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Economic Evaluation

Cost-Effectiveness of Pulmonary Rehabilitation in Patients With Bronchial Asthma: An Analysis of the EPRA Randomized Controlled Trial

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ABSTRACT

Objectives: At 3 months after the intervention, this study evaluates the cost-effectiveness of a 3-week inpatient pulmonary rehabilitation (PR) in patients with asthma compared with usual care alongside the single-center randomized controlled trial—Effectiveness of Pulmonary Rehabilitation in Patients With Asthma.

Methods: Adopting a societal perspective, direct medical costs and productivity loss were assessed using the Questionnaire for Health-Related Resource Use-Lung, a modification of the FIM in an Elderly Population. The effect side was operationalized as minimal important differences (MIDs) of the Asthma Control Test (ACT) and the Asthma Quality of Life Questionnaire (AQLQ) and through quality-adjusted life-years (QALYs) gained. Adjusted mean differences in costs (gamma-distributed model) and each effect parameter (Gaussian-distributed model) were simultaneously calculated within 1000 bootstrap replications to determine incremental cost-effectiveness ratios (ICERs) and to subsequently delineate cost-effectiveness acceptability curves.

Results: PR caused mean costs per capita of €3544. Three months after PR, we observed higher mean costs (Δ€3673; 95% confidence interval (CI) €2854-€4783) and improved mean effects (ACT Δ1.59 MIDs, 95% CI 1.37-1.81; AQLQ Δ1.76 MIDs, 95% CI 1.46-2.08; QALYs gained Δ0.01, 95% CI 0.01-0.02) in the intervention group. The ICER was €2278 (95% CI €1653-€3181) per ACT-MID, €1983 (95% CI €1430-€2830) per AQLQ-MID, and €312 401 (95% CI €209 206-€504 562) per QALY gained.

Conclusions: Contrasting of PR expenditures with ICERs suggests that the intervention, which achieves clinically relevant changes in asthma-relevant parameters, has a high probability to be already cost-effective in the short term. However, in terms of QALYs, extended follow-up periods are likely required to comprehensively judge the added value of a one-time initial investment in PR.

Keywords: asthma, asthma control, health economic evaluation, health-related quality of life, inpatient rehabilitation.

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Introduction

According to the Global Initiative for Asthma, bronchial asthma is a common, heterogeneous respiratory disease characterized by chronic airway inflammation[1] that manifests in wheeze, shortness of breath, chest tightness, and cough. These symptoms vary over time, especially in terms of to their intensity.[1,2] Asthma prevalence in the adult German population is estimated at 6.2%.[2]

Because asthma is currently incurable, treatment is aimed at achieving asthma control through combinations of medication (eg, inhaled corticosteroids [ICS]), correct inhalation techniques and nonpharmacologic interventions (eg, patient education, breathing retraining) for symptom control, optimizing lung function, and risk reduction of acute worsening of symptoms (so-called exacerbations).[1] However, asthma control in Europe remains poor, highlighting the need for new and improved approaches for asthma management.[3]

Despite scarce evidence, pulmonary rehabilitation (PR) is recommended in German asthma guidelines as a multimodal therapy in the event of physical, social, or psychological consequences of asthma affecting the patient's ability to perform routine activities or participate in daily life.[4,5] In Germany, rehabilitation services are usually implemented as a 3-week inpatient program funded by several payers of the social insurance system (ie, [predominately] Statutory Pension Insurance, Statutory Health Insurance, Statutory Occupational Accident Insurance).[6]

Most evidence on the effectiveness of PR is based on observational studies, but only very few randomized controlled trials (RCTs) have been conducted in the field of asthma: one of only 2 RCTs reported reduced work absenteeism after inpatient PR,[7] and the other reported improved health-related quality of life (HRQoL) after outpatient PR.[8] In addition, several RCTs and reviews reported positive effects of the individual core components of PR, such as patient education, exercise training, and breathing retraining on asthma control and HRQoL.[9-15]

In the light of scarce resources, effectiveness data are not sufficient to comprehensively appraise the additional value of an intervention. Therefore, it becomes all the more important to determine whether additional effects and therewith associated costs are well balanced. In addition, regarding PR in asthma, cost-effectiveness information is urgently required: Asthma is the most common reason for conducting PR in Germany,[16] and asthma that is not well controlled is associated with high socioeconomic burden.[17]

The single-center RCT Effectiveness of Pulmonary Rehabilitation for Patients with Asthma (EPRA) conducted in the Bad Reichenhall Clinic in Germany investigated—in addition to clinical effectiveness—the cost-effectiveness of a 3-week inpatient PR with regard to asthma control and asthma-specific HRQoL, both measured 3 months after rehabilitation. Furthermore, a quality-adjusted life-year (QALY)–based cost-utility analysis was conducted.

