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the cluster-randomized Danish Telecare North Trial

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ORIGINAL RESEARCH

Subgroup analysis of telehealthcare for patients with chronic obstructive pulmonary disease: the cluster-randomized Danish Telecare North Trial

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Purpose: Results from the Danish cluster-randomized trial of telehealthcare to 1,225 patients with chronic obstructive pulmonary disease (COPD), the Danish Telecare North Trial, concluded that the telehealthcare solution was unlikely to be cost-effective, by applying international willingness-to-pay threshold values. The purpose of this article was to assess potential sources of variation across subgroups, which could explain overall cost-effectiveness results or be utilized in future economic studies in telehealthcare research.

Methods: First, the cost-structures and cost-effectiveness across COPD severities were analyzed. Second, five additional subgroup analyses were conducted, focusing on differences in cost-effectiveness across a set of comorbidities, age-groups, genders, resource patterns (resource use in the social care sector prior to randomization), and delivery sites. All subgroups were investigated post hoc. In analyzing cost-effectiveness, two separate linear mixed-effects models with treatment-by-covariate interactions were applied: one for quality-adjusted life-year (QALY) gain and one for total healthcare and social sector costs. Probabilistic sensitivity analysis was used for each subgroup result in order to quantify the uncertainty around the cost-effectiveness results.

Results: The study concludes that, across the COPD severities, patients with severe COPD (GOLD 3 classification) are likely to be the most cost-effective group. This is primarily due to lower hospital-admission and primary-care costs. Telehealthcare for patients younger than 60 years is also more likely to be cost-effective than for older COPD patients. Overall, results indicate that existing resource patterns of patients and variations in delivery-site practices might have a strong influence on cost-effectiveness, possibly stronger than the included health or sociodemographic sources of heterogeneity.

Conclusion: Future research should focus more on sources of heterogeneity found in the implementation context and the way telehealthcare is adopted (eg, by integrating formative evaluation into cost-effectiveness analyses).

Trial registration: Clinicaltrials.gov, NCT01984840.

Keywords: COPD, telemonitoring, telehealth, health economics, heterogeneity, Denmark

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Introduction

Trial-based evidence on the cost-effectiveness of telehealthcare for patients with chronic obstructive pulmonary disease (COPD) is accumulating.[1–8] This evidence addresses whether or not the relative treatment effect of an intervention (ie, telehealthcare) compared to some alternative (ie, typically usual care) is worth any additional costs.[9] Most of these studies have too few patients to make subgroup analysis meaningful,

and the large-scale Whole System Demonstrator study has only reported main cost-effectiveness results from all included patients with diabetes, chronic heart failure, and COPD. Because patients are heterogeneous and have complex healthcare needs, cost-effectiveness is likely to vary with different baseline factors, such as health status, sociodemographic characteristics, or other baseline characteristics.[10] Although some studies have reported a direct relationship between COPD severity and costs,[11,12] there is very little knowledge of the relative cost-structures and heterogeneity of cost-effectiveness for patients with COPD that are specific for telehealthcare research.[13]

The recently reported Danish cluster-randomized trial of telehealthcare (Danish Telecare North Trial) among 1,225 patients with COPD reported additional costs, similar gain in quality-adjusted life-years (QALYs), and a relatively high incremental cost-effectiveness ratio (ICER) compared to international willingness-to-pay threshold (WTP) values, making the telehealthcare solution unlikely to be cost-effective.[14] However, subgroups of patients with COPD within the trial could be more or less cost-effective, and these tendencies are important in order to explain the overall cost-effectiveness outcome, as input to decision-models such as the recently conducted study by Hofer et al[15] or simply to create informed hypotheses for use in the design of future trial-based economic evaluations.

The objective of this article is to present cost-effectiveness results across a range of plausible subgroups in the cluster-randomized Danish Telecare North Trial. The subgroups are COPD severity in particular (classified according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD]), but also three different comorbidities (coronary heart disease, diabetes, or mental health problems), gender, age, and existing resource patterns as well as delivery site.

Methods

The study protocol[16] and the overall results from the economic evaluation[14] have been published elsewhere, but a brief summary is provided in Table 1.

Patients in the intervention group received a set of telehealthcare equipment and were monitored by a municipality-based healthcare team consisting primarily of nurses. Furthermore, patients received disease-specific education. The control group received usual care. In total, 1,225 patients satisfied the exclusion and inclusion criteria; 26 municipality districts across 10 different municipalities/delivery sites defined the randomization units (13 in each arm). These districts were matched, so that all municipalities/delivery sites contained municipality districts with patients who received telehealthcare or usual care[16]; 578 patients were randomized to telehealthcare, and 647 to usual care.

