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Cost-effectiveness of integrated COPD care: the RECODE cluster randomized trial

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Abstract

Background

We conducted a cost-effectiveness analysis of a COPD disease management (COPD-DM) program in primary care, called RECODE, in the Netherlands. A multidisciplinary team of caregivers was trained in motivational interviewing, setting-up individual care plans, exacerbation management, implementing clinical guidelines and redesigning the care process. In addition, clinical decision making was supported by feedback reports provided by an ICT program.

Methods

In a two-year cluster-randomized trial (1086 COPD patients, 40 clusters), the COPD-DM program was compared to usual care. We investigated impact on health outcomes and costs.

Results

The intervention costs were €324 per patient. Excluding these costs, the intervention group had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both groups, except for 0.04 (95% CI -0.07 to -0.01) less quality-adjusted life-years in the intervention group.

Conclusion

This integrated care program for COPD patients that mainly included professional-directed interventions was not cost-effective in primary care.

Strengths and limitations of this study

- It is the largest and most pragmatic Dutch RCT trial to date assessing the cost-effectiveness of COPD disease management in primary care.
- The 2-year follow-up period, the broad range of health outcomes and costs (including program costs) measured and the statistically sophisticated analyses ensure the robustness of the results.
- The uncertainty in the cost-effectiveness of the disease management programs is adequately estimated and illustrated enabling the appropriate interpretation of the results.
- The control group was likely to be exposed to quality improvement initiatives as part of usual care.

Introduction

Disease management programs for Chronic Obstructive Pulmonary Disease (herein, COPD-DM) have been developed to change COPD care from acute, reactive and one-size-fits-all into integrated, pro-active and tailor-made. To stimulate the implementation of such programs in the Netherlands, a new payment policy (i.e. bundled payment) was recently implemented.[1] However, the wide implementation of these programs in the Netherlands, as is currently ongoing would benefit by a justification from a cost-effectiveness perspective.

Recent systematic literature reviews of COPD-DM programs showed favourable effects on both health outcomes and costs (mainly due to decreased hospitalization).[2,3] However, previous economic studies had poor methodological quality.[2,4] Most studies did not measure all relevant costs and health outcomes and did not perform incremental cost-effectiveness analyses.[2] Furthermore, the generalizability of the outcomes of these studies was low, due to the inclusion of mainly severe COPD patients and the exclusion of patients with multi-morbidity.[2,5,6]

We aimed to conduct a comprehensive cost-effectiveness analysis (CEA) of a COPD-DM program in primary care compared to usual care in the Netherlands. This CEA was performed as part of a two-year cluster randomized controlled trial (RCT) evaluating the clinical effects of this RECODE program (acronym for Randomized clinical trial on Effectiveness of integrated COPD management in primary carE). Design and full clinical results of this study have been reported elsewhere).[7,8]

Methods

This study was approved by the medical ethics committee, performed according to the study protocol[7], national[9] and international[10] guidelines for pharmaco-economic research, and reported according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).[11]

Design and Intervention

RECODE is a 2-year cluster randomized trial in which 40 clusters of primary care teams were randomized to the COPD-DM program or usual care. The 20 teams of the intervention group were trained in essential components of effective COPD-DM: proper diagnosis, optimizing medication adherence, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation, and nutritional support. In addition, the teams learned the details of a web-based computer program for measuring and reporting process and outcome performance indicators, named ZORGDRAAD. This ICT application included a patient and provider portal that facilitated the communication within the multi-disciplinary teams as well as between care providers and patients. At the end of the 2-day course, each team developed a plan with steps to be taken in order to redesign the care process and integrate the COPD-DM program into their daily practice. After the course, the teams were invited to join refresher courses, received regular feedback reports on patients' outcomes and had access to ZORGDRAAD. The local healthcare insurer reimbursed physical reactivation for patients with an Medical Research Council (MRC) dyspnoea score >2, also if these patients had no supplementary insurance. All practices were flexible in determining and following their individual plans. Therefore, the mix and intensity of interventions for individual patients depended upon their health status, personal needs and preferences, as well as the actions taken by the team. Healthcare providers in the usual care group were asked to continue providing care as usually. Indicators of care as usual are reported before.[7]

Target population

The enrolment of primary care teams and their COPD patients took place between September 2010 and September 2011. Participating teams included at least one general practitioner(GP), one practice nurse and one physiotherapist. Patients had physician-diagnosed COPD according to GOLD guidelines.[12] Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion criterion. The GPs verified that the included patients fulfilled the inclusion and exclusion

criteria. All participating GPs and COPD patients provided written informed consent before participation.

Outcomes

Costs were related to the following outcome measures:

I. quality-adjusted life years(QALYs) based on the EuroQol-5D (EQ-5D) utility values using the Dutch value set[13,14];

II. proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement ≥ 0.4) on the Clinical COPD Questionnaire(CCQ)[15,16];

III. proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory Questionnaire(SGRQ)[17,18];

IV. total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic corticosteroids and/or antibiotics, but did not require hospitalization. This information was extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as a worsening of symptoms that required a hospital admission. Hospital admissions were obtained from the resource use questionnaires and the EMR.

The EQ-5D, CCQ, SGRQ, and resource use questionnaire were administered at baseline, 6, 9, 12, 18, and 24 months.

Costs

Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a societal perspective. The healthcare perspective included all costs covered by the healthcare budget, i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse, physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions, emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective additionally included travel costs and costs of productivity loss due to absence from paid work.

Patients reported the healthcare utilization (excluding medication), travel costs, days of absence from paid work due to illness (absenteeism) and lost productivity while being at work (presenteeism) in a resource use questionnaire with a recall period of three months.

The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs were obtained from the Dutch manual for costing research[9] and inflated to 2013 using the general consumer price index.[19] The costs of medications were obtained from the GIP-Databank and

included value added tax and pharmacist dispensing fees.[20] The productivity costs were estimated using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick employee is not replaced (the friction period).[21] We used a friction period of 115 days.[9]

The intervention costs, defined as costs of training the teams, costs of the ICT support, and costs of the monitoring reports, were calculated based on (refresher) course attendance, computer-documented ICT-use, and estimated time involved in producing monitoring reports.

Statistical analysis

Data analysis was performed according to the intention-to-treat principle. Data from patients who discontinued the trial prematurely were included in the analysis up to the point of drop-out. Additionally, patients that dropped-out during the first year were asked to fill in a CCQ questionnaire at 12 months, if possible.

We used repeated measures models to assess differences between RECODE and usual care, correcting for time, age, gender, MRC dyspnoea score >2, baseline score and clustering of patients. The distribution and link function for each outcome was selected after comparing the goodness-of-fit of models with different specifications of the distribution and link functions. Models that had the lowest Akaike's Information Criterion were selected.

EQ-5D utilities were analysed using linear mixed models with a normal distribution and identity link. We calculated the number of QALY's for each patient as the area under the predicted utility curve, using linear interpolation between two utility measurements. Generalized linear mixed models with a binary distribution and logit link were used to analyse the proportion of patients with a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated using generalized linear mixed models with negative binomial distribution and log link. Costs were analysed with generalized linear mixed models using a log-normal distribution and identity link. The cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly extrapolated to include month 0 to 3.[22] The same was done for the cost estimate of month 15 to 18 and 21 to 24.

Cost-effectiveness

Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented. Taking a multi-outcome approach is in line with recent guidelines.[23]

Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times. Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[24] Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs. The 5,000 ICERs were plotted on cost-effectiveness planes.[25] In a cost-effectiveness plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs. The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 1). Finally, the probability that the RECODE program is cost-effective using different thresholds for the monetary value of a QALY was shown in cost-effectiveness acceptability curves.[26] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

Sensitivity and subgroup analyses

Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other with a one year instead of a two year time horizon. Five subgroup analyses were performed to study the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-specified in the study protocol and the power calculation was based on the subgroup analyses by MRC dyspnoea score>2.[7]

Results

Patients

The flowchart of patient inclusion has been presented elsewhere.[8] In total, we included 1086 COPD patients from 40 teams in the trial, 554 in the RECODE group and 532 in the usual care group. The baseline characteristics of the patients in the RECODE and usual care group are summarized in Table 1. The only statistically significant difference was a higher percentage of males in the usual care group (51 vs. 57%).

The proportion of patients who completed the trial was 76% in the RECODE group and 74% in the usual care group. Length of follow-up among the drop-outs was not significantly different between groups, with a mean (±sd) follow-up of 20.5 (±0.29) and 20.0 (±0.33) months, respectively. Patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ, SGRQ, MRC-dyspnoea, and EQ-5D. Baseline characteristics between the drop-outs of the RECODE group and the usual care group were not significantly different.

[TABLE 1]

Costs

The intervention costs are presented in Table 2. The total intervention costs per patient ranged from €103 to €587 across clusters, with a mean (±sd) of €324 (±156) per patient. This variation is explained by the number of COPD patients per team, the use of the ICT system, the number of healthcare providers participating in the courses, and the different locations of the courses. The labour costs of the attendees of the RECODE courses were the main driver of the intervention costs (54%).