Methods

Study Population

Between June 2015 and August 2017, 436 patients were randomized. The inclusion criterion was a confirmed diagnosis of asthma, which was not well controlled according to the Asthma Control Test (ACT $<$ 20). The ACT assesses the level of asthma control using 5 items related to asthma symptoms that are answered on a 5-point Likert scale. Responses to each item are summed up to yield a score ranging from 25 (complete asthma control) to 5 (no asthma control) with scores of $<$20 indicating asthma that is not well controlled.[18]

Patients were excluded if they had inadequate German language ability, cognitive impairments, or severe concomitant diseases that most likely mask the results of asthma rehabilitation (eg, cancer, severe cardiac or psychiatric comorbidities).[19]

Study Design and Data Collection

The EPRA trial followed a waiting-list design. Randomization to the intervention group (IG) or the control group (CG) was performed in order of receipt of written declarations of consent. The randomization list was stratified by age categories (≤54 years vs 55-64 years vs ≥65 years) drawn up externally by one of the authors (M.S.).

The 3-week PR followed recommendations of international guidelines[20,21] and included as mandatory nonpharmacologic group-based components physical training with endurance and strength training, whole-body-vibration training, comprehensive patient education regarding asthma and practical medical inhalation training, respiratory physiotherapy, and smoking cessation (for smokers only). In addition, patients received a guideline-oriented optimization of their asthma medication if needed.[22]

Furthermore, depending on patient needs, the following facultative group-based interventions were provided: education on allergen avoidance, Buteyko training, and counseling on adequate coughing techniques. Facultative individual offers included inspiration muscle and inhalation therapy. Finally, some optional components were offered on both an individual and a group basis. This applies to psychosocial support, psychotherapeutic interventions, and comprehensive nutrition counseling.[19]

The IG started PR within 4 weeks after randomization. The CG received care as usual until the end of the waiting period. Data were simultaneously collected for both groups at randomization as baseline (T0), beginning (T1), end (T2), and 3 months after PR (T3) of the IG. The CG started the same type of PR at T3. Data assessment points are visualized in the online supplement (Appendix Figure S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017).

The trial was approved by the ethics committee of the Bavarian Chamber of Physicians (Nr. 15017) and registered in the German Clinical Trials Register (DRKS00007740). Further details on the study design are found in the study protocol[19]; results of the main study question (ie, effectiveness with regard to asthma control) have been published elsewhere.[22]

Effects

Our primary analysis targeted at clinically relevant changes of asthma control, which was defined based on the minimal important difference (MID) of the ACT. This translates to a change of ≥3 points.[23]

Our secondary analysis addressed clinically relevant changes in asthma-specific HRQoL measured by the standardized version of the Asthma Quality of Life Questionnaire (AQLQ).[24] The AQLQ contains 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli) answered on 7-point Likert scales (1 = severely impaired; 7 = not impaired at all). The mean of all 32 items builds the AQLQ overall score with an established MID of 0.5 points.[25]

As a tertiary analysis, QALYs were assessed based on generic HRQoL measured using the 5-level EQ-5D questionnaire (EQ-5D-5L). We converted health states into utilities using the German time trade-off scoring algorithm.[26] Asthma-specific MIDs of EQ-5D are 12.3 points for the visual analog scale (VAS) part and 0.08 points for the utility part.[27] QALYs were subsequently calculated as the area under the curve of utilities measured at T0 and T3, respectively, in relation to a 1-year time frame.[28]

Costs

All-cause resource utilization was assessed by the Questionnaire for Health-Related Resource Use-Lung (FIM-Lu), a lung disease–specific modification of the validated FIM in an Elderly Population (FIMA).[29] At T0, FIM-Lu refers to the previous 12 months to incorporate usual service utilization (eg, medication, physician visits) but also episodic events (such as hospitalization). To best possibly focus on PR-induced changes, at T3, FIM-Lu addresses the previous 3 months (which reflect time between the end of PR for the IG and data assessment).

To reflect direct medical cost, we considered outpatient physician care (general practitioner [GP] and medical specialist), inpatient hospital care (general ward and intensive care unit), and prescribed medication. Indirect costs were operationalized based on days of work absenteeism. To achieve the monetary value of a lost working day, we assessed loss of gross value added per day through population-level data on annual working days lost and gross value added per year of acquisition provided by the Federal Statistical Office of the Federal Republic of Germany. In case of part-time work, indirect costs were adapted correspondingly. Adopting a societal perspective, costs were calculated from patients' self-reported resource utilization and days of work absenteeism, multiplied with the resource-specific unit costs in euro (Appendix Table S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017) by Bock et al[30] using 2015 as the base year.