The primary outcome for the cost-effectiveness analysis was total healthcare and social sector costs per QALY gained. Costs included intervention costs, healthcare costs (patient-level hospital-, medicine-, and primary sector costs), and social sector costs (patient-level costs associated with practical help and care at home, home-based nursing care, and rehabilitation). The duration of the study was 12 months.[16]

No subgroup analyses were pre-defined in the trial protocol, but different baseline characteristics were collected as part of the trial. These included forced expiratory volume

Table 1 Overview of economic evaluation of the Danish Telecare North Trial

Perspective of analysis	Healthcare sector and social care sector
Outcomes	Total costs per QALY gained
Compared alternatives	IG: a set of telehealthcare equipment and were monitored by a community-based healthcare team (based in social care sector). Patients also received disease-specific education
	CG: usual care
Duration of study	12 months
Patients included	All patients with COPD that may benefit from telehealthcare. Fixed residence in North Denmark Region, Danish speaking, GSM coverage or phone line. No cognitive impairments. N=1,225 patients; 578 in IG and 647 in CG
Clusters	Municipality districts (social care sector), 26 clusters in total, 13 in each treatment arm. Each municipality had at least one district in both the intervention and control groups
Cost categories	Hospital admissions, outpatient visits including emergency contacts, primary-care contacts, prescribed medicine, personal care, practical help, at-home nursing care, and rehabilitation
Conclusion	Incremental QALYs was 0.0132 (rounded)
	Incremental total costs were €728 (rounded)
	ICER was €55.327 per QALY gained
	Telehealthcare is unlikely to be cost-effective

Abbreviations: QALY, quality-adjusted life-year; IG, intervention group; CG, control group; COPD, chronic obstructive pulmonary disease; GSM, global system for mobiles; ICER, incremental cost-effectiveness ratio.

in 1 second (FEV1%) measured by the patients' general practitioner. Presence of comorbidities was ascertained from questionnaires that were filled out by the patients' general practitioner. Age and gender were identified from the patients' social security number. Patient-level resource use from both within the trial period and 1 year prior to randomization was collected from medical registers by applying patients' social security number. National-level patient data for all hospital contacts were collected from the Danish National Patient Register;[17] all contacts between patients and the primary care sector from the National Health Insurance Service Register;[18] and medication use was taken from The Danish Register of Medicinal Product Statistics.[19] Patient-level community care service was taken from care systems in each of the 26 included municipality districts. Intervention costs included costs of hardware and peripherals, installation and deinstallation costs, maintenance and support costs, training costs for health care professionals, patient-specific training, monitoring costs, and project management costs. QALYs were calculated by linear interpolation of EQ5D-3L scores with Danish societal weights.[20] More details on the data are described in the overall within-trial economic evaluation.[14]

The study was conducted in accordance with the Declaration of Helsinki. The trial has been presented to the Regional Ethical Committee for Medical Research in the North Denmark Region, where it was determined that no ethical approval was necessary. The trial has also been authorized by the Danish Data Protection Agency. All patients signed an informed consent form before taking part in the clinical trial. Trial registration: Clinicaltrials.gov, NCT01984840.

Statistical analysis

The statistical analysis employed in this article followed the analytical strategy from a cost-effectiveness article published previously.[14] An intention-to-treat principle was applied. Missing data were assumed missing at random (MAR) and were imputed according to methodological guidelines.[21]

To allow for inclusion of particularly COPD severity-specific costs in future decision-modeling studies, the unadjusted cost structure across treatment alternatives was analyzed. These cost-structures are presented for each of the applied cost-categories mentioned earlier. Results are presented as means [standard deviation (SD)] and between-group differences are reported as raw mean difference and standardized difference (SMD = difference between randomization group averages/SD of the total sample) to allow for meta-analyses.

Estimation of incremental total costs and incremental QALYs in all subgroups was based on two separate linear mixed-effects models with treatment-by-covariate interactions. Total costs were controlled for relevant subgroup interaction on the treatment variable, baseline EQ5D score, baseline costs, age, baseline FEV1%, presence of musculoskeletal disease, and clustering. Similarly, QALYs gained were controlled for the relevant subgroup interaction term on the treatment identifier, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer, and clustering. By applying the "mi estimate: xtmixed" command with robust standard errors in STATA12.1, a deterministic ICER estimate was calculated for each subgroup by linear combination of the relevant treatment beta-coefficients in both models. More details on the applied linear mixed-effects models are available in the Supplementary material. To quantify the uncertainty around these estimates, a series of probabilistic sensitivity analyses were conducted. The output from both models was exported to Microsoft Excel 2010 along with Cholesky's decomposition matrix, and 5,000 new parameter estimates from the analytical models from normal distributions were drawn. Estimates of incremental QALYs and incremental total costs were created to present the probability that telehealthcare was cost-effective as a function of decision-makers; WTP for extra QALYs. The probabilities that telehealthcare is cost-effective are presented at €25,000 and €40,000, which is roughly the threshold values applied in the UK (1€=0.73 £).