Complete 2-year medication data of 500 patients (90%) in the RECODE group and 478 (90%) in the usual care group were extracted from the EMRs. More than 85% of the participants used medication for obstructive airway diseases in the 2-year trial period (Table 3).

Of the 1086 patients 93% had complete health care utilization data at 6 months, 79% at 9 months, 88% at 12 months, 73% at 18 months, and 75% at 24 months. This was similar for both groups. The unit costs, observed mean use of resources, and associated costs, as reported by the patients are presented in Table 3. In both groups, important cost drivers were hospital admissions, home care, and productivity loss. Excluding intervention costs, the adjusted mean total 2-year costs (estimated from the generalized linear mixed model) were significant higher in the RECODE group

than in the usual care group by €584 from the healthcare perspective and €645 from the societal perspective (Table 4).

[TABLE 2]

[TABLE 3]

[TABLE 4]

Outcomes

Over a two year period, the number of QALYs was 0.04 (p=0.02) lower in the RECODE group than in the usual care group while there was no significant difference in percentage of patients with a MCID in CCQ, nor in any of the other outcomes (Table 4).

Cost-effectiveness

From a healthcare and societal perspective, the point-estimates of costs and effects pointed towards higher costs and lower effects of the RECODE program, resulting in negative ICERs. The CE-planes of the different outcomes showed that the majority of the bootstrap replications (>98%) had higher costs. Furthermore, more than half of the bootstrap replications fell within the north-west quadrant of the plane indicating that RECODE was dominated by the usual care group, e.g. more costs and less effects.

Sensitivity analyses

When including the intervention costs, the cost difference, which favoured usual care, further increased to a difference of €883 from the healthcare perspective and €1,005 from the societal perspective (Appendix 2).

Using a 12-month instead of a 24 month time horizon, the costs per patient were significantly higher in the RECODE group in comparison with the usual care group by €408 from the healthcare perspective and €370 from the societal perspective (Appendix 3). After 12 months, there was no significant difference in QALYs, or any of the other outcomes, except for the percentage of patients improving at least the MCID in CCQ, which was 7% less in the RECODE group than in the usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was

8% and 79%, respectively (Appendix 4). From a societal perspective these probabilities were slightly higher, i.e. 15% and 81%.

Subgroup analyses

Only age showed a significant interaction with the effect of RECODE on costs (Appendix 5,6). The difference in costs (healthcare and societal perspective) between RECODE and usual care was significantly lower in patients younger than 65 years, than in patients above 65 years. There was also a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that RECODE is cost-effective within the subgroup of patients <65 years.

Discussion

This study compared the costs and health effects of a COPD-DM program in primary care (RECODE) with usual care in the Netherlands. Our results show that RECODE is not cost-effective from a healthcare as well as a societal perspective. The point-estimates of costs and effects pointed towards higher costs and no significant difference in effects, except for 0.04 fewer QALYs. The majority of bootstrap replications in the CE-planes showed that RECODE was dominated by usual care.

These unexpected findings cannot be related to weaknesses in the research design. The strength of our study lies in the inclusion of a large and representative group of COPD patients recruited in primary care. To avoid contamination, randomization was performed at cluster level. Since blinding of participants and clinicians was impossible, blinded research nurses collected the data, while patients were instructed not to report back on their type of intervention. Additional strengths of this study are the 2-year follow-up period, the broad range of health outcomes and costs categories included and the sophisticated analyses that took into account the hierarchical nature of the data. The decrease in utility, especially in the second year, might have been caused by the consistent pattern of no effect or a worse effect on the intermediate outcomes. The reduction in utility and increase in costs might also result from the increased awareness by patients of their health problems as an effect of being enrolled in the RECODE program.

There are several possible explanations why the RECODE intervention was not found to be cost-effective. Firstly, it may be due to the relatively low intensity of our pragmatic intervention. The RECODE program did not require the teams to implement all elements of the program. For instance, 70% of the intervention teams attended the refresher courses and 50% actively used the ICT system ZORGDRAAD. Consequently, the intensity of the intervention for individual patients was not only dependent upon health status, personal needs and preferences of the individual patients, but also on the level of implementation of the DM interventions and the context within which each team operates. Further research is required to understand the conditions for a successful implementation and thus cost-effectiveness of a DM program.

Secondly, it is questionable whether the pragmatic provider-oriented interventions of the RECODE program were optimally translated into patient-oriented interventions. This is important because it has been shown that successful COPD-DM programs mainly include patient-oriented interventions.[2,3] Literature showed that exercise is an important success factor of a COPD-DM program[3] and education, exercise and relaxation are important factors for reducing the use of

urgent and unscheduled healthcare among people with COPD.[27] In our study, physical exercise was not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

Thirdly, there was limited room for improvement in comparison with previous studies due to the relatively high standard of COPD care in the Netherlands[28] , the low proportion of severe COPD patients in this study[2,3] and the selective drop-out of patients who are more severely ill and thus had the greatest potential for improvement.[29]

Fourthly, changes in healthcare occurred during the study period that affected COPD care in the RECODE as well as the usual care group. Since July 2010, a new bundled payment scheme for COPD patients has been introduced in the Netherlands to stimulate the integration of care.[30] In this scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes secondary care and medications, it primarily stimulates the cooperation between different providers in the primary care setting. This increased attention for integrated chronic and the ability to reimburse COPD interventions such as smoking cessation and nutritional counselling could have stimulated integrated care in the usual care group too.

In conclusion, this comprehensive economic evaluation of an integrated care program in primary care showed that the program increased costs but did not improve health outcomes. It even reduced QALYs. This is most likely due to the fact that the interventions targeted professionals instead of patients and were sub-optimally implemented, the relatively mild COPD population, and the national reforms in COPD care.

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CONTRIBUTORSHIP : MPHMR, WJJA, JG, and NHC conceived and designed the study. MRSB, ALK, AT, and CB acquired the data. MRSB, AT, and MPHMR analysed and interpreted the data. MRSB drafted the manuscript. ALK, NHC, AT, JG, WJJA, and MPHMR advised on the preparation of the manuscript. All authors read, edited, and approved the final version of the manuscript.

CONFLICT OF INTEREST: There are no competing interests.

ETHICAL APPROVAL: The study was reviewed and approved by the medical ethical committee of the Leiden University Medical Centre, the Netherlands. All general practitioners and participants gave written informed consent.

DATA SHARING: No additional data available.

DECLERATION OF TRANSPARENCY: The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Baseline characteristics

	RECODE (n=554)	usual care (n=532)
Age (years), mean (SD)	68.2±11.3	68.4±11.1
Male sex (%)	50.5	57.3*
Employment (%)	27.7	28.8
Low education/ low Social Economic Status (%)	39.2	41.5
Marital status: Single (%)	37.0	38.3
FEV1% predicted , mean (SD)	67.7 (20.3)	67.9 (20.5)
Current smoker (%)	34.8	38.7
Former smoker (%)	53.8	52.6
Moderate exacerbation in the last year, mean (SD)	0.36 (0.83)	0.33 (0.78)
Severe exacerbation in the last three months, mean (SD)	0.02 (0.18)	0.02 (0.17)
Charlson comorbidity index	2.35 (1.26)	2.32 (1.27)
Major cardiovascular disease (%)	14.6	17.7
Hypertension (%)	35.4	38.3
Diabetes (%)	14.6	14.8
Depression (%)	9.8	10.1
MRC score, mean (SD)	2.06 (1.30)	1.95 (1.26)
MRC score > 2 (%)	35.1	31.6
CCQ score, mean (SD)	1.54 (0.98)	1.46 (0.96)
SGRQ total score, mean (SD)	36.7 (21.1)	34.5 (19.8)
EQ-5D score, mean (SD)	0.74 (0.25)	0.73 (0.28)

**Significant (p<0.05), FEV1= forced expiratory volume in 1 second, MRC=Medical Research Counsil, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire,EQ-5D=EuroQoL-5D ,*

Table 2. Intervention costs (in euros, 2013)

DM intervention	Cost description	% teams with any use of	Mean cost per team ± SD (€)	Mean cost per patient ± SD (€)
RECODE Course	*Catering*	100	119 ± 56	4.78 ± 2.45
	Location	100	3 ± 4	0.15 ± 0.21
	Presenters	100	84 ± 37	50.9 ± 36.31
	*Other costs**	100	1,174 ± 587	3.63 ± 2.39
	Labour costs attendees	100	4,008 ± 1,683	163.72 ± 87.65
	Travel	100	48 ± 30	1.94 ± 1.24
Refresher course	*Catering*	70	29 ± 25	1.1 ± 0.97
	Location	70	-	-
	Presenters	70	146 ± 123	5.94 ± 6.63
	*Other costs**	70	-	-
	Labour costs attendees	70	273 ± 273	10.84 ± 11.69
	Travel	70	7 ± 6	0.25 ± 0.23
ICT system ZORGDRAAD	*Labour costs of ICT use*	50	42 ± 86	1.45 ± 2.65
	Labour costs of ICT support	100	1,354 ± 0	57.80 ± 24.07
Monitoring reports	*Labour costs of feedback report at baseline*	100	333 ± 141	13.56 ± 6.2
	Labour costs of feedback report at 6 months	100	67 ± 28	2.71 ± 1.24
	Labour costs of feedback report at 12 months	100	133 ± 57	5.42 ± 2.48
Total			7,862 ± 2,543	324 ± 156