In Germany, inpatient rehabilitation is reimbursed by a per diem fee covering all services provided at the rehabilitation clinic. Thus, intervention costs reflect the per diem fee for PR (€145.06) as reported by the accounting system of the study center multiplied by the duration of PR.

Statistical Analyses

The main analysis included those 412 randomized patients for whom at least 1 measurement at T0 was available (intention to treat). Missing data were imputed using means stemming from a multiple imputation with 10 data sets.[31] All missing data were simultaneously imputed using a Markov Chain Monte Carlo approach with full-data imputation according to a zero truncated multivariate Gaussian distribution.

All applied models were adjusted for baseline values of the outcome parameter and age category. To compare adjusted mean differences (AMDs) in ACT, AQLQ, QALYs, utility score, and VAS including two-sided 95% confidence intervals (CIs) between IG and CG, we applied Gaussian-distributed generalized linear models (GLMs). To contrast resource utilization, we ran GLMs with negative binomial distribution.

To analyze costs, we calculated gamma-distributed GLMs with log-link to account for the skewed distribution of the data.[32] Here, we decided on a one-part GLM for categories with a share of zero expenditures of <10% (total cost, physician cost, and medication costs) and on a two-part GLM given a higher share of zero expenditures (all other cost categories).[33] Because gamma models are defined for positive values only, in the one-part approach, we assigned a small fictive amount of €10 to the few individuals without any costs to keep them in the analyses. In the two-part approach, the first part estimates the probability of positive expenditures using logistic regression and the second part calculates mean cost per user based on gamma regression. Multiplying the estimates of both parts with each other yields mean per capita costs. For one- and two-part models, AMDs adjusted for age categories and baseline value were estimated through recycled predictions.[34] Here, we estimated a two-sided 95% CI based on 1000 nonparametric bootstrap replications.[35]

To calculate the incremental cost-effectiveness ratio (ICER) and uncertainty around, we simultaneously bootstrapped total costs and each distinct effect parameter (ACT, AQLQ, QALY) 1000 times and plotted the results on a cost-effectiveness plane. Subsequently, the ICER was calculated as the ratio of differences in mean costs and mean effects.[36] Regarding effects, we rescaled ACT change and AQLQ change into MIDs (1 ACT point = 1/3 MID; 1 AQLQ point = 2 MIDs) reached to mirror clinically relevant changes.

Because there is no established willingness-to-pay (WTP) threshold for ACT-MIDs and AQLQ-MIDs, we decided on a pragmatic threshold: inpatient rehabilitation services are already regularly reimbursed within the German healthcare system. The expected expenditures of such a 3-week program amount to €3045 (€145 × 21 days). Hence, we considered the intervention as most probably cost-effective in case of an ICER below €3000 per effect unit (ACT-MID, AQLQ-MID). For the tertiary analysis, we applied the usual WTP threshold of €33 000 (£30 000) per QALY gained.[37] Subsequently, cost-effectiveness acceptability curves (CEACs) were calculated based on the obtained ICER distribution to visualize the probability of the intervention being cost-effective at different WTP thresholds.[36]

To judge the robustness of our results, we performed 2 sensitivity analyses (SAs). SA_1 reflects a complete case analysis of those 385 patients remaining in the study until T3.[31] In SA_2, we modeled pointwise change of ACT and AQLQ. Furthermore, we conducted a VAS-based QALY calculation.[38]

All statistical analyses were performed with a significance level of 5% using SAS (version 9.4; SAS Institute Inc, Cary, NC). Graphics were edited in RStudio (version 3.5.1; RStudio, PBC, Boston, MA).

Results

From 436 patients randomized, 24 patients were retrospectively excluded owing to withdrawal of consent or not fulfilling the inclusion criteria. Thus, intention-to-treat analyses included 202 IG members and 210 CG members. Data were imputed for 21 IG (10.3%) and 6 CG (2.9%) members, who were lost to follow-up. A CONSORT diagram (see Appendix Figure S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017) and detailed information on missingness pattern (see Appendix Table S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017) are provided in the online supplement. Randomization achieved a well-balanced sample (Table 1).

Effects

At T0, level of asthma control was comparable for both groups and so was generic and disease-specific HRQoL (Table 1). At T3, IG members consistently presented significantly better outcomes. The 95% CIs for ACT difference (4.76 points = 1.59 MIDs) and AQLQ-difference (0.88 points = 1.76 MIDs) indicated clinical relevance, and in addition, the point estimates for VAS (14.57 points = 1.18 MIDs) and utilities (0.09 points = 1.12 MIDs) were above the respective MIDs (Table 2).

Resource Utilization

At T0, unadjusted healthcare utilization was similar in IG and CG (Appendix Table S3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017). At T3, after an average of 24.2 days of PR, IG members had less physician visits but also more drug prescriptions (Table 3).

Costs

At T0, unadjusted healthcare expenditures were comparable across all domains (Appendix Table S3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017). At T3, the IG incurred by €3673 (95% CI €2854-€4783) higher costs (Table 3). This difference was to 96.5% driven by intervention costs themselves (€3544 per patient in IG). Within the different healthcare service domains, the IG presented by trend lower costs. These differences were significant for GP care (−€17 [−€30 to −€5]), pulmonologists' care (−€24 [−€39 to −€11]), and work absenteeism (−€559 [−€1044 to −€54]). As exception in the opposite direction, IG members incurred higher medication expenditures (€281 [€102-€478]).

Cost-Effectiveness

At 3 months after PR, the ICER was €2278 per ACT-MID, with all corresponding bootstrap replications located in the north-east quadrant of the cost-effectiveness plane, which indicates higher effects at higher cost (Fig. 1). At our pragmatic WTP threshold of €3000, the CEAC (per ACT-MID as effect unit) indicated a probability of PR being cost-effective at 94.8% (Appendix Figure S4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017).

The ICER per AQLQ-MID was €1983 with all corresponding bootstrap replications located in the north-east quadrant of the cost-effectiveness plane (Fig. 2). At the pragmatic WTP threshold of €3000, the CEAC (per AQLQ-MID as effect unit) indicated a probability of PR being cost-effective at 98.5% (Appendix Figure S4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017).

Table 1. Patient characteristics at randomization (T0).

Patient characteristics	IG, *N* = 202	CG, *N* = 210
Age (y)	50.7 (8.8)	51.6 (8.7)
Age, n (%)		
≤54	124 (61.4)	122 (58.1)
55-64	75 (37.1)	86 (40.9)
≥65	3 (1.5)	2 (1.0)
Gender, n (%)		
Males	121 (59.9)	119 (56.7)
BMI (kg/m^2)	29.4 (6.4)	30.2 (5.9)
BMI (kg/m^2), n (%)		
Normal weight (18.5 ≤ BMI < 25)	57 (28.2)	34 (16.2)
Overweight (25 ≤ BMI < 30)	62 (30.7)	77 (36.7)
Obese (BMI ≥ 30)	81 (40.1)	94 (44.8)
Underweight (BMI < 18.5)	1 (0.5)	0 (0)
Missing	1 (0.5)	5 (2.3)
Smoking history, n (%)		
Current smoker	34 (16.8)	34 (16.2)
Former smoker	88 (43.6)	75 (37.1)
Never smoker	78 (38.6)	100 (47.6)
Missing	2 (1.0)	1 (0.5)
Employment status, n (%)		
Full-time	144 (71.3)	148 (70.5)
Part-time	39 (19.3)	44 (20.9)
Unemployed	10 (4.9)	10 (4.8)
Pension (prematurely)	1 (0.5)	1 (0.5)
Other (eg, housewife or houseman)	8 (4.0)	7 (3.3)
ACT	12.9 (3.7)	13.1 (3.8)
AQLQ	3.99 (0.94)	3.88 (0.94)
EQ-5D utilities	0.76 (0.22)	0.77 (0.20)
EQ-5D VAS	56.30 (16.46)	56.83 (17.41)

Note. All data are presented as mean (standard deviation) unless indicated otherwise.
ACT indicates Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; CG, control group; IG, intervention group; QALY, quality-adjusted life-year; VAS, visual analog scale.

The ICER per additional QALY was €312 401 with all corresponding bootstrap replications located in the north-east quadrant of the cost-effectiveness-plane (Fig. 3). At the pragmatic WTP threshold of €3000, the resulting CEAC (per QALY) indicated a probability of PR being cost-effective at 0% (Appendix Figure S5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017).

Sensitivity Analyses

SA_1 with complete cases confirmed the results of the main analysis. AMDs were stable (QALYs gained) or slightly increased (ACT: AMD 4.89 = 1.63 MIDs [1.51-1.84] ||AQLQ: AMD 0.96 = 1.92 MIDs [1.58-2.22]). The mean cost difference was slightly reduced (€3442 [€2628-€4417]) and so was the ICER for ACT (€2071/

Table 2. Adjusted mean effect parameter 3 months after the end of rehabilitation of the IG (T3).

Outcome parameter	3 mo after PR (T3)			
	IG N = 202	CG *N* = 210	Difference [95% CI]	Difference in MIDs [95% CI]
ACT	20.41	15.65	4.76 [4.10-5.43]	1.59 [1.37-1.81]
AQLQ	5.30	4.42	0.88 [0.73-1.04]	1.76 [1.46-2.08]
EQ-5D utilities	0.92	0.83	0.09 [0.06-0.12]	1.12 [0.75;1.5]
EQ-5D VAS	72.18	57.61	14.57 [11.44-17.70]	1.18 [0.93-1.43]
QALYs gained	0.2110	0.1994	0.0115 [0.0077-0.0153]	–
VAS-QALYs gained	0.1597	0.1401	0.0196 [0.0159-0.0232]	–

ACT indicates Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CG, control group; IG, intervention group; QALY, quality-adjusted life-year; VAS, visual analog scale.

Table 3. Adjusted mean per capita healthcare utilization figures and costs in Euro and 3 months after the end of rehabilitation of IG (T3).

Outcome parameter	Utilization			Cost		
	IG *N* = 202	CG *N* = 210	Difference [95% CI]	IG *N* = 202	CG *N* = 210	Difference* [95% CI]
Indirect costs						
Work absenteeism	2.94	4.52	−1.58 [−0.41 to 0.04]	1183	1742	−559 [−1044 to −54]*
Direct costs						
Physician visits	5.23	6.92	−1.69 [−2.40 to −0.87]*	190	216	−26 [−65 to 15]
Pulmonologist	0.97	0.99	−0.02 [−0.33 to 0.24]	48	72	−24 [−39 to −11]*
General practitioner	3.15	3.95	−0.80 [−1.21 to −0.31]*	55	72	−17 [−30 to −5]*
Other specialists	1.06	1.53	−0.47 [−0.93 to −0.00]*	57	66	−9 [−32 to 15]
Inpatient care	0.22	0.34	−0.12 [−0.41 to 0.04]	306	545	−239 [−736 to 122]
General ward	0.20	0.31	−0.11 [−0.35 to 0.04]	370	665	−295 [−692 to 116]
ICU	0.011	0.012	0.001 [−0.0145 to 0.0001]	27	63	−36 [−128 to 26]
Medication	4.47	4.02	0.45 [0.15 to 0.73]*	612	331	281 [102 to 478]*
Intervention/PR	24.2	−/−	–	3544	−/−	–
Sum of overall costs				6256	2583	3673 [2854 to 4783]*

Note. All means are adjusted for age categories and baseline value, based on previous 3 months. Utilization figures stem from a negative binomial model and costs are derived from (1- and 2-part) gamma models calculated with 1000 bootstrap replications. Results of differences are model based; summing of distinct cost categories yields different results.
CI indicates confidence interval; CG, control group; ICU, intensive care unit; IG, intervention group; PR, pulmonary rehabilitation.
*Significant estimates on a level of $p < .05$.

ACT-MID) (Appendix Figure S6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017), AQLQ (€1766/AQLQ-MID) (Appendix Figure S7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017) and QALYs (€330 680/QALY) (Appendix Figure S8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017). The probability of PR being cost-effective at the pragmatic WTP threshold of €3000 did not change substantially for any effect measure (ACT-MID, AQLQ-MID, QALY) (Appendix Figures S9-S11 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017).

In SA_2, reflecting linear changes of ACT and AQLQ revealed ICERs of €754 per 1-point increase in ACT (=1/3 MID) (Appendix Figure S12 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017) and of €3974 per 1-point increase in AQLQ (=2 MIDs) (Appendix Figure S13 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017) and an ICER of €185 838 per VAS-QALY gained (Appendix Figure S14 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017). The ACT-CEAC indicated a 100% probability of PR being cost-effective at a WTP threshold of €1614 (Appendix Figure S15 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017); at a WTP threshold of €3000, the AQLQ-CEAC indicated a probability of PR being cost-effective at 4.3% (Appendix Figure S16 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017), and the VAS-QALY-CEAC a probability of 0% (Appendix Figure S17 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.01.017).

Discussion

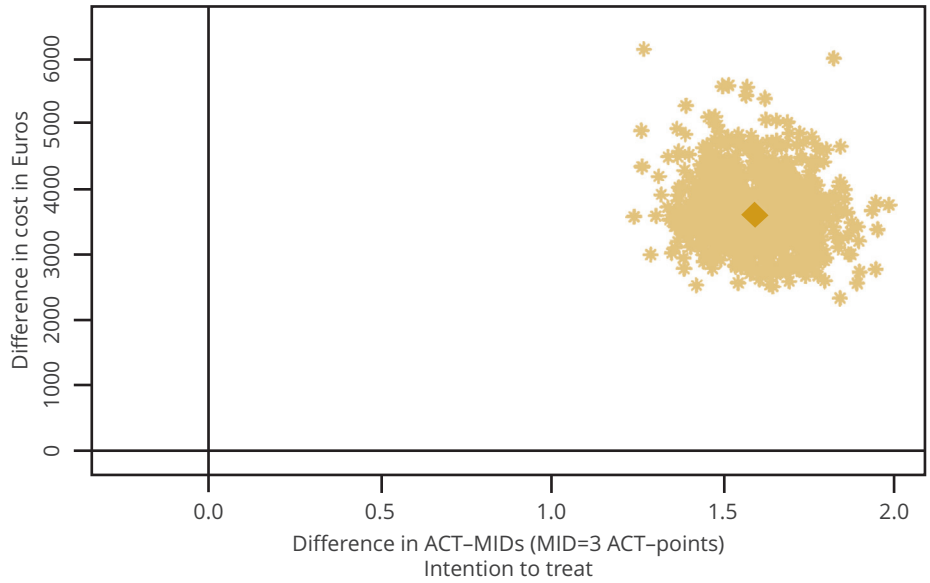
This study assessed the cost-effectiveness of a 3-week PR in patients with not-well-controlled asthma with usual care as the comparator and asthma control and HRQoL at 3 months after the end of PR as the effectiveness criteria. Focusing on the cost side, IG members incurred significantly higher overall per capita costs than CG members, with the difference being basically attributable to intervention costs themselves.

Within the distinct healthcare service domains, we observed by trend lower costs in the IG. This beneficial economic impact was most pronounced regarding indirect costs (−€559), which reflect fewer days of work absenteeism. A beneficial impact of PR on work absenteeism was already reported by Nathell et al[7] Here, a small subgroup of never smokers and former smokers profited from a 4-week inpatient PR even 3 years after the intervention. However, this study did not explicitly address related economic implications. Our results suggest that economic burden of work absenteeism is substantially reduced in the context of PR at least in the short term. If this effect persists—as suggested by Nathell et al—improved productivity has high potential to outweigh the initial PR expenditures. Furthermore, our study suggested lower costs for follow-up care by pulmonologists and GPs in the IG. We believe this is related to the achieved improvement of asthma control and enhanced coping capabilities in context of PR. Here, long-term studies investigating the sustainability of these effects—and thus structural changes in physician expenditures—are pending.

Focusing on the effect side, our study detected significantly better ACT and AQLQ scores together with higher QALYs gains in IG members. For ACT and AQLQ, differences between IG and CG were also clinically relevant.[23,25] This substantiates the findings of several studies that emphasized a beneficial impact of individual components of PR, such as exercise training[9,11] or breathing retraining[13–15] on asthma control and disease-specific HRQoL. Referring to this previous evidence, we observed even higher AMDs in favor of the IG. We consider this as a result of the synergetic effect of combining various effective components within the complex multimodal intervention PR. Nevertheless, the multimodal approach renders a direct comparison of effects a sensitive issue, because we cannot disentangle the distinct contribution of those several PR components to ACT and AQLQ change, respectively.

The ICER for reaching the MIDs of ACT (€2278) and AQLQ (€1983) was below the cost of PR. Thus, assuming a pragmatic threshold of €3000 (which reflects expected PR reimbursement), corresponding CEACs indicated a probability of PR being

Figure 1. Cost-effectiveness plane of overall costs and ACT. The rhombus represents the original ICER. ACT indicates Asthma Control Test; ICER, incremental cost-effectiveness ratio; MID, minimal important difference.



cost-effective close to 100% per effect unit (ACT-MID and AQLQ-MID). However, these findings lack an external benchmark, because there are no asthma-specific cost-effectiveness analyses evaluating PR. Thus, in the absence of an established WTP threshold regarding asthma-relevant outcomes, statements on cost-effectiveness are a sensitive issue. Indeed, PR is a regular service of the German Health or Pension Insurance scheme and factual PR expenses of these payers amount to approximately €3500. Thus, we consider PR most probably a cost-effective intervention for achieving clinically relevant changes in 2 important asthma-related outcome criteria.

However, referring to generic HRQoL, the obtained ICER of €312 401/QALY is far beyond the broadly accepted threshold of €33 000/QALY. Here, a broader perspective on cost-utility information for pharmacological treatment strategies might help to put our findings into context: two recent reviews[39,40] unveiled favorable ICERs for different treatment regimens with ICS, long-acting β-agonists, and long-acting muscarinic antagonists (usually <€30 000/QALY). However, they also detected a substantial variance in ICERs for persistent add-on treatment with biologicals in patients not reaching asthma control with standard long-acting β-agonist–ICS treatment (omalizumab, €23 800/QALY to

Figure 2. Cost-effectiveness plane of overall costs and AQLQ. The rhombus represents the original ICER. AQLQ indicates Asthma Quality of Life Questionnaire; ICER, incremental cost-effectiveness ratio; MID, minimal important difference.

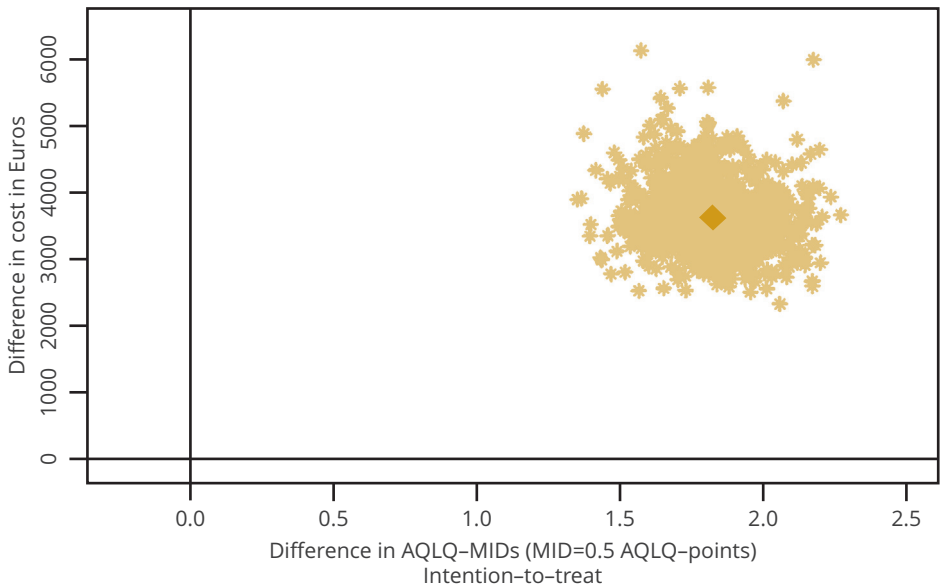
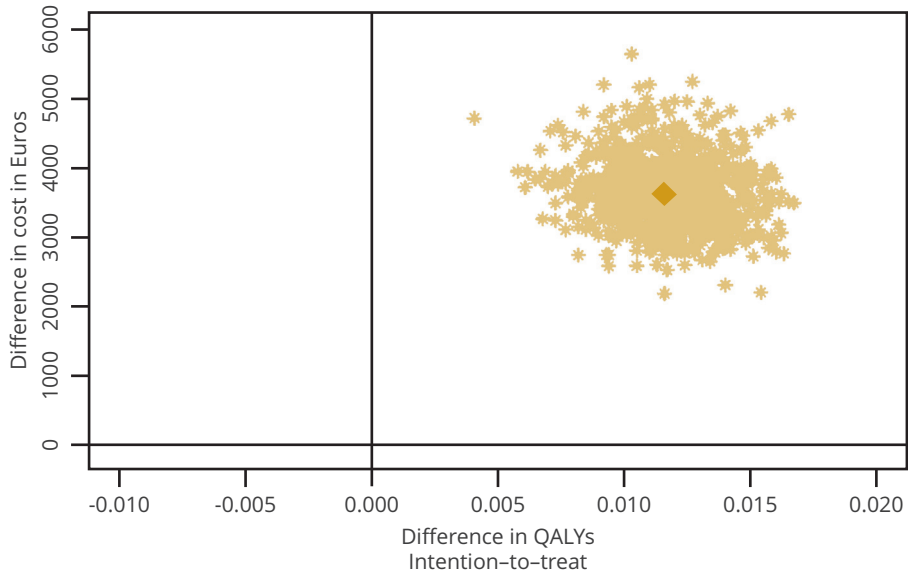


Figure 3. Cost-effectiveness plane of overall costs and QALYs. The rhombus represents the original ICER. ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.



$821 000/QALY; mepolizumab, $200 000/QALY to $385 000/QALY). Unsatisfactory asthma control despite comprehensive medication regimens also applies to the EPRA sample. Thus, despite being high, our ICER is in line with previous evidence. Furthermore, it has to be considered that a potential stabilization of QALY differences is not reflected in our short-term ICER. Indeed, follow-up data of the cohort part of the EPRA trial suggest utilities to stay at a similar level from 3 months to 12 months after PR.[22] Under the assumption that costs of follow-up care remain stable during this period, too, a reduced cost difference (€2900) and an increased QALY difference (0.04) can be expected 12 months after PR. This translates to an anticipated 12-month ICER of €72 500/QALY. Therefore, initial PR expenditures ought to be interpreted as a one-time investment requiring extended amortization periods.

This perspective matches a cost-utility analysis of an outpatient structured education PR program for chronic obstructive pulmonary disease (COPD), even though direct comparisons to our data are limited owing to different clinical courses of COPD and asthma. Similar to our study, Gillespie et al[41] indicated higher costs in the IG (AMD €1205)—mainly driven by intervention costs themselves—combined with slightly more QALYs gained (AMD 0.002). Given an ICER of €472 000/QALY, the authors raised the question whether EQ-5D is sensitive enough to unveil clinically relevant changes of health status in COPD.

A lack of sensitivity is also a subject for discussion in asthma, because several studies demonstrated that changes in asthma control (ACT) and improvements in disease-specific HRQoL (AQLQ) are not necessarily linked to corresponding EQ-5D changes.[42-44] Thus, the suitability of EQ5D to portray asthma-relevant HRQoL impairments seems limited.[45]

The results presented should be interpreted keeping following caveats in mind: First, effectiveness of the intervention has to be considered under possible expectation bias. Especially in the CG, the patients' knowledge about upcoming rehabilitation might have beneficially affected HRQoL and to lesser extent perceived symptom burden compared with the normal population with asthma. This introduces a risk for underestimating the effect of PR. Second, costs incurred by IG members shortly after PR might not represent persistent utilization patterns because patients often receive follow-up treatment shortly after rehabilitation.[20] Therefore, cost differences between IG and CG might be more favorable at later points of follow-up. Owing to the waiting-list design of the EPRA trial, medium-term cost-effectiveness cannot be calculated because the CG also entered PR 3 months after the end of PR in the IG. Thus, even though follow-up information from the cohort part of the trial is available until 12 months after PR, a comparison of IG and CG is only feasible until T3. Furthermore, intervention costs were not derived from microcosting but reflect a per diem fee. This type of shadow pricing has been applied previously[46] and is in line with the unit cost approach for the other cost components (eg, hospitalization and physician visits). However, it might not reflect all cost components (eg, staff and patient time) in a fully adequate manner. Indeed, a recent German report calculated per diem fees of cardiac (€157) and orthopedic (€164) rehabilitation based on microcosting.[47] Given that these figures refer to other indication areas and do not substantially exceed the per diem fee for PR applied in our study (€145), we believe that our shadow price reflects intervention costs in an appropriate way.

Fourth, accepted WTP thresholds only exist for QALYs but not for other generic or disease-specific outcomes. Therefore, as in any other cost-effectiveness analysis, our statements on societally accepted WTP rely on distinct assumptions. Because PR is not an innovative approach but a concept with long tradition in the German healthcare system, we consider it a socially accepted intervention for patients with asthma. The reimbursement of this intervention is (eventually) borne by the entire society through insurance contributions and is hence regarded a societally accepted price. Based on this rationale and in the absence of a prespecified WTP threshold, we defined a pragmatic threshold reflecting expected PR expenditures. We are aware that this pragmatic threshold does not precisely reflect opportunity costs, but it might help to better examine, whether PR offers good value for money. Finally, lacking sensitivity of EQ-5D in the field of asthma might have required a better suited measure of utilities instead of QALYs. In this regard, the AQLQ-based AQL-5D has been gaining practical relevance because of its good discriminative abilities.[48,49] However, at the time the EPRA trial was conceived, AQL-5D was not yet established in Germany's health policy

decision making, and the score cannot be calculated ex post out of the data at hand. Thus, we tried to mitigate the presumed lacking sensitivity to change of utility-based QALYs by also providing VAS-based QALYs, which have been reported to be more sensitive to change.[33] This alternate approach reduced the ICER by 40%.

Keeping these drawbacks in mind, we present the first RCT-based cost-effectiveness analysis on PR in the field of asthma, which ensures a high level of internal validity. Assessment of resource use was based on a standardized, validated tool, which, in combination with Germany-specific unit costs, provided generalizable cost estimates. Furthermore, we combined MID-based and linear changes of ACT and AQLQ (cost-effectiveness analyses) with QALYs (cost-utility analysis) to portray both, an objective clinical effectiveness criterion and 2 subjective (asthma-specific and generic) patient-reported outcome measures. Given that previous studies reported a neglectable impact of (non-pharmacologic) interventions on QALYs, the informative value of pure cost-utility analyses has to be scrutinized critically in the field of asthma. Thus, the provision of ICERs targeting at clinically relevant changes in asthma-related outcomes supports a more comprehensive appraisal of PR in bronchial asthma.

Conclusion

A 3-week PR results in clinically relevant improvement of asthma control and asthma-specific HRQoL, which at least persists until 3 months after the intervention. In parallel, indirect costs are significantly reduced and direct costs of follow-up care tend to be lower. Taking the societally accepted factual spending on inpatient PR into account, the intervention is hence most probably cost-effective with regard to relevant asthma-related outcomes. However, regarding QALYs, short-term cost-effectiveness is falling short to comprehensively judge the added value of PR. Here, a long-term perspective portraying the sustainability of the observed beneficial spending and HRQoL trends is strongly encouraged to comprehend whether the one-time investment in PR translates to cost-effectiveness or even reaches a break-even after an extended period.

Supplemental Material

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Consent to Participate: A written informed consent has been obtained from all participants.

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