Results

Complete data for both total costs (ie, all cost-categories) and EQ5D scores at baseline and follow-up were available for 751 patients (61%; 325 in the telehealthcare group; 426 in the control group). Incomplete data stemmed primarily from non-response or from incomplete registration of EQ5D questionnaire items (8% had missing EQ5D summary scores at baseline; 27% at follow-up); 12% had missing values on one cost-category – rehabilitation; 103 patients died during the trial period (8%).

The telehealthcare and usual care group were similar at baseline (Table 2). The general tendency is that patients in the intervention group have slightly worse health (higher proportion of patients with severe COPD [GOLD 3], more comorbidities, and greater resource use in municipalities prior to randomization). There were also more men in the telehealthcare group. Between-group difference across delivery sites was expected given the randomization procedure.

Table 2 Baseline characteristics

Subgroup category	Telehealthcare	Usual care	Difference	Fisher's exact test
	n=578	**n=647**	**Raw**	***P*-value**
COPD severity (GOLD classification 1–4)				
Mild, GOLD 1	3.98 (n=23)	4.64 (n=30)	−0.66	
Moderate, GOLD 2	31.49 (n=182)	31.07 (n=201)	0.42	
Severe, GOLD 3	32.18 (n=186)	30.60 (n=198)	1.58	0.937
Very severe, GOLD 4	13.84 (n=80)	13.91 (n=90)	−0.07	
Missing	18.51 (n=107)	19.78 (n=128)	−1.27	
Comorbidities				
Coronary heart disease	32.70 (n=189)	31.84 (n=206)	0.86	0.927
Diabetes	10.21 (n=59)	9.89 (n=64)	0.32	0.962
Mental health problem	4.84 (n=28)	4.79 (n=31)	0.05	0.991
Missing	8.13 (n=47)	7.88 (n=51)	0.25	
Age§				
<60 years	16.78 (n=97)	14.68 (n=95)	2.10	
60–69 years	34.08 (n=197)	31.68 (n=205)	2.40	0.445
70–79 years	36.33 (n=210)	40.19 (n=260)	−3.86	
≥80 years	12.80 (n=74)	13.45 (n=87)	−0.65	
Men§	48.27 (n=279)	43.74 (n=283)	4.53	0.063
Existing resource pattern				
No resource use in social sector 12 months prior to randomization	52.25 (n=302)	57.50 (n=372)	−5.25	
Resource use in social sector 12 months prior to randomization	39.62 (n=229)	36.32 (n=235)	3.30	0.136
Missing	8.13 (n=47)	6.18 (n=40)	1.95	
Delivery site				
Delivery site 1	8.13 (n=47)	6.18 (n=40)	1.95	
Delivery site 2	16.09 (n=93)	4.33 (n=28)	11.76	
Delivery site 3	10.73 (n=62)	9.58 (n=62)	1.15	
Delivery site 4	5.54 (n=32)	5.10 (n=33)	0.44	
Delivery site 5	6.40 (n=37)	7.88 (n=51)	−1.48	0.000
Delivery site 6	3.46 (n=20)	4.17 (n=27)	−0.71	
Delivery site 7	4.50 (n=26)	4.33 (n=28)	0.17	
Delivery site 8	15.40 (n=89)	6.49 (n=42)	8.91	
Delivery site 9	10.55 (n=61)	10.05 n=65)	0.50	
Delivery site 10	19.30 (n=111)	41.89 (n=271)	−22.59	

Note: Data are presented as percentages (number of patients). §Variable has no missing values.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Subgroups defined by COPD severity

The unadjusted cost-structure across GOLD classifications is presented in Table 3. For patients with mild COPD (GOLD 1), telehealthcare was associated with higher total costs (raw mean difference €2401) giving rise to an SMD of 23.37%. This was primarily driven by higher social sector costs – that is, help and care at home (raw mean difference €513; SMD 12.82%), home nursing care (raw mean difference €1380; SMD 26.21%), and rehabilitation (raw mean difference €89; SMD 35.85%). Patients in the telehealthcare group had fewer costs due to primary-care visits (raw mean difference −€123, standardized between-group difference; −25.01%).

Telehealthcare was associated with higher total costs for patients with moderate COPD (GOLD 2; raw mean

difference €1424; SMD 16.94%). The telehealthcare group had higher costs due to hospital admissions (raw mean difference €489; SMD 11.72%) and home nursing care (raw mean difference €236; SMD 9.40%). There were fewer costs due to help and care at home (raw mean difference −€186; SMD −4.81%).

Total costs for patients with very severe COPD (GOLD 4) was associated with higher total costs in the telehealthcare group (raw mean difference €6400; SMD 31.87%). Higher costs were accrued across all cost categories.

In contrast to other COPD severities, patients with severe COPD (GOLD 3) had fewer total costs in the telehealthcare group (raw mean difference −€717; SMD −4.49%). This was driven by cost savings in hospital admissions (raw mean

Table 3 Average costs (€) per patient across treatment groups at 12-month follow-up for all COPD severities

Cost categories across COPD severities	Telehealthcare	Usual care	Between-group difference	
	Mean (SD)	Mean (SD)	Raw mean	Standardized (%)*
Mild COPD (GOLD 1)				
Hospital contacts				
Admissions	768 (4879)	813 (2449)	−45.16	−1.22
Outpatient/emergency department visits	111 (291)	97 (274)	14.58	5.17
Primary-care contacts	602 (420)	725.7 (535)	−123.32	−25.01
Municipality-care contacts				
Help and care at home	1174 (5128)	661 (2868)	512.96	12.82
Home nursing care	1857 (7782)	477 (1524)	1379.50	26.21
Rehabilitation§	106 (325)	17 (157)	88.90	35.85
Medicine	1025 (714)	1085.3 (726)	−60.85	−8.43
Total service costs (excluding intervention costs)	5645 (14486)	3878 (6079)	1766.58	17.22
Total costs (including intervention costs)	6280 (14464)	3878 (6079)	2401.58	23.37
Moderate COPD (GOLD 2)				
Hospital contacts				
Admissions	1299 (5369)	811 (2653)	488.67	11.72
Outpatient/emergency department visits	194 (450)	123 (348)	71.80	17.90
Primary-care contacts	618 (397)	616 (475)	1.93	0.44
Municipality-care contacts				
Help and care at home	946 (3495)	1132 (4168)	−186.12	−4.81
Home nursing care	625 (2893)	388 (2111)	236.36	9.40
Rehabilitation§	50 (265)	24 (191)	25.56	11.14
Medicine	1312 (856)	1240 (795)	71.79	8.70
Total service costs (excluding intervention costs)	5045 (8992)	4334 (7796)	709.98	8.46
Total costs (including intervention costs)	5759 (8988)	4334 (7796)	1424.25	16.94
Severe COPD (GOLD 3)				
Hospital contacts				
Admissions	2686 (8818)	4116 (16371)	−1429.47	−10.73
Outpatient/emergency department visits	347 (564)	346 (583)	0.92	0.16
Primary-care contacts	602 (460)	679 (582)	−76.39	−14.46
Municipality-care contacts				
Help and care at home	1990 (5654)	1968 (5934)	22.58	0.39
Home nursing care	680 (1805)	638 (2559)	42.72	1.92
Rehabilitation§	116 (462)	106 (533)	10.64	2.13
Medicine	1722 (855)	1721 (1035)	0.54	0.06
Total service costs (excluding intervention costs)	8144 (11826)	9572 (19000)	−1428.47	−8.94
Total costs (including intervention costs)	8855 (11807)	9572 (19000)	−716.92	−4.49
Very severe COPD (GOLD 4)				
Hospital contacts				
Admissions	6670 (21124)	4619 (12368)	2051.10	12.02
Outpatient/emergency department visits	728 (801)	527 (737)	200.35	25.88
Primary care contacts	571 (422)	518 (408)	53.01	12.76
Municipality care contacts				
Help and care at home	4202 (9588)	1340 (3435)	2862.11	39.93
Home nursing care	775 (2475)	616 (1934)	158.84	7.20
Rehabilitation§	133 (422)	57 (246)	75.43	22.04
Medicine	2176 (1659)	1863 (946)	312.54	23.36
Total service costs (excluding intervention costs)	15255 (24517)	9541 (14497)	5713.38	28.52
Total costs (including intervention costs)	15941 (24506)	9541 (14497)	6399.81	31.87

Note: *Standardized difference, difference between randomization group averages divided by the standard deviation (SD) of the total sample. §Imputed data.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

difference −€1429; SMD −10.73%) and primary sector contacts (raw mean difference −€76; SMD −14.46%).

From Table 4, the ICER point estimates indicate that the telehealthcare intervention was dominant for patients with severe COPD (GOLD 3), with a probability of achieving cost-effectiveness of 68% at a WTP threshold of €25,000 and 70% at €40,000. The probability that telehealthcare is cost-effective remains consistently lower across different

Table 4 Cost-effectiveness of telehealthcare compared to usual care across COPD severities

COPD severity (GOLD classification 1–4)#	QALY	Wald test*	Total costs (€)	Wald test*	ICER	Pr(cost-effective)	Pr(cost-effective)
	Between group difference (95% CI)	*P*-value	Between group difference (95% CI)	*P*-value	(€ per QALY)	at €25,000	at €40,000
Mild, GOLD 1 (6%)	0.0281 (–0.0551; 0.1113)	0.4131	1872 (–5337; 9082)	0.3998	66,577	39%	44%
Moderate, GOLD 2 (38%)	–0.0113 (–0.0469; 0.0243)		1455 (–94; 3003)		UC dominant	35%	35%
Severe, GOLD 3 (39%)	0.0302 (–0.0075; 0.0678)		–964 (–3750; 1822)		THC dominant	68%	70%
Very severe, GOLD 4 (17%)	0.0229 (–0.0261; 0.0719)		2959 (–2087; 8005)		129,035	29%	33%

Note: *Wald test for interaction between treatment and the subgroup variables. #QALYs and total costs were not simultaneously controlled for baseline FEV1%. All results are imputed.
Abbreviations: QALY, quality-adjusted life-years; COPD, chronic obstructive pulmonary disease; UC, usual care; THC, telehealthcare; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICER, incremental cost-effectiveness ratio; Pr, probability.
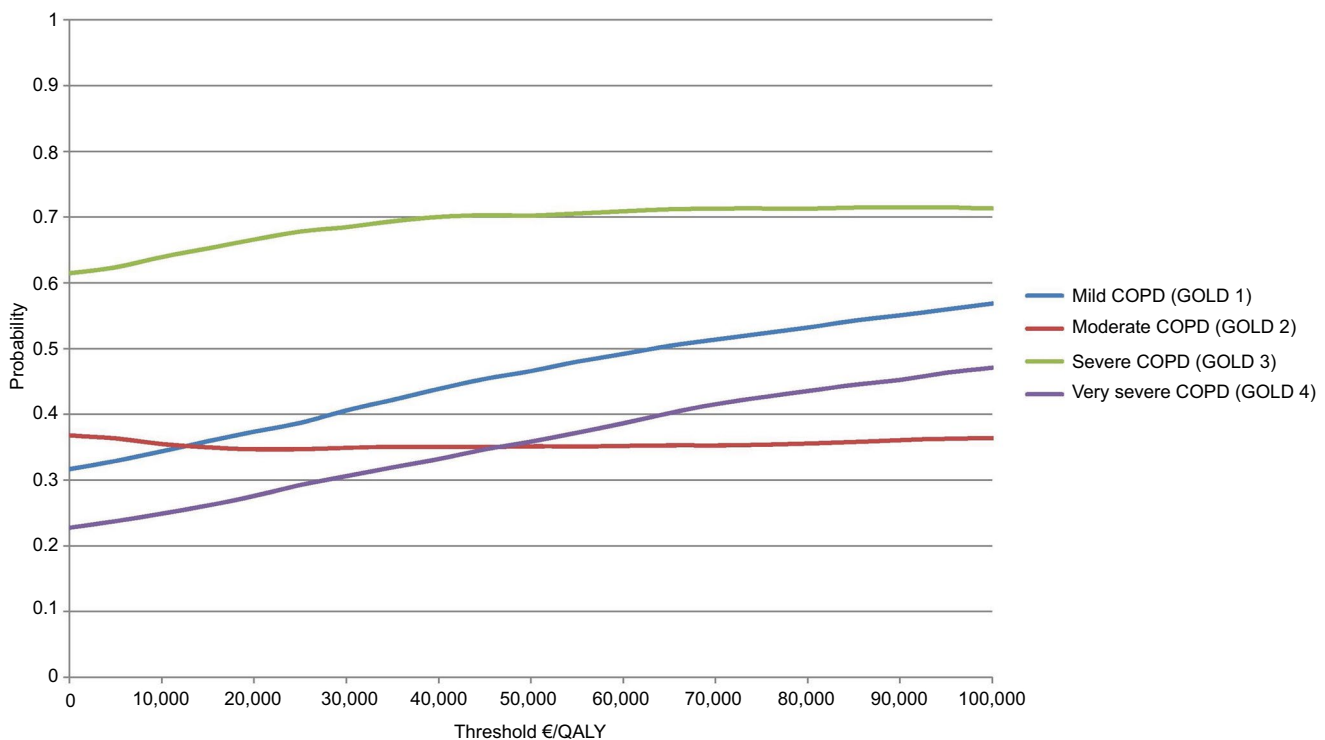
Figure 1 Probability of telehealthcare being cost-effective, depending on the severity of COPD (by GOLD classification).
Abbreviations: COPD, chronic obstructive pulmonary disease; QALY, quality-adjusted life-years; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

levels of WTP threshold values for other COPD severities (Figure 1). Usual care was dominant for moderate COPD (GOLD 2), with a probability of achieving cost-effectiveness of 35% at a WTP threshold of €25,000 and 35% at €40,000.

Subgroups defined by comorbidities, gender, age, resource patterns, and delivery site

In Table 5, the ICER point estimate is dominant for telehealthcare for patients younger than 60 years, with a probability of achieving cost-effectiveness of 69% at a WTP threshold of

€25,000 and 68% at €40,000. A relatively high probability of achieving cost-effectiveness is present for patients aged 80 and older (62% at a WTP threshold of €25,000 and 71% at €40,000). Telehealthcare is dominant and has a high probability of achieving cost-effectiveness, given the data for the subgroup with patients having resource use (practical help, home nursing care, and rehabilitation) in the municipalities at some point 12 months prior to randomization (89% at a WTP threshold of €25,000 and 89% at €40,000). Across municipalities/delivery sites, there are large variations in cost-effectiveness with probabilities of cost-effectiveness

Table 5 Cost-effectiveness of telehealthcare compared to usual care in subgroups

Subgroup category	QALY	Wald test*	Total costs (€)	Wald test*	ICER	Pr(cost-effective)	Pr(cost-effective)
	Between group difference (95% CI)	*P*-value	Between group difference (95% CI)	*P*-value	(€ per QALY)	at €25,000	at €40,000
Comorbidities							
Coronary heart disease							
No (65%)	0.0168 (–0.0059; 0.0394)	0.636	445 (–1604; 2493)	0.566	26,527	49%	57%
Yes (35%)	0.0068 (–0.0315; 0.0451)		1290 (–650; 3229)		189,373	28%	31%
Diabetes							
No (89%)	0.0112 (–0.0116; 0.3402)	0.577	309 (–1340; 1957)	0.182	27,573	49%	56%
Yes (11%)	0.0294 (–0.0312; 0.090)		4731 (–1085; 10547)		160,728	8%	12%
Mental health problem							
No (95%)	0.0130 (–0.0094; 0.0354)	0.911	772 (–770; 2314)	0.815	59,378	29%	39%
Yes (5%)	0.0178 (–0.0627; 0.0983)		38 (–5837; 5913)		2,135	55%	58%
Gender							
Female (54%)	0.0052 (–0.0172; 0.0276)	0.347	407 (–1471; 2286)	0.573	77,890	39%	42%
Male (46%)	0.0225 (–0.0108; 0.0557)		1122 (–888; 3132)		49,917	44%	55%
Age##							
<60 years (16%)	0.0046 (–0.0403; 0.0495)	0.692	–560 (–2972; 1851)	0.707	THC dominant	69%	68%
60–69 years (33%)	0.0009 (–0.0322; 0.0340)		1622 (–1170; 4415)		1,764,487	22%	25%
70–79 years (38%)	0.01607 (–0.0211; 0.0532)		528 (–1848; 2903)		32,845	47%	51%
≥80 years (13%)	0.0489 (–0.0202; 0.1180)		484 (–2117; 3085)		9,900	62%	71%
Patients with previous resource use in social sector							
No resource use in social sector 12 months prior to randomization (64%)	0.0180 (–0.0054; 0.0414)	0.894	1396 (290; 2503)	0.228	77,622	7%	18%
Resource use in social sector 12 months prior to randomization (36%)	0.0143 (–0.0322; 0.0607)		–1205 (–5144; 2734)		THC dominant	89%	89%
Delivery site							
Delivery site 1 (7%)	0.0675 (0.0357; 0.0993)	0.102	3952 (2952; 4952)	0.000	58,520	0%	6%
Delivery site 2 (10%)	–0.0033 (–0.0311; 0.0245)		3375 (1870; 4881)		UC dominant	1%	3%
Delivery site 3 (10%)	0.0033 (–0.0712; 0.0779)		–12 (–2344; 2319)		THC dominant	55%	56%
Delivery site 4 (5%)	0.0397 (0.0061; 0.0732)		–290 (–1026; 446)		THC dominant	90%	93%
Delivery site 5 (7%)	–0.0007 (–0.0322; 0.0308)		–981 (–2985; 1023)		1,389,780	71%	70%
Delivery site 6 (4%)	0.0308 (–0.0117; 0.0733)		–9138 (–12087; –6188)		THC dominant	100%	100%
Delivery site 7 (4%)	0.0193 (–0.0171; 0.0557)		262 (–248; 772)		13,549	58%	64%
Delivery site 8 (11%)	0.0383 (–0.0027; 0.0792)		–2545 (–2848; –2242)		THC dominant	100%	100%
Delivery site 9 (10%)	0.0160 (–0.0032; 0.0353)		416 (72; 759)		25,921	51%	59%
Delivery site 10 (32%)	0.0028 (–0.0379; 0.0435)		1062 (94; 2029)		376,794	19%	26%

Note: *Wald test for interaction between treatment and the subgroup variable. ##QALYs and total costs were not simultaneously controlled for age. All results are imputed.
Abbreviations: QALY, quality adjusted life year; COPD, chronic obstructive pulmonary disease; UC, usual care; THC, telehealthcare; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICER, incremental cost-effectiveness ratio; Pr, probability.

ranging from low probabilities of cost-effectiveness (eg, 0%) to very high (eg, 100%) at the applied WTP threshold values. This is primarily due to cost savings.

Furthermore, from Table 5, it can be seen that no dominant courses of action can be found for comorbidities or gender. There is a tendency for coronary heart disease and diabetes to reduce the likelihood of achieving cost-effectiveness of telehealthcare (ICER point estimates increases from €26,527

per QALY with no comorbidities to €189,373 per QALY with coronary heart disease, and from €27,573 per QALY to €160,724 per QALY with diabetes). Telehealthcare for patients with mental illness, on the other hand, seems more likely to be cost-effective, since the ICER point estimate changes from €59,378 per QALY without mental illness to €2,135 per QALY with mental health problems. The results also contain tendencies for telehealthcare to men to be more

cost-effective than for women (ICER €49,917 per QALY for men and €77,890 per QALY for women), because they achieve a higher QALY gain, albeit also higher costs. But uncertainties, particularly surrounding gender, are large.

Discussion

Based on the trial-based economic evaluation in the cluster-randomized Danish Telecare North Trial,[14] this subgroup analysis demonstrates no statistically significant differences in incremental QALYs and incremental total costs, except for costs across municipalities/delivery sites. The tendency is that incremental QALYs are small and positive across subgroups (except for patients with moderate COPD [GOLD 2] and for patients in some delivery sites). Therefore, cost-effectiveness results in subgroups mostly reflect that cost savings have occurred here.

Telehealthcare for patients with severe COPD (GOLD 3) is more likely to be cost-effective than in other COPD severities. This was primarily driven by cost savings in hospital admissions and primary-care contacts. Telehealthcare for patients with other COPD severities is less likely to be cost-effective due to higher total costs. Results also indicate that existing resource patterns of patients and delivery site might have a strong influence on cost-effectiveness, possibly stronger than the included health or sociodemographic characteristics. Furthermore, telehealthcare for patients younger than 60 years is more likely to be cost-effective. No firm cost-effectiveness conclusions could be made of the included comorbidities and gender.

Strengths and limitations

To date, there is almost no knowledge of heterogeneity in cost-effectiveness for COPD patients in telehealthcare research. This study has sought to nuance the available evidence by presenting incremental costs, incremental QALYs, and the uncertainty around these estimates in a set of subgroups from an economic evaluation alongside a relatively large clinical trial. These subgroup analyses follow analytical good practices when presenting heterogeneity analyses in cost-effectiveness research by presenting treatment-by-covariate interaction from a single clinical trial[22] that makes use of patient-level data routinely captured in Danish registers. We have also quantified the uncertainty surrounding the cost and QALY estimates by probabilistic sensitivity analysis.[22]

On the other hand, if the study should be used for inferential purposes, it is a limitation that analyses were conducted post hoc and that there is no statistical power to conclude that the differences found are no more than random noise in the data. However, this is a weakness that is shared with most cost-effectiveness studies conducted alongside clinical trials, which are usually only powered to test differences in some clinical measure. Another limitation of the study is that only 61% of the participants had complete registrations of all cost categories and EQ5D summary scores.

Comparison with other studies

Early studies on cost-effectiveness of patients with COPD have focused on patients with severe or very severe COPD (GOLD 3 and GOLD 4).[1–6] They all demonstrate a potential for cost savings without sacrificing effect, although the methodological quality is rather low.[23] This study included patients with all GOLD 1–4 severities and pinpoints that telehealthcare for GOLD 3 classified patients is more likely to be cost-effective and even potentially cost saving. Furthermore, a recently published economic evaluation for GOLD 3 patients concluded that telehealthcare was not likely to be cost-effective, except maybe for patients without comorbidities.[24] Although the uncertainty around this conclusion is high, the fact that the absence of comorbidities is important for achieving cost-effectiveness – depending on the type of comorbidity – is also indicated in this study. Another recently published economic evaluation concluded that telehealthcare was unlikely to be cost-effective for the patients with COPD who were included.[8] The study included 256 patients with all COPD severities, but only 34% patients with severe COPD. Moreover, 68% of subjects had one or more comorbidities. Applying the conclusions from this subgroup analysis might explain this result.

Implications for clinicians and decision-makers

A major challenge in assessing telehealth is that its adoption may give rise to various organizational impacts.[25] Cost-effectiveness may depend on how it is embodied in existing healthcare delivery practices (eg, differences in healthcare practices or motivation and experiences of caregivers and patients). This study indicates that patient's existing resource pattern is important for achieving cost-effectiveness. A plausible reason could be that, if healthcare professionals responsible for monitoring the patients are unfamiliar with a particular patient's history or exacerbation behavior, telehealthcare might be at risk of being an add-on to usual care and not a substitute, because it is difficult for them to evaluate whether a patient is in need of hospital admission during an exacerbation or if the exacerbation could be handled in another more cost-effective way. Furthermore, when

telehealthcare is implemented, patients could become more aware of their disease, or delivery sites could discover patients with COPD that had an unmet need for treatment and care that would not have been discovered otherwise. In our study, this could explain the probabilities of cost-effectiveness for patients with or without resource use in municipalities prior to randomization. This would mean that the implementation context of telehealthcare is important for achieving cost-effectiveness. Variations in practices, workflow, and management attention across healthcare delivery sites are also plausible,[26,27] but not quantified in this study.

Future studies

Despite more than two decades of research, it is still not possible unequivocally to identify which types of telehealthcare technologies would be cost-effective for certain patient types.[28] One possible reaction is to suggest that it is "time to pause" the widespread application of telehealthcare until well-designed longer term multicenter studies with appropriate follow-up (ie, continue summative evaluation but possibly with more ambitious or complicated analytical designs) have proven the benefits of the technology.[29] Another reaction is to focus more on the context of implementation by seeking to integrate formative evaluation designs in cost-effectiveness analyses. Future research should focus more on contextual and/or implementation factors for telehealthcare adoption – for example, behavior and engagement of patients and health professionals; how organizational cultures, incentive systems, and management support the adoption of telehealthcare; or how telehealthcare could be embedded in existing workflows. This work should be focused on explaining how context and implementation factors are related to differences in included cost-categories or perceptions of health-related quality of life in order to achieve cost-effectiveness.

Some contexts and implementation factors may be difficult to identify or define a priori. In fact, one could argue that valuable information would be lost if post hoc subgroup analyses are not conducted due to clinical research practices and the fear of data-dredging. That a heterogeneity analysis has been conducted post hoc must, therefore, not routinely be an obstacle for learning more about the consequences of implementing medical technologies such as telehealthcare.

Acknowledgments

Author contributions

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material
Details of the applied linear mixed-effects models

This study applied linear mixed-effects models, which are also known in the literature as random effects models, multilevel models, or hierarchical linear models. Linear mixed-effects models are used to analyze data that have a hierarchical or nested structure[1] (eg, patients nested in hospitals, repeated measurements taken from the same in individuals, or, as in this case, patients within municipality districts).

Linear mixed-effects models can be used in cost-effectiveness research conducted alongside cluster-randomized trials (ie, where randomization is conducted at a different level than the individual patients – in this case, municipality districts),[2–4] because it is plausible that resource consumption or costs, health-related quality of life, or death to a certain degree, might be more similar within clusters than they are across clusters. This cluster effect must be taken into account in order to obtain valid parameter estimates and standard errors due to the violation of the independence assumption between observations in ordinary least squares regression.[1–3]

Mixed models contain both fixed effects and random effects. Fixed effects are analogous to standard OLS regression coefficients and are estimated directly. However, random effects are not directly estimated but are summarized according to the variance–covariance structure of the model.[1]

A basic two-level linear mixed-effects model with two covariates for both total costs and QALY gain with treatment-by-covariate interaction is presented below:

$$\text{Total cost}_{ij} = \gamma_0 + \gamma_1 T_j * Z_{ij} + X_{ij} + r_j + \varepsilon_{ij}$$
$$\text{QALY}_{ij} = \beta_0 + \beta_1 T_j * Z_{ij} + X_{ij} + s_j + u_{ij}$$

Where i is the patient identification number; j the cluster identification number; β_0 and γ_0 are model intercepts, and T_j the treatment indicator ($T_j = 0$ for clusters in control group; $T_j = 1$ for clusters in intervention group). γ_1 and β_1 are incremental total costs and incremental QALYs; Z_{ij} is the covariate variable used in the particular subgroup analysis; X_{ij} is an additional covariate, r_j and s_j are random components, which represent the differences in the cluster mean costs and outcomes from the overall means in each treatment group, and, finally, ε_{ij} and u_{ij} are error terms to the model that are assumed normally distributed.

In our study, this basic tow-level model was expanded with the mentioned additional covariates to allow for baseline adjustment of the treatment effects found in each subgroup analysis (total costs models were controlled for baseline EQ5D-score, baseline costs, age, baseline FEV1%, presence of musculoskeletal disease, and clustering; QALY models were controlled for baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer, and clustering).

In STATA 12.1 the xtmixed procedure can be used to fit linear mixed models by maximum likelihood estimation.[5]

A reference category in each subgroup was used, and treatment effects for other subgroup categories were found by linear combination of treatment effects within subgroups. A deterministic incremental cost-effectiveness ratio (ICER) is then found by dividing each treatment effect found in the totalcost regression (γ_1) with each treatment effect found in the QALY regression (β_1).

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