** Other costs includes material and equipment used during the course*

Table 3. Unit costs, data sources, mean use of resources and associated costs over the 2-years, as reported by the patients (unadjusted)

	Unit cost (€)	Source*	RECODE			usual care		
			Any use (%)	Mean use	Mean cost ± SD (€)	Any use (%)	Mean use	Mean cost ± SD (€)
Costs from healthcare perspective								
GP, (home) visits, phone contacts	15-46	a	91	16.23	476 ± 504	89	14.02	401 ± 450
Practice nurse, visits	23	b	74	5.51	131 ± 277	75	5.18	109 ± 166
Specialist, visits	78	a	78	10.05	784 ± 1,037	78	9.84	768 ± 973
Emergency department, visits	163	a	26	0.78	127 ± 284	23	0.79	129 ± 346
Physiotherapist, visits	39	a	53	25.82	1,007 ± 1,770	45	16.33	637 ± 1,260
Dietician, visits	29	a	21	1.45	42 ± 141	19	1.21	35 ± 148
Podiatrist, visits	32	b	43	3.78	121 ± 203	40	3.27	105 ± 167
Speech therapist, visits	36	a	3	0.12	4 ± 42	2	0.28	10 ± 158
Occupational therapy, visits	24	a	4	0.29	7 ± 76	3	0.32	8 ± 83
Rehabilitation centre, visits	78	a	12	3.86	459 ± 2,157	12	3.01	358 ± 1,731
Home care, hours of household help	26	a	22	34.42	895 ± 2,287	20	31.01	806 ± 2,171
Home care, hours of personal care	47	a	9	8.28	389 ± 1,995	8	9.49	446 ± 2,327
Home care, hours of nursing	70	a	6	2.11	148 ± 1,108	6	2.39	167 ± 1,064
Home care, other, hours	48	a	1	0.47	22 ± 262	2	0.65	31 ± 309
Hospital stay, days	493	a	25	4.65	2,293 ± 5,915	25	4.84	2,388 ± 7,522
Intensive care unit, days	2,356	a	5	0.49	1,161 ± 11,316	2	0.14	328 ± 2,658
Drugs for obstructive airway diseases	-	c	84	-	945 ± 814	84	-	934 ± 1,024
Other medication	-	c	91	-	1,367 ± 3,421	90	-	1,131 ± 2,506
Costs from societal perspective								
Travel expenses, public transport/car, KM	0.22	a	94	189.00	42 ± 56	92	174.43	38 ± 59
Productivity loss, absenteeism hours	31-43	a	11	47.74	1,698 ± 8,344	11	42.89	1,649 ± 8,448
Productivity loss, presenteeism hours	31-43		8	10.38	376 ± 2,304	9	10.92	374 ± 1,774

** Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research[9], (b) The Dutch Healthcare Authority NZA (c) GIP Databank [20]*

Table 4. Results from the cost-utility and cost-effectiveness analysis from the base case (in euros, 2013)

		Costs			Effect			cost-effectiveness planes				
		RECODE	Usual Care	Difference (95% CI)	RECODE	Usual Care	Difference (95% CI)	ICER	NW C↑E↓	SW C↓E↓	NE C↑E↑	SE C↓E↑
Cost per QALY	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-15,720**	97.9	1.3	0.8	0.0
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-17,358**	97.3	1.9	0.8	0.0
Cost per exacerbation avoided	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-4,211**	91.3	1.2	7.4	0.1
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-4,650**	90.7	1.8	7.4	0.1
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-35,772**	75.2	1.0	23.5	0.3
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-39,498**	74.8	1.4	23.3	0.5
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-46,508**	66.5	0.9	32.3	0.4
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-51,353**	66.1	1.3	32.0	0.6

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west (more cost and less effects), SW=south-west (less cost and less effects), NE=north-east (more cost and more effects) , SE=south-east (more cost and less effects), C= difference in costs, E=difference in effects.*

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Appendix 1. Sensitivity analyses: impact on cost-utility and cost-effectiveness, with intervention costs

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
With intervention costs												
Cost per QALY	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-23,792**	99.1	0.0	0.9	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-27,053**	99.0	0.2	0.9	0.0
Cost per exacerbation avoided	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-6,373**	92.5	0.0	7.5	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-7,247**	92.4	0.2	7.5	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-54,139**	76.2	0.0	23.8	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-61,559**	76.1	0.1	23.8	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-70,388**	67.4	0.0	32.6	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-80,035**	67.3	0.1	32.6	0.1

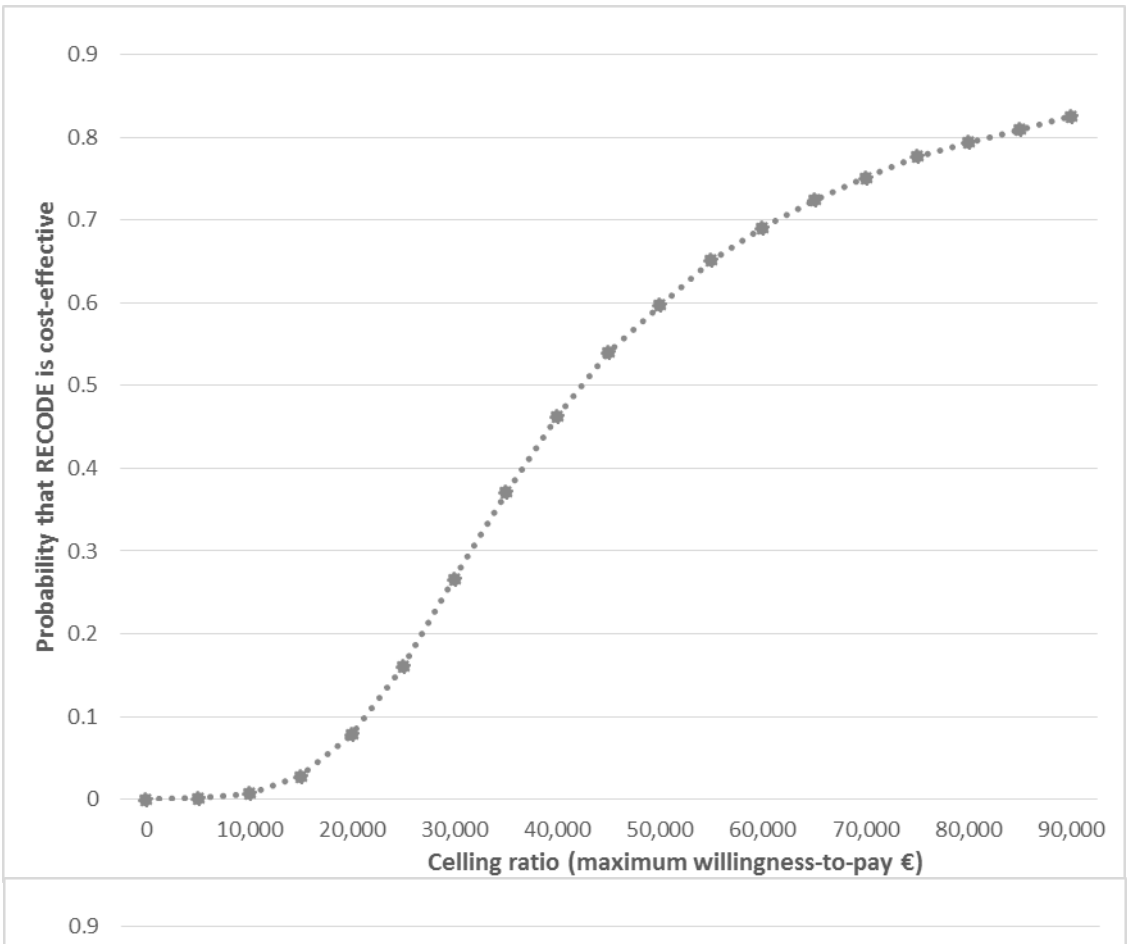
** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 2. Sensitivity analyses: impact on cost-utility and cost-effectiveness, 12 months' time horizon

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
12 months' time horizon												
Cost per QALY	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.71	0.70	0.01 (-0.001 – 0.02)	**42,458**	3.6	0.0	96.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.71	0.70	0.01 (-0.001 – 0.02)	**38,471**	3.6	0.0	95.8	0.6
Cost per exacerbation avoided	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.38	0.32	-0.06 (-0.14 – 0.05)	**-7,401**	87.3	0.0	12.7	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.38	0.32	-0.06 (-0.14 – 0.05)	**-6,706**	86.8	0.5	12.7	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.19	0.26	-0.07** (-0.14 – -0.02)	**-5,582**	99.6	0.0	0.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.19	0.26	-0.07** (-0.14 – -0.02)	**-5,058**	99.0	0.6	0.4	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.36	0.37	-0.01 (-0.05 – 0.03)	**-36,869**	69.4	0.0	30.6	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.36	0.37	-0.01 (-0.05 – 0.03)	**-33,408**	69.1	0.3	30.3	0.2

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 3. Cost-effectiveness acceptability curves, healthcare (upper) and societal perspective (lower) with a 12 months' time horizon



Appendix 4. Subgroup analyses (age, gender MRC)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY age subgroups															
HP	<65 years	N=411	€ 3,975	€ 3,801	€ 174 (-434 – 711)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-9,820**	58.0	20.4	15.8	5.9
	≥65 years	N=675	€ 6,029	€ 5,028	€ 1,001* (248 – 1,701)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,698**	98.8	0.5	0.7	0.0
SP	<65 years	N=411	€ 5,374	€ 5,158	€ 216 (-737 – 1,035)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-12,171**	54.1	24.2	15.1	6.5
	≥65 years	N=675	€ 6,064	€ 5,079	€ 985* (224 – 1,679)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,409**	98.7	0.6	0.7	0.0
Cost per QALY gender subgroups															
HP	Men	N=585	€ 4,725	€ 4,344	€ 381 (-250 – 963)	0.92	1.53	1.57	-0.04* (-0.08 – -0.01)	0.10	**-8,951**	88.4	10.5	1.1	0.1
	Women	N=501	€ 5,527	€ 4,756	€ 771 (-44 – 1,472)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-35,680**	80.4	2.7	16.4	0.4
SP	Men	N=585	€ 5,226	€ 4,924	€ 302 (-502 – 1,000)	0.75	1.53	1.57	-0.04* (-0.08 – -0.01)	0.10	**-7,090**	78.2	20.7	0.9	0.2
	Women	N=501	€ 6,302	€ 5,331	€ 971* (106–1,748)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-44,939**	81.8	1.4	16.7	0.2
Cost per QALY MRC subgroups															
HP	MRC≤2	N=725	€ 3,927	€ 3,500	€ 427 (-29– 821)	0.67	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,060**	99.5	2.9	1.5	0.1
	MRC>2	N=361	€ 8,721	€ 7,231	€ 1,489 (-164 – 2,881)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-42,301**	81.2	2.8	15.5	0.5
SP	MRC≤2	N=725	€ 4,543	€ 4,101	€ 443 (-191 – 1,029)	0.52	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,464**	90.8	7.6	1.3	0.2
	MRC>2	N=361	€ 9,358	€ 7,744	€ 1,614 (-161 – 3,115)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-45,846**	81.0	3.0	15.5	0.5

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, MRC=Medical Research Counsil, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 5. Subgroup analyses (FEV1, SES)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY lung function subgroups															
HP	FEV1≥50	N=674	€ 4,797	€ 4,025	€ 773** (198 – 1,287)	0.85	1.47	1.51	-0.04 (-0.07 – 0.003)	0.11	**-21,762**	96.0	0.5	3.5	0.0
	FEV1<50	N=193	€ 7,744	€ 7,415	€ 329 (-1,499 – 1,837)		1.39	1.34	-0.05 (-0.12 – 0.03)		**-10,044**	60.3	29.4	6.9	3.4
SP	FEV1≥50	N=674	€ 5,359	€ 4,537	€ 822* (159 – 1,420)	0.82	1.47	1.51	-0.04 (-0.07 – 0.003)	0.11	**-23,155**	95.5	1.0	3.5	0.0
	FEV1<50	N=193	€ 8,622	€ 8,170	€ 452 (-1,536 –2,139)		1.39	1.34	-0.05 (-0.12 – 0.03)		**-7,310**	63.3	26.5	7.2	3.1
Cost per QALY Social economic status (SES) subgroups															
HP	Low SES	N=399	€ 5,124	€ 4,562	€ 562 (-434 – 1,423)	0.46	1.04	1.09	-0.05 (-0.11 – 0.01)	0.11	**-11,505**	84.2	10.8	4.4	0.5
	Moderate/ high SES	N=590	€ 5,347	€ 4,598	€ 749 (74 – 1,362)		1.54	1.57	-0.03 (-0.07 – 0.01)		**-24,627**	91.9	1.5	6.5	0.1
SP	Low SES	N=399	€ 5,534	€ 4,859	€ 675 (-415 – 1,632)	0.49	1.04	1.09	-0.05 (-0.11 – 0.01)	0.11	**-13,801**	85.3	9.7	4.4	0.6
	Moderate/ high SES	N=590	€ 6,089	€ 5,372	€ 717 (-125 – 1,459)		1.54	1.57	-0.03 (-0.07 – 0.01)		**-23,560**	89.1	4.3	6.2	0.4

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, FEV1= forced expiratory volume in 1 second, SES=Social Economic Status, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

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Cost-effectiveness of integrated COPD care: the RECODE cluster randomized trial

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Abstract

Objectives: To investigate the cost-effectiveness of a Chronic Obstructive Pulmonary Disease (COPD) disease management (COPD-DM) program in primary care, called RECODE, compared to usual care.

Design: two-year, cluster-randomised controlled trial

Setting: 40 general practices in the western part of the Netherlands

Participants: 1086 patients with COPD according to GOLD (Global Initiative for COPD) criteria. Exclusion criteria were terminal illness, cognitive impairment, alcohol or drug misuse, and inability to fill in Dutch questionnaires. Practices were included if they were willing to create a multidisciplinary COPD team.

Interventions: A multidisciplinary team of caregivers was trained in motivational interviewing, setting-up individual care plans, exacerbation management, implementing clinical guidelines and redesigning the care process. In addition, clinical decision making was supported by feedback reports provided by an ICT program.

Main outcome measures: We investigated impact on health outcomes (quality-adjusted life years (QALYs), Clinical COPD Questionnaire, St. George's Respiratory Questionnaire, and exacerbations) and costs (healthcare and societal perspective).

Results: The intervention costs were €324 per patient. Excluding these costs, the intervention group had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both groups, except for 0.04 (95% CI -0.07 to -0.01) less QALYs in the intervention group.

Conclusions: This integrated care program for COPD patients that mainly included professional-directed interventions was not cost-effective in primary care.

Trial registration: Netherlands Trial Register NTR2268

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Strengths and limitations of this study

- It is the largest and most pragmatic Dutch RCT trial to date assessing the cost-effectiveness of COPD disease management in primary care.
- The 2-year follow-up period, the broad range of health outcomes and costs (including program costs) measured and the statistically sophisticated analyses ensure the robustness of the results.
- The uncertainty in the cost-effectiveness of the disease management programs is adequately estimated and illustrated enabling the appropriate interpretation of the results.
- The control group was likely to be exposed to quality improvement initiatives as part of usual care.

Introduction

Disease management programs for Chronic Obstructive Pulmonary Disease (herein, COPD-DM) have been developed to change COPD care from acute, reactive and one-size-fits-all into integrated, pro-active and tailor-made. To stimulate the implementation of such programs in the Netherlands, a new payment policy (i.e. bundled payment) was recently implemented.[1] However, the wide implementation of these programs in the Netherlands, as is currently ongoing would benefit by a justification from a cost-effectiveness perspective.

Recent systematic literature reviews of COPD-DM programs showed favourable effects on both health outcomes and costs (mainly due to decreased hospitalization).[2,3] However, previous economic studies had poor methodological quality.[2,4] Most studies did not measure all relevant costs and health outcomes and did not perform incremental cost-effectiveness analyses.[2] For instance, there is little knowledge on the required investments in implementation of these programs. Furthermore, the generalizability of the outcomes of these studies was low, due to the inclusion of mainly severe COPD patients and the exclusion of patients with multi-morbidity.[2,5,6]

We aimed to conduct a comprehensive cost-effectiveness analysis (CEA) of a COPD-DM program in primary care compared to usual care in the Netherlands. This CEA was performed as part of a two-year cluster randomized controlled trial (RCT) evaluating the clinical effects of this RECODE program (acronym for Randomized clinical trial on Effectiveness of integrated COPD management in primary carE). [7,8]

In the clinical paper we concluded that, after 12 months, the RECODE program did not significantly improve the score on the Clinical COPD Questionnaire (CCQ) compared to usual care, despite an improved level of integrated care and a higher degree of self-reported physical activity.[7] Our current paper includes additional outcome measures not reported in the clinical paper and it reports 24-months results. This is important because it is often argued that it takes time before the effect of DM programs become clearly visible. The added value of a cost-effectiveness analysis is that we report the joint uncertainty in both effects and costs, allowing us to report the probability that the RECODE program would be cost-effective at various threshold values of the maximum acceptable costs per quality-adjusted life year (QALY) gained. Moreover, the publication of results in terms of cost-effectiveness is important to avoid selective reporting of positive studies. The published evidence is used to inform decision makers all across developed countries about whether and which COPD-DM programs to reimburse on a wider scale.

Methods

This study was approved by the medical ethics committee, performed according to the study protocol[8], national[9] and international[10] guidelines for pharmaco-economic research, and reported according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).[11]

Design and Intervention

RECODE is a 2-year cluster randomized trial in which 40 clusters of primary care teams were randomized to the COPD-DM program or usual care. The 20 teams of the intervention group were trained in essential components of effective COPD-DM: proper diagnosis, optimizing medication adherence, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation, and nutritional support. In addition, the teams learned the details of a web-based computer program for measuring and reporting process and outcome performance indicators, named ZORGDRAAD. This Information and Communications Technologies (ICT) application included a patient and provider portal that facilitated the communication within the multi-disciplinary teams as well as between care providers and patients. At the end of the 2-day course, each team developed a plan with steps to be taken in order to redesign the care process and integrate the COPD-DM program into their daily practice. After the course, the teams were invited to join refresher courses, received regular feedback reports on patients' outcomes and had access to ZORGDRAAD. The local healthcare insurer reimbursed physical reactivation for patients with a Medical Research Council (MRC) dyspnoea score >2, also if these patients had no supplementary insurance. All practices were flexible in determining and following their individual plans. Therefore, the mix and intensity of interventions for individual patients depended upon their health status, personal needs and preferences, as well as the actions taken by the team. Healthcare providers in the usual care group were asked to continue providing care as usually. Indicators of care as usual are reported before.[8]

Target population

The enrolment of primary care teams and their COPD patients took place between September 2010 and September 2011. Participating teams included at least one general practitioner (GP), one practice nurse and one physiotherapist. Patients had physician-diagnosed COPD according to GOLD guidelines.[12] Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion criterion. The GPs verified that the included patients fulfilled the inclusion and exclusion

criteria. All participating GPs and COPD patients provided written informed consent before participation.

Outcomes

Costs were related to the following outcome measures:

I. QALYs based on the EuroQol-5D (EQ-5D) utility values using the Dutch value set[13,14];
II. proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement ≥ 0.4) on the CCQ[15,16];
III. proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory Questionnaire(SGRQ)[17,18];
IV. total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic corticosteroids and/or antibiotics, but did not require hospitalization. This information was extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as a worsening of symptoms that required a hospital admission. Hospital admissions were obtained from the resource use questionnaires and the EMR.

The EQ-5D, CCQ, SGRQ, and resource use questionnaire were administered at baseline, 6, 9, 12, 18, and 24 months.

Costs

Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a societal perspective. The healthcare perspective included all costs covered by the healthcare budget, i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse, physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions, emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective additionally included travel costs and costs of productivity loss due to absence from paid work.

Patients reported the healthcare utilization (excluding medication), travel costs, days of absence from paid work due to illness (absenteeism) and lost productivity while being at work (presenteeism) in a resource use questionnaire with a recall period of three months.

The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs were obtained from the Dutch manual for costing research[9] and inflated to 2013 using the general consumer price index.[19] The costs of medications were obtained from the GIP-Databank and included value added tax and pharmacist dispensing fees.[20] The productivity costs were estimated

using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick employee is not replaced (the friction period).[21] We used a friction period of 115 days, i.e. the average duration of vacancies (87 days) increased with the expected number of weeks employers need before taking the decision to place a vacancy for temporary or permanent replacement of the worker (28 days).[22]

The intervention costs, defined as costs of training the teams, costs of the ICT support, and costs of the monitoring reports, were calculated based on course attendance (initial 2-day course and refresher courses), computer-documented ICT-use, and time involved in producing monitoring reports (for each practice, the estimated labour time was 2.5, 0.5, and 1 hour to produce the reports at baseline, 6 months and 12 months, respectively).

Statistical analysis

Data analysis was performed according to the intention-to-treat principle. Data from patients who discontinued the trial prematurely were included in the analysis up to the point of drop-out. Additionally, patients that dropped-out during the first year were asked to fill in a CCQ questionnaire at 12 months, if possible.

We used repeated measures models to assess differences between RECODE and usual care, correcting for time, age, gender, MRC dyspnoea score >2, baseline score and clustering of patients. The distribution and link function for each outcome was selected after comparing the goodness-of-fit of models with different specifications of the distribution and link functions. Models that had the lowest Akaike's Information Criterion were selected.

EQ-5D utilities were analysed using linear mixed models with a normal distribution and identity link. We calculated the number of QALY's for each patient as the area under the predicted utility curve, using linear interpolation between two utility measurements. Generalized linear mixed models with a binary distribution and logit link were used to analyse the proportion of patients with a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated using generalized linear mixed models with negative binomial distribution and log link. Costs were analysed with generalized linear mixed models using a log-normal distribution and identity link. The cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly extrapolated to include month 0 to 3.[23] The same was done for the cost estimate of month 15 to 18 and 21 to 24.

Cost-effectiveness

Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented. Taking a multi-outcome approach is in line with recent guidelines.[24]

Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times. Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[25] Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs. The 5,000 ICERs were plotted on cost-effectiveness planes.[26] In a cost-effectiveness plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs. The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 1). Finally, the probability that the RECODE program is cost-effective using different thresholds for the monetary value of a QALY was shown in cost-effectiveness acceptability curves.[27] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

Sensitivity and subgroup analyses

Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other with a one year instead of a two year time horizon. Five subgroup analyses were performed to study the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-specified in the study protocol and the power calculation was based on the subgroup analyses by MRC dyspnoea score>2.[8]

Results

Patients

The flowchart of patient inclusion has been presented elsewhere.[7] In total, we included 1086 COPD patients from 40 teams in the trial, 554 in the RECODE group and 532 in the usual care group. The baseline characteristics of the patients in the RECODE and usual care group are summarized in Table 1. The only statistically significant difference was a higher percentage of males in the usual care group (51 vs. 57%).

The proportion of patients who completed the trial was 76% in the RECODE group and 74% in the usual care group. Length of follow-up among the drop-outs was not significantly different between groups, with a mean (±sd) follow-up of 20.5 (±0.29) and 20.0 (±0.33) months, respectively. Patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ, SGRQ, MRC-dyspnoea, and EQ-5D. Baseline characteristics between the drop-outs of the RECODE group and the usual care group were not significantly different.

[TABLE 1]

Costs

The intervention costs are presented in Table 2. The total intervention costs per patient ranged from €103 to €587 across clusters, with a mean (±sd) of €324 (±156) per patient. This variation is explained by the number of COPD patients per team, the use of the ICT system, the number of healthcare providers participating in the courses, and the different locations of the courses. The labour costs of the attendees of the RECODE courses were the main driver of the intervention costs (54%).

Complete 2-year medication data of 500 patients (90%) in the RECODE group and 478 (90%) in the usual care group were extracted from the EMRs. More than 85% of the participants used medication for obstructive airway diseases in the 2-year trial period (Table 3).

Of the 1086 patients 93% had complete health care utilization data at 6 months, 79% at 9 months, 88% at 12 months, 73% at 18 months, and 75% at 24 months. This was similar for both groups. The unit costs, observed mean use of resources, and associated costs, as reported by the patients are presented in Table 3. In both groups, important cost drivers were hospital admissions, home care, and productivity loss. Excluding intervention costs, the adjusted mean total 2-year costs (estimated from the generalized linear mixed model) were significant higher in the RECODE group

than in the usual care group by €584 from the healthcare perspective and €645 from the societal perspective (Table 4).

[TABLE 2]

[TABLE 3]

[TABLE 4]

Outcomes

Over a two year period, the number of QALYs was 0.04 (p=0.02) lower in the RECODE group than in the usual care group while there was no significant difference in percentage of patients with a MCID in CCQ, nor in any of the other outcomes (Table 4).

Cost-effectiveness

From a healthcare and societal perspective, the point-estimates of costs and effects pointed towards higher costs and lower effects of the RECODE program, resulting in negative ICERs for all outcome measures (QALYs, exacerbation avoided, additional patient with a MCID in the CCQ score, and additional patient with a MCID in the SGRQ score). The CE-planes of the different outcomes showed that the majority of the bootstrap replications (>98%) had higher costs. Furthermore, more than half of the bootstrap replications fell within the north-west quadrant of the plane indicating that RECODE was dominated by the usual care group, e.g. more costs and less effects.

Sensitivity analyses

When including the intervention costs, the cost difference, which favoured usual care, further increased to a difference of €883 from the healthcare perspective and €1,005 from the societal perspective (Appendix 2).

Using a 12-month instead of a 24 month time horizon, the costs per patient were significantly higher in the RECODE group in comparison with the usual care group by €408 from the healthcare perspective and €370 from the societal perspective (Appendix 3). After 12 months, there was no significant difference in QALYs, or any of the other outcomes, except for the percentage of patients improving at least the MCID in CCQ, which was 7% less in the RECODE group than in the usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was

8% and 79%, respectively (Appendix 4). From a societal perspective these probabilities were slightly higher, i.e. 15% and 81%.

Subgroup analyses

Only age showed a significant interaction with the effect of RECODE on costs (Appendix 5,6). The difference in costs (healthcare and societal perspective) between RECODE and usual care was significantly lower in patients younger than 65 years, than in patients above 65 years. There was also a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that RECODE is cost-effective within the subgroup of patients <65 years.

Discussion

This study compared the costs and health effects of a COPD-DM program in primary care (RECODE) with usual care in the Netherlands. Our results show that RECODE is not cost-effective from a healthcare as well as a societal perspective. The point-estimates of costs and effects pointed towards higher costs and no significant difference in effects, except for 0.04 less QALYs. The majority of bootstrap replications in the CE-planes showed that RECODE was dominated by usual care. The decrease in utility, especially in the second year, might be explained by the consistent pattern of no effect or a worse effect on the outcomes. The reduction in utility might also result from the increased awareness by patients of their health problems as an effect of being enrolled in the RECODE program.

These unexpected findings cannot be related to weaknesses in the research design. The strength of our study lies in the inclusion of a large and representative group of COPD patients recruited in primary care. To avoid contamination, randomization was performed at cluster level. Since blinding of participants and clinicians was impossible, blinded research nurses collected the data, while patients were instructed not to report back on their type of intervention. Additional strengths of this study are the 2-year follow-up period, the broad range of health outcomes and costs categories included and the sophisticated analyses that took into account the hierarchical nature of the data. A limitation of our study is that we collected healthcare resource utilization at baseline, 6, 12, 18 and 24 months using a questionnaire with a 3-months recall period, necessitating the extrapolation of the 3-month data to 6 months to estimate the costs of month 3 to 6, 15 to 18 and 21 to 24. We chose to collect intermittent data for two reasons. The first was to avoid study drop-outs resulted from endless questionnaires or daily diaries over a long follow-up period. The second reason was that evidence from the literature suggests that intermittent data provides reliable estimates of total annual health expenditures.[23] A second limitation is that patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ, SGRQ, MRC-dyspnoea, and EQ-5D, thus potentially jeopardizing the generalizability of the results. However, baseline characteristics between the drop-outs of the RECODE group and the usual care group were not significantly different. Moreover, after correction for baseline scores no evidence of benefits of the intervention were found, indicating that dropout is unlikely to have biased the results.

There are several possible explanations why the RECODE intervention was not found to be cost-effective. Firstly, it may be due to the relatively low intensity of our pragmatic intervention. The RECODE program did not require the teams to implement all elements of the program. For instance, 70% of the intervention teams attended the refresher courses and 50% actively used the ICT system

ZORGDRAAD. Consequently, the intensity of the intervention for individual patients was not only dependent upon health status, personal needs and preferences of the individual patients, but also on the level of implementation of the DM interventions and the context within which each team operates. Further research is required to understand the conditions for a successful implementation and thus cost-effectiveness of a DM program.

Secondly, it is questionable whether the pragmatic provider-oriented interventions of the RECODE program were optimally translated into patient-oriented interventions. This is important because it has been shown that successful COPD-DM programs mainly include patient-oriented interventions.[2,3] Literature showed that exercise is an important success factor of a COPD-DM program[3] and education, exercise and relaxation are important factors for reducing the use of urgent and unscheduled healthcare among people with COPD.[28] In our study, physical exercise was not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

Thirdly, there was limited room for improvement in comparison with previous studies due to the relatively high standard of COPD care in the Netherlands[29] and the low proportion of severe COPD patients in this study.[2,3] It could be that a program like RECODE would have led to more positive results in settings where the COPD care is less advanced. For instance, in 2005, when the standards of good COPD care in developed countries were less well developed, a Spanish study did find that a community-based integrated care program in frail COPD patients improved clinical outcomes including survival and decreased the emergency department visits.[30] Moreover, Bourbeau and collegues[31,32] demonstrated positive results of a COPD-DM program in patients recruited from 7 hospitals in Canada in 1999, while a similar program in 15 general practices in the Netherlands in 2006[29] found no long-term benefits and a study in the US in 2009 did even find negative results in patients recruited from 20 hospital-based outpatient clinics.[33] It might well be that as time passes and quality of COPD care improves, there is less room for improvement.

Fourthly, changes in healthcare occurred during the study period that affected COPD care in the RECODE as well as the usual care group. Since July 2010, a new bundled payment scheme for COPD patients has been introduced in the Netherlands to stimulate the integration of care.[34] In this scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes secondary care and medications, it primarily stimulates the cooperation between different providers in the primary care setting. This increased attention for integrated chronic care and the ability to reimburse COPD interventions such as smoking cessation and nutritional counselling could have stimulated integrated care in the usual care group too.

Future research should determine the cost-effectiveness of more intensive COPD-DM programs in primary care using a long(er) time horizon. Hence, the gains from preventing patients with moderate COPD to progress to severe COPD are likely to be detected only in the long run.

In conclusion, this comprehensive economic evaluation of an integrated care program in primary care showed that the program increased costs but did not improve health outcomes. It even reduced QALYs. This is most likely due to the fact that the interventions targeted professionals instead of patients and were sub-optimally implemented, the relatively mild COPD population, and the national reforms in COPD care.

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CONTRIBUTORSHIP : MPHMR, WJJA, JG, and NHC conceived and designed the study. MRSB, ALK, AT, and CB acquired the data. MRSB, AT, and MPHMR analysed and interpreted the data. MRSB drafted the manuscript. ALK, NHC, AT, JG, WJJA, and MPHMR advised on the preparation of the manuscript. All authors read, edited, and approved the final version of the manuscript.

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DATA SHARING: No additional data available.

DECLERATION OF TRANSPARENCY: The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Baseline characteristics

	RECODE (n=554)	usual care (n=532)
Age (years), mean (SD)	68.2±11.3	68.4±11.1
Male sex (%)	50.5	57.3*
Employment (%)	27.7	28.8
Low education/ low Social Economic Status (%)	39.2	41.5
Marital status: Single (%)	37.0	38.3
FEV1% predicted , mean (SD)	67.7 (20.3)	67.9 (20.5)
Current smoker (%)	34.8	38.7
Former smoker (%)	53.8	52.6
Moderate exacerbation in the last year, mean (SD)	0.36 (0.83)	0.33 (0.78)
Severe exacerbation in the last three months, mean (SD)	0.02 (0.18)	0.02 (0.17)
Charlson comorbidity index	2.35 (1.26)	2.32 (1.27)
Major cardiovascular disease (%)	14.6	17.7
Hypertension (%)	35.4	38.3
Diabetes (%)	14.6	14.8
Depression (%)	9.8	10.1
MRC score, mean (SD)	2.06 (1.30)	1.95 (1.26)
MRC score > 2 (%)	35.1	31.6
CCQ score, mean (SD)	1.54 (0.98)	1.46 (0.96)
SGRQ total score, mean (SD)	36.7 (21.1)	34.5 (19.8)
EQ-5D score, mean (SD)	0.74 (0.25)	0.73 (0.28)

**Significant (p<0.05), FEV1= forced expiratory volume in 1 second, MRC=Medical Research Council, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire,EQ-5D=EuroQoL-5D ,*

Table 2. Intervention costs (in euros, 2013)

DM intervention	Cost description	% teams with any use of	Mean cost per team ± SD (€)	Mean cost per patient ± SD (€)
RECODE Course	*Catering*	100	119 ± 56	4.78 ± 2.45
	Location	100	3 ± 4	0.15 ± 0.21
	Presenters	100	84 ± 37	50.9 ± 36.31
	*Other costs**	100	1,174 ± 587	3.63 ± 2.39
	Labour costs attendees	100	4,008 ± 1,683	163.72 ± 87.65
	Travel	100	48 ± 30	1.94 ± 1.24
Refresher course	*Catering*	70	29 ± 25	1.1 ± 0.97
	Location	70	-	-
	Presenters	70	146 ± 123	5.94 ± 6.63
	*Other costs**	70	-	-
	Labour costs attendees	70	273 ± 273	10.84 ± 11.69
	Travel	70	7 ± 6	0.25 ± 0.23
ICT system ZORGDRAAD	*Labour costs of ICT use*	50	42 ± 86	1.45 ± 2.65
	Labour costs of ICT support	100	1,354 ± 0	57.80 ± 24.07
Monitoring reports	*Labour costs of feedback report at baseline*	100	333 ± 141	13.56 ± 6.2
	Labour costs of feedback report at 6 months	100	67 ± 28	2.71 ± 1.24
	Labour costs of feedback report at 12 months	100	133 ± 57	5.42 ± 2.48
Total			7,862 ± 2,543	324 ± 156

** Other costs includes material and equipment used during the course*

Table 3. Unit costs, data sources, mean use of resources and associated costs over the 2-years, as reported by the patients (unadjusted)

	Unit cost (€)	Source*	RECODE			usual care		
			Any use (%)	Mean use	Mean cost ± SD (€)	Any use (%)	Mean use	Mean cost ± SD (€)
Costs from healthcare perspective								
GP, (home) visits, phone contacts	15-46	a	91	16.23	476 ± 504	89	14.02	401 ± 450
Practice nurse, visits	23	b	74	5.51	131 ± 277	75	5.18	109 ± 166
Specialist, visits	78	a	78	10.05	784 ± 1,037	78	9.84	768 ± 973
Emergency department, visits	163	a	26	0.78	127 ± 284	23	0.79	129 ± 346
Physiotherapist, visits	39	a	53	25.82	1,007 ± 1,770	45	16.33	637 ± 1,260
Dietician, visits	29	a	21	1.45	42 ± 141	19	1.21	35 ± 148
Podiatrist, visits	32	b	43	3.78	121 ± 203	40	3.27	105 ± 167
Speech therapist, visits	36	a	3	0.12	4 ± 42	2	0.28	10 ± 158
Occupational therapy, visits	24	a	4	0.29	7 ± 76	3	0.32	8 ± 83
Rehabilitation centre, visits	78	a	12	3.86	459 ± 2,157	12	3.01	358 ± 1,731
Home care, hours of household help	26	a	22	34.42	895 ± 2,287	20	31.01	806 ± 2,171
Home care, hours of personal care	47	a	9	8.28	389 ± 1,995	8	9.49	446 ± 2,327
Home care, hours of nursing	70	a	6	2.11	148 ± 1,108	6	2.39	167 ± 1,064
Home care, other, hours	48	a	1	0.47	22 ± 262	2	0.65	31 ± 309
Hospital stay, days	493	a	25	4.65	2,293 ± 5,915	25	4.84	2,388 ± 7,522
Intensive care unit, days	2,356	a	5	0.49	1,161 ± 11,316	2	0.14	328 ± 2,658
Drugs for obstructive airway diseases	-	c	84	-	945 ± 814	84	-	934 ± 1,024
Other medication	-	c	91	-	1,367 ± 3,421	90	-	1,131 ± 2,506
Costs from societal perspective								
Travel expenses, public transport/car, KM	0.22	a	94	189.00	42 ± 56	92	174.43	38 ± 59
Productivity loss, absenteeism hours	31-43	a	11	47.74	1,698 ± 8,344	11	42.89	1,649 ± 8,448
Productivity loss, presenteeism hours	31-43		8	10.38	376 ± 2,304	9	10.92	374 ± 1,774

** Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research[9], (b) The Dutch Healthcare Authority NZA (c) GIP Databank [20]*

Table 4. Results from the cost-utility and cost-effectiveness analysis from the base case (in euros, 2013)

		Costs			Effect			cost-effectiveness planes				
		RECODE	Usual Care	Difference (95% CI)	RECODE	Usual Care	Difference (95% CI)	ICER	NW C↑E↓	SW C↓E↓	NE C↑E↑	SE C↓E↑
Cost per QALY	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-15,720**	97.9	1.3	0.8	0.0
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-17,358**	97.3	1.9	0.8	0.0
Cost per exacerbation avoided	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-4,211**	91.3	1.2	7.4	0.1
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-4,650**	90.7	1.8	7.4	0.1
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-35,772**	75.2	1.0	23.5	0.3
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-39,498**	74.8	1.4	23.3	0.5
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-46,508**	66.5	0.9	32.3	0.4
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-51,353**	66.1	1.3	32.0	0.6

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west (more cost and less effects), SW=south-west (less cost and less effects), NE=north-east (more cost and more effects) , SE=south-east (more cost and less effects), C= difference in costs, E=difference in effects.*

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Appendix 1. Health economic terms

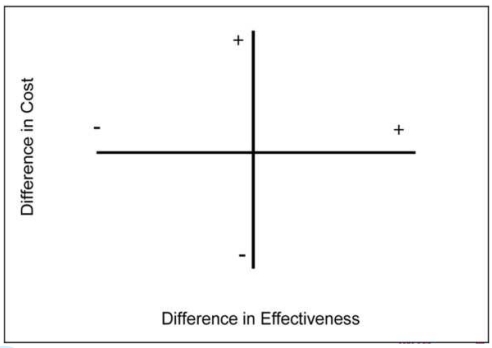
Incremental costs
= Difference in costs between the intervention and usual care group
= $\text{Costs}_{\text{intervention group}} - \text{Costs}_{\text{usual care group}}$

Incremental effects
= Difference in effects between the intervention and usual care group
= $\text{Effect}_{\text{intervention group}} - \text{Effect}_{\text{usual care group}}$

Incremental cost-effectiveness ratios (ICERs)
= Incremental costs / Incremental effects
= $(\text{Costs}_{\text{intervention group}} - \text{Costs}_{\text{usual care group}}) / (\text{Effect}_{\text{intervention group}} - \text{Effect}_{\text{usual care group}})$

Bootstrapping
Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[1] That is to say the same record can occur more than once in a given bootstrap sample. Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs.

Cost-effectiveness plane
We plot the uncertainty around the difference in costs and effects in a cost-effectiveness plane (CE-plane). In a CE-plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs.[2] The results of the bootstrap replications fall into one of four quadrants:



- North-east quadrant: more cost and more effects;
- South-east quadrant: less cost and more effects (intervention is dominant);
- South-west quadrant: less cost and less effects;
- North-west quadrant: more cost and less effects (intervention is dominated).

In the most ideal situation, all the results of the bootstraps lay in lower-right corner of the plane, indicating lower costs and improved outcomes.

Cost-effectiveness acceptability curves
The cost-effectiveness acceptability curve shows the probability that the RECODE program is cost-effective using different thresholds for the willingness to pay for a quality adjusted life year.[3] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

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Appendix 2. Sensitivity analyses: impact on cost-utility and cost-effectiveness, with intervention costs

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
With intervention costs												
Cost per QALY	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-23,792**	99.1	0.0	0.9	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-27,053**	99.0	0.2	0.9	0.0
Cost per exacerbation avoided	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-6,373**	92.5	0.0	7.5	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-7,247**	92.4	0.2	7.5	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-54,139**	76.2	0.0	23.8	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-61,559**	76.1	0.1	23.8	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-70,388**	67.4	0.0	32.6	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-80,035**	67.3	0.1	32.6	0.1

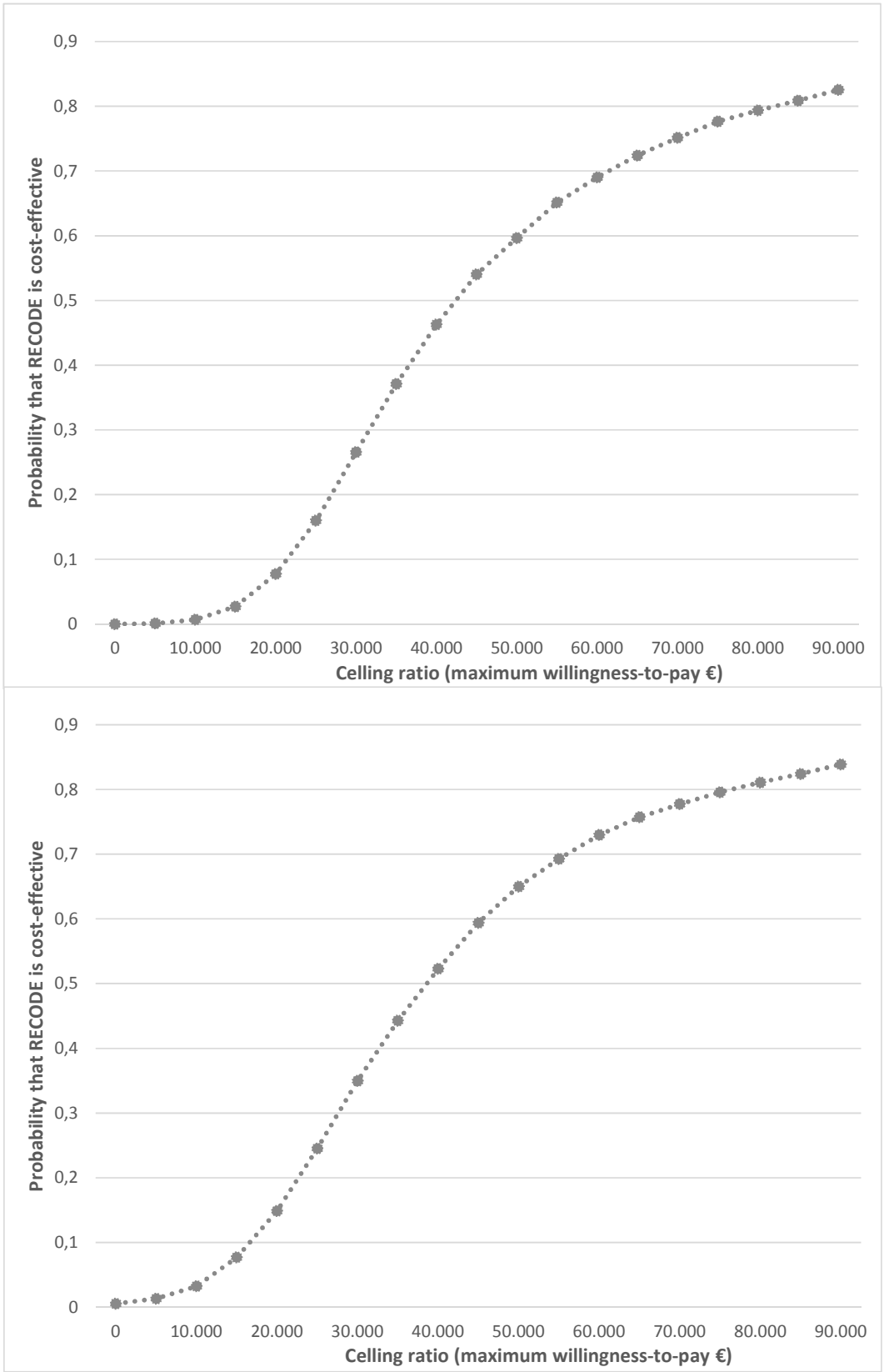
** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 3. Sensitivity analyses: impact on cost-utility and cost-effectiveness, 12 months' time horizon

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
12 months' time horizon												
Cost per QALY	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.71	0.70	0.01 (-0.001 – 0.02)	**42,458**	3.6	0.0	96.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.71	0.70	0.01 (-0.001 – 0.02)	**38,471**	3.6	0.0	95.8	0.6
Cost per exacerbation avoided	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.38	0.32	-0.06 (-0.14 – 0.05)	**-7,401**	87.3	0.0	12.7	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.38	0.32	-0.06 (-0.14 – 0.05)	**-6,706**	86.8	0.5	12.7	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.19	0.26	-0.07** (-0.14 – -0.02)	**-5,582**	99.6	0.0	0.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.19	0.26	-0.07** (-0.14 – -0.02)	**-5,058**	99.0	0.6	0.4	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.36	0.37	-0.01 (-0.05 – 0.03)	**-36,869**	69.4	0.0	30.6	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.36	0.37	-0.01 (-0.05 – 0.03)	**-33,408**	69.1	0.3	30.3	0.2

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 4. Cost-effectiveness acceptability curves, healthcare (upper) and societal perspective (lower) with a 12 months' time horizon



Appendix 5. Subgroup analyses (age, gender, Medical Research Council (MRC) Dyspnoea scale)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY age subgroups															
HP	<65 years	N=411	€ 3,975	€ 3,801	€ 174 (-434 – 711)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-9,820**	58.0	20.4	15.8	5.9
	≥65 years	N=675	€ 6,029	€ 5,028	€ 1,001* (248 – 1,701)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,698**	98.8	0.5	0.7	0.0
SP	<65 years	N=411	€ 5,374	€ 5,158	€ 216 (-737 – 1,035)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-12,171**	54.1	24.2	15.1	6.5
	≥65 years	N=675	€ 6,064	€ 5,079	€ 985* (224 – 1,679)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,409**	98.7	0.6	0.7	0.0
Cost per QALY gender subgroups															
HP	Men	N=585	€ 4,725	€ 4,344	€ 381 (-250 – 963)	0.92	1.53	1.57	-0.04* (-0.08 – -0.01)	0.16	**-8,951**	88.4	10.5	1.1	0.1
	Women	N=501	€ 5,527	€ 4,756	€ 771 (-44 – 1,472)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-35,680**	80.4	2.7	16.4	0.4
SP	Men	N=585	€ 5,226	€ 4,924	€ 302 (-502 – 1,000)	0.75	1.53	1.57	-0.04* (-0.08 – -0.01)	0.16	**-7,090**	78.2	20.7	0.9	0.2
	Women	N=501	€ 6,302	€ 5,331	€ 971* (106–1,748)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-44,939**	81.8	1.4	16.7	0.2
Cost per QALY MRC subgroups															
HP	MRC≤2	N=725	€ 3,927	€ 3,500	€ 427 (-29– 821)	0.67	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,060**	99.5	2.9	1.5	0.1
	MRC>2	N=361	€ 8,721	€ 7,231	€ 1,489 (-164 – 2,881)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-42,301**	81.2	2.8	15.5	0.5
SP	MRC≤2	N=725	€ 4,543	€ 4,101	€ 443 (-191 – 1,029)	0.52	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,464**	90.8	7.6	1.3	0.2
	MRC>2	N=361	€ 9,358	€ 7,744	€ 1,614 (-161 – 3,115)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-45,846**	81.0	3.0	15.5	0.5

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, MRC=Medical Research Council, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 5. Subgroup analyses (FEV1, SES)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY lung function subgroups															
HP	FEV1≥50	N=674	€ 4,797	€ 4,025	€ 773** (198 – 1,287)	0.85	1.47	1.51	-0.04 (-0.07 – 0.003)	0.15	**-21,762**	96.0	0.5	3.5	0.0
	FEV1<50	N=193	€ 7,744	€ 7,415	€ 329 (-1,499 – 1,837)		1.39	1.34	-0.05 (-0.12 – 0.03)		**-10,044**	60.3	29.4	6.9	3.4
SP	FEV1≥50	N=674	€ 5,359	€ 4,537	€ 822* (159 – 1,420)	0.82	1.47	1.51	-0.04 (-0.07 – 0.003)	0.15	**-23,155**	95.5	1.0	3.5	0.0
	FEV1<50	N=193	€ 8,622	€ 8,170	€ 452 (-1,536 –2,139)		1.39	1.34	-0.05 (-0.12 – 0.03)		**-7,310**	63.3	26.5	7.2	3.1
Cost per QALY Social economic status (SES) subgroups															
HP	Low SES	N=399	€ 5,124	€ 4,562	€ 562 (-434 – 1,423)	0.46	1.04	1.09	-0.05 (-0.11 – 0.01)	0.15	**-11,505**	84.2	10.8	4.4	0.5
	Moderate/ high SES	N=590	€ 5,347	€ 4,598	€ 749 (74 – 1,362)		1.54	1.57	-0.03 (-0.07 – 0.01)		**-24,627**	91.9	1.5	6.5	0.1
SP	Low SES	N=399	€ 5,534	€ 4,859	€ 675 (-415 – 1,632)	0.49	1.04	1.09	-0.05 (-0.11 – 0.01)	0.15	**-13,801**	85.3	9.7	4.4	0.6
	Moderate/ high SES	N=590	€ 6,089	€ 5,372	€ 717 (-125 – 1,459)		1.54	1.57	-0.03 (-0.07 – 0.01)		**-23,560**	89.1	4.3	6.2	0.4

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, FEV1= forced expiratory volume in 1 second, SES=Social Economic Status, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N.A.
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5,6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N.A.
Sample size	7a	How sample size was determined	Details in published protocol paper
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N.A.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Details in published protocol paper
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details in

			published protocol paper
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Details in published protocol paper
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Details in published protocol paper
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Details in published protocol paper
	11b	If relevant, description of the similarity of interventions	N.A.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6,7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	N.A.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8-10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8-10

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11,12
Other information			
Registration	23	Registration number and name of trial registry	Details in published protocol paper
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Cost-effectiveness of integrated COPD care: the RECODE cluster randomized trial

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Abstract

Objectives: To investigate the cost-effectiveness of a Chronic Obstructive Pulmonary Disease (COPD) disease management (COPD-DM) program in primary care, called RECODE, compared to usual care.

Design: two-year, cluster-randomised controlled trial

Setting: 40 general practices in the western part of the Netherlands

Participants: 1086 patients with COPD according to GOLD (Global Initiative for COPD) criteria. Exclusion criteria were terminal illness, cognitive impairment, alcohol or drug misuse, and inability to fill in Dutch questionnaires. Practices were included if they were willing to create a multidisciplinary COPD team.

Interventions: A multidisciplinary team of caregivers was trained in motivational interviewing, setting-up individual care plans, exacerbation management, implementing clinical guidelines and redesigning the care process. In addition, clinical decision making was supported by feedback reports provided by an ICT program.

Main outcome measures: We investigated impact on health outcomes (quality-adjusted life years (QALYs), Clinical COPD Questionnaire, St. George's Respiratory Questionnaire, and exacerbations) and costs (healthcare and societal perspective).

Results: The intervention costs were €324 per patient. Excluding these costs, the intervention group had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both groups, except for 0.04 (95% CI -0.07 to -0.01) less QALYs in the intervention group.

Conclusions: This integrated care program for COPD patients that mainly included professional-directed interventions was not cost-effective in primary care.

Trial registