132	0 (–)	0 (–)	0 (–)		9 (43)	4 (22)	8 (45)	
Home care (cleaning)	20	54 (164)	63 (179)	46 (165)		29 (146)	18 (90)	14 (82)	
Personal care	51	48 (294)	271 (1328)	170 (750)		72 (452)	70 (414)	36 (210)	
Visiting nurse	75	203 (1025)	66 (289)	206 (906)		249 (814)	90 (532)	0 (–)	
Medication	Differs	152 (232)	218 (376)	172 (337)		122 (341)	56 (67)	102 (247)	
Support groups	65	75 (299)	65 (306)	159 (527)		28 (137)	0 (–)	212 (934)	
Specialist	167				1078 (755)				759 (622)
Day treatment	310				566 (2127)				47 (173)
Hospitalization	487				445 (1942)				1122 (3635)
Costs for patients and their families		440 (1153)	125 (326)	92 (279)		213 (574)	290 (638)	123 (300)	
Alternative medicine	62	1 (9)	1 (9)	0 (–)		4 (27)	4 (21)	0 (–)	
Informal care	15	426 (1152)	108 (318)	82 (278)		203 (574)	280 (638)	116 (297)	
Transport and parking costs	0.19	13 (15)	15 (31)	10 (14)		6 (11)	7 (11)	6 (8)	
Other costs (e.g. productivity losses)		272 (1845)	215 (1426)	12 (74)		170 (918)	141 (633)	142 (450)	
Absenteeism paid work	36.38	272 (1845)	215 (1426)	0 (–)		126 (628)	42 (246)	58 (239)	
Presenteeism paid work	36.38	0 (–)	0 (–)	12 (74)		45 (300)	100 (590)	84 (289)	
Total cost		1719 (3011)	1520 (2431)	1238 (1645)		1089 (1622)	880 (1267)	832 (1323)	

Abbreviations: SD, standard deviation; n, sample size
[1] Measured using the iMCQ and iPCQ with a recall period of 3 months.
[2] Measured using data of the hospital information system from baseline up to 6 months follow-up.
[3] Reference price for contact via telephone, practice visit and home visit respectively.

C30 sum score for healthcare costs), utility scores (education, Shoulder Disability Questionnaire total score [39] and EORTC QLQ-C30 sum score for EQ-5D and education and living situation for the EORTC QLU-C10D), SwalQol score (education, living situation, Speech Handicap Index total score [33] and EORTC QLQ-C30 sum score) or missing data (none) were included in the multiple imputation model. Per imputation ten imputed data sets were created. Results of the ten data sets were pooled using Rubin's (1987) rules.

Results

Study population

In total, 253 patients were approached to participate in this study, of which 233 patients responded (92%). Of these patients, 92 patients were willing to participate (39%) and were randomized in the intervention group (n = 46) or control group (n = 46) (Table 1). No significant differences were shown between the two groups regarding sociodemographic and clinical characteristics. However, as previously described [16], significant baseline differences were found on sleep (SwalQol) and

Table 3
Mean EQ-5D and EORTC QLU-C10D utility score and total SwalQol score per time point of patients with complete data.

Time point	Control group Mean (SD)	Intervention group Mean (SD)
EQ-5D-3L		
Baseline (n = 92)	0.76 (0.26)	0.85 (0.17)
3 months follow-up (n = 80)	0.75 (0.28)	0.86 (0.21)
6 months follow-up (n = 79)	0.77 (0.26)	0.88 (0.19)*
EORTC QLU-C10D		
Baseline (n = 88)	0.73 (0.24)	0.88 (0.13)*
3 months follow-up (n = 79)	0.78 (0.25)	0.87 (0.20)
6 months follow-up (n = 77)	0.79 (0.21)	0.85 (0.20)
SwalQol		
Baseline (n = 91)	32.7 (16.3)	29.2 (16.9)
3 months follow-up (n = 81)	31.4 (17.6)	28.4 (16.2)
6 months follow-up (n = 78)	35.0 (17.9)	25.8 (17.1)*

Abbreviations: SD, standard deviation; n, sample size.
[*] Significant difference (p-value <0.05).

Table 4
Results of the different cost-utility and cost-effectiveness analyses.

	Costs (€) Mean (SEM)	QALYs Mean (SEM)	Incremental costs € [95% CI]	Incremental effects QALYs or SwalQol [95% CI]	Quadrant[1] North-east	South-east	South-west	North-west
Base case analysis			−685 [−2957 to 1365]	0.06 [0.01 to 0.10]*	27%	73%	0%	0%
– Control group (n = 46)	4859 (885)	0.38 (0.02)						
– Intervention group (n = 46)	4174 (683)	0.44 (0.01)						
Complete case analysis			−1461 [−3706 to 182]	0.05 [−0.001 to 0.10]	7%	90%	2%	0%
– Control group (n = 38)	4617 (901)	0.38 (0.02)						
– Intervention group (n = 32)	3156 (367)	0.43 (0.02)						
Analysis adjusted for societal costs and EQ-5D utility score			364 [−1278 to 2221]	0.03 [−0.01 to 0.06]	63%	31%	1%	5%
– Control group (n = 46)	N.A.	N.A.						
– Intervention group (n = 46)	N.A.	N.A.						
Analysis from a healthcare perspective[2,3]			218 [−1210 to 2044]	0.02 [−0.01 to 0.06]	52%	37%	3%	8%
– Control group (n = 46)	N.A.	N.A.						
– Intervention group (n = 46)	N.A.	N.A.						
Analysis with lower intervention costs[2,4]			119 [−1305 to 1928]	0.03 [−0.01 to 0.06]	48%	41%	4%	7%
– Control group (n = 46)	N.A.	N.A.						
– Intervention group (n = 46)	N.A.	N.A.						
Analysis using the EORTC QLU-C10D to measure QALYs[2,5]			741 [−991 to 2623]	−0.01 [−0.04 to 0.01]	11%	4%	17%	69%
– Control group (n = 46)	N.A.	N.A.						
– Intervention group (n = 46)	N.A.	N.A.						
Analysis using the total SwalQol score at 6 months follow-up[2,6,7]			232 [−1421 to 2171]	6 [2 to 11]*	61%	39%	0%	0%
– Control group (n = 46)	N.A.	N.A.						
– Intervention group (n = 46)	N.A.	N.A.						

Abbreviations: n, sample size; N.A., not applicable; SEM, standard error of the mean; 95% CI, 95% confidence interval, ICER/ICUR, incremental cost-effectiveness/utility ratio.

* Significant difference between the two groups ($p < 0.05$).

[1] Probability that the incremental costs and effects lies in the north-east (more expensive and more effective), south-east (less expensive and more effective, i.e. the most favorable outcome), south-west (less expensive and less effective) and north-west (more expensive and less effective, i.e. the least favorable outcome) quadrant.

[2] As adjustment for costs and EQ-5D utility score at baseline had a major influence on incremental costs and incremental effects (change of >20%), all other sensitivity analyses were also adjusted for baseline values.

[3] Adjusted for healthcare costs and EQ-5D utility score at baseline.

[4] Adjusted for societal costs and EQ-5D utility score at baseline.

[5] Adjusted for societal costs and EORTC QLU-C10D utility score at baseline.

[6] Adjusted for societal costs and total SwalQol score at baseline.

[7] Patients in the intervention group had on average a 6 points lower (i.e. better) SwalQol score. To facilitate interpretation of the cost-effectiveness analysis in such a way that it is in line with the interpretation of the cost-utility analyses, the incremental effects on the SwalQol score were reverse scored.

several EORTC QLQ-C30 domains, in favor of the intervention group.

Costs, utility scores and SwalQol score at baseline in the control and intervention group

Mean total costs as measured using the iMCQ and iPCQ over the last 3 months at baseline were €1719 (standard deviation (SD) = 3011) in the control group and €1089 (SD = 1622) in the intervention group ($p = 0.22$). The utility score at baseline was 0.76 (SD = 0.26) in the control group and 0.85 (0.17) in the intervention group as measured using the EQ5D ($p = 0.06$) and 0.73 (0.24) and 0.88 (0.13) as measured using the EORTC QLU-C10D ($p = 0.001$). Total SwalQol score at baseline was 32.7 (16.3) in the control group and 29.2 (16.96) in the intervention group ($p = 0.32$). Tables 2 and 3 present the costs, utility scores and SwalQol scores of patients with complete data at all other timepoints.

Cost-utility analyses

Results of all cost-utility and cost-effectiveness analyses are presented in Table 4. In the base case analysis, total costs were non-significantly lower (-€685) and QALYs were significantly higher (+0.06) in the intervention group compared to the control group. This resulted in a probability of 73% that the intervention is both less costly and more effective in terms of QALYs (Fig. 1). Of the sensitivity analyses, the complete case analysis showed more or less comparable findings (non-significantly lower costs (-€1461) and non-significantly higher QALYs (+0.05)). All other EQ-5D sensitivity analyses (with adjustment for baseline costs and EQ-5D scores), however, showed evidence for non-significantly higher costs in the intervention group compared to the control group (+€119 to +€364) and non-significantly higher effects (+0.02 to +0.03 QALY). When willing to pay €20,000 per QALY the probability that the intervention is cost-effective ranged from 57% to 64% in these three sensitivity analyses, this increased to 65%-70% at a willingness to pay threshold of €30,000/QALY. Fig. 2 shows the cost-

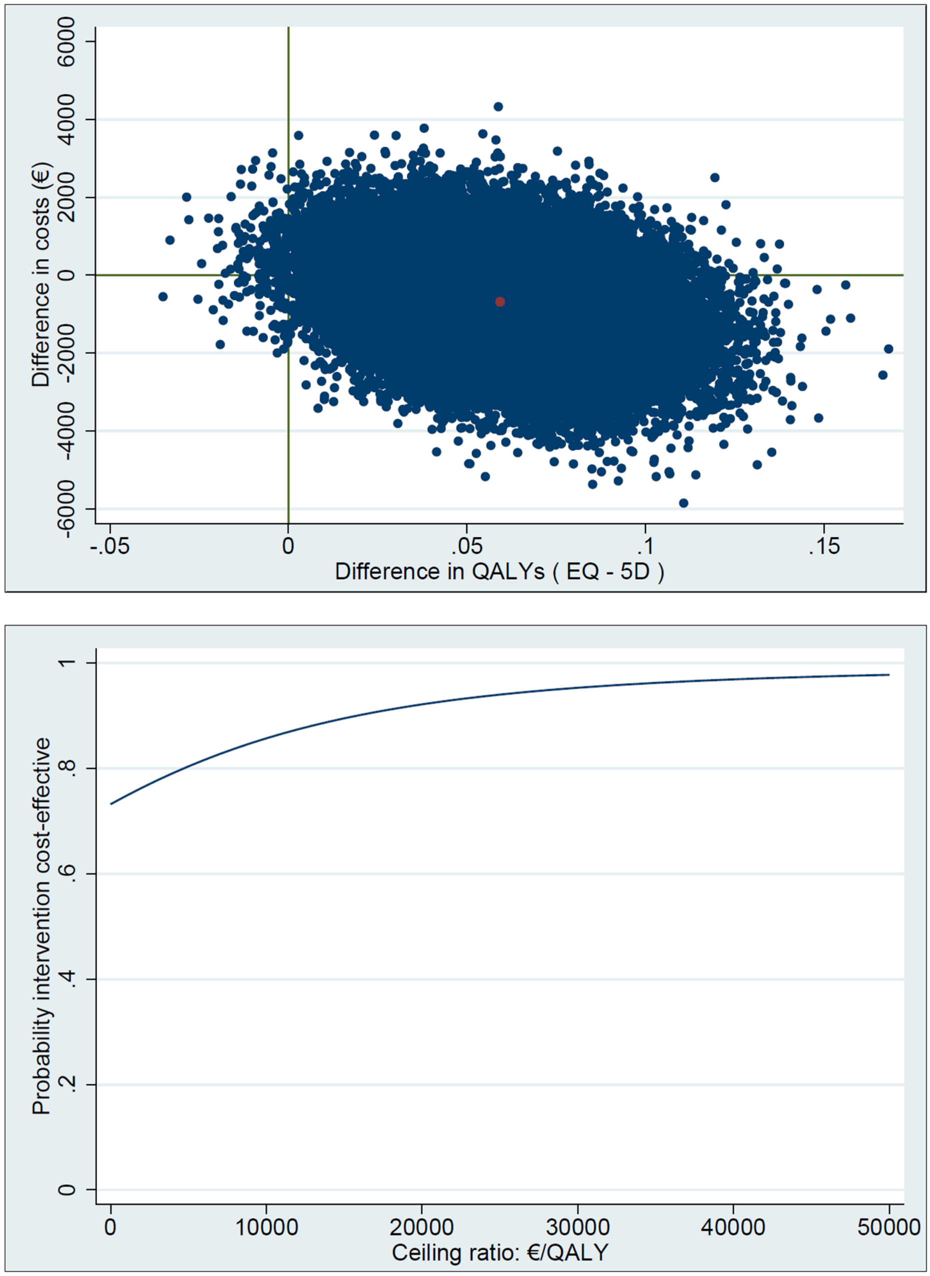


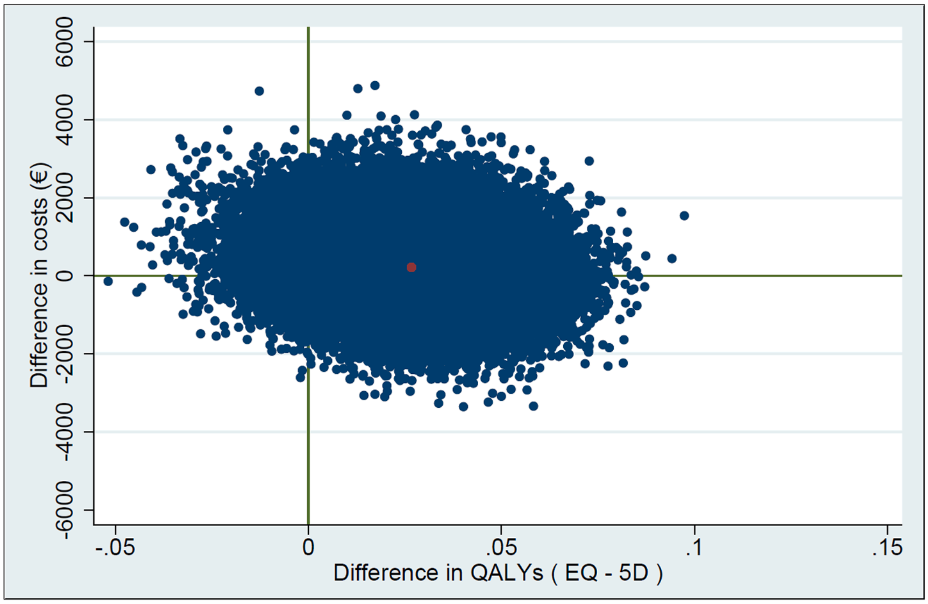
Fig. 1. Cost-utility plane and cost-utility acceptability curve of the base case analysis (without adjustment).

utility acceptability curve of the analysis with lower intervention costs, as an example. In the sensitivity analyses in which QALYs were calculated using EORTC QLU-C10D utility scores (with adjustment for baseline costs and EORTC QLU-C10D scores), total costs were €741 higher and QALYs were 0.01 lower in the intervention group (both non-significant). The probability that the intervention group is inferior to the control group, that is higher costs with lower effects, was 69%. Finally, the cost-effectiveness analysis on SwalQol scores at 6 months follow-up (with adjustment for baseline costs and SwalQol scores) showed that total costs were €232 higher, while effects were significantly better (difference of 6 points on a 0–100 scale) in the intervention group compared to the control group. At a willingness-to-pay threshold of €100 per point improvement, the intervention had a probability of 67% to be cost-effective increasing to 98% at a willingness to pay threshold of €500.

Discussion

This study investigated the cost-utility and cost-effectiveness of a guided self-help exercise program to prevent or diminish speech, swallowing and neck and shoulder problems in patients treated with TL. The base case analysis and complete case analysis suggest that the intervention is more effective in terms of QALYs and slightly less costly than control care. However, four sensitivity analyses suggest that the intervention is slightly more effective in terms of QALYs and swallowing problems, but at additional costs. One additional sensitivity analysis using the EORTC QLU-C10D as utility instrument showed that the intervention is slightly less effective and more costly.

In all cost-utility analyses that used the EQ-5D utility instrument and the cost-effectiveness analysis using swallowing problems as outcome, it was found that the intervention group is slightly more effective. Although not in all analyses statistically significant and clinically relevant (e.g. the difference of 6 points on the SwalQoL is lower than the



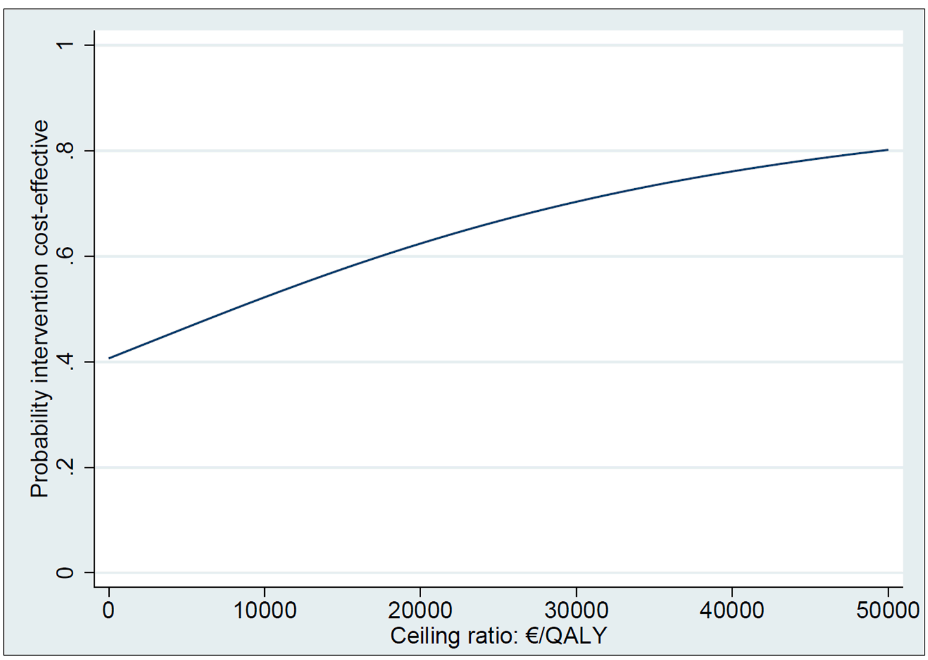


Fig. 2. Cost-utility plane and cost-utility acceptability curve of the analysis with lower intervention costs and with adjustment for costs and EQ-5D utility score at baseline.

clinical relevant difference of 12 points [33]). Findings on these effects are, however, supported by results of our effectiveness study that showed that the guided self-help exercise intervention is effective in improving patient-reported swallowing problems and communication among TL patients [16]. In the sensitivity analysis that used the EORTC QLU-C10D utility instrument (which is based on 13 items of the EORTC QLQ-C30 [31,32]) to measure QALYs, it was found that the intervention is slightly (non-significantly) less effective in terms of QALYs compared to the control group. To our knowledge, this is the first study that uses the EORTC QLU-C10D in cost-utility analyses of supportive care interventions. Further insight is needed into the additional value of using the EORTC QLU-C10D alongside the EQ-5D in such studies. The absence of an effect on QALYs as measured using the EORTC QLU-C10D in this study may result from the statistically significant difference in favor of the intervention group at baseline, for which we adjusted in this sensitivity analyses. In our effectiveness study, also no statistically significant differences were found on the different EORTC QLQ-C30 domains after adjustment for baseline differences [16].

Results on incremental costs differed from on average €1472 lower costs (complete case analysis) to €741 higher costs in the intervention group compared to the control group (EORTC QLU-C10D analyses). All analyses that adjusted for baseline differences in effects and costs showed non-significantly higher costs in the intervention group, suggesting that the guided self-help exercise intervention is effective at additional costs. Previous studies on the cost-utility of interventions targeting swallowing or voice problems also found mixed results on incremental costs [17–20]. These mixed results on incremental costs may be related to the type of intervention investigated. However, it may also be related to the design of the study. Previous studies showed higher healthcare costs when the intervention group was compared to a less active control group (without preventive exercises, with independent patient-directed therapy or vocal hygiene advice only) [17,19,20].

Lower or more or less equal costs were found in case the intervention was compared to a comprehensive care as usual group (therapy provided by a speech language therapist) [18,19]. In our study we also compared our intervention group to a less active control group (self-care education only), although both groups also received standard care usual, which might explain the higher costs in the intervention group when adjusted for baseline differences.

Whether the additional expenses of the guided self-help exercise intervention are acceptable depends on the willingness to pay per additional QALY. In the Netherlands the willingness to pay threshold ranges from 20,000 €/QALY to 50,000 €/QALY, depending on the severity of the illness or condition [40]. In other countries, based on the National Institute for Health and Care Excellence (NICE) often a willingness to pay threshold of 20,000–30,000 £/QALY is used (currently equaling to approximately 22,400–33,600 €/QALY) [41]. Also, the gross domestic product per capita is often recommended as willingness to pay threshold, which was €43,088 per capita in the Netherlands in 2017 [42,43]. Using a willingness to pay threshold of €20,000, we found that the guided self-help exercise intervention has a probability of 57% to be cost-effective (base case analyses adjusted for baseline differences). This increased to 62% in the analysis with lower intervention costs. At a willingness to pay threshold of 30,000 €/QALY this further increased to 65% and 70%. Currently, the intervention costs are relatively high due to the ICT costs of the intervention and the limited number of potential users (it is estimated that 150–160 patients are treated with TL per year in the Netherlands) [44,45]. To realize ICT costs reductions, it may be beneficial to combine various eHealth interventions targeting (head and neck) cancer patients on one eHealth platform.

A strength of this study is that multiple sensitivity analyses were performed. In addition, both healthcare costs and other societal costs were included in the analyses. A limitation is that this study was not powered to perform cost-utility analyses. Another limitation is the low participation rate of 39% in our study, which may limit representativeness of our findings to all TL patients. Also, all patients in the control group received the self-care education program of ITwC in addition to care as usual, which may have limited the effectiveness of the study.

In conclusion, our study indicate that the self-help exercise program added to the self-care education program of ITwC is slightly more effective compared to the control group who only received the self-care education program, but possibly at slightly higher expenses. This study increases the evidence on self-help interventions targeting cancer patients and contributes to sustainable supportive cancer care in a (cost-) effective manner.

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Conflict of interest statement

IV obtained funding for research related to In Tune without Cords from the Michel Keijzer Fund (institutional funding). The other authors declare that they have no competing interests.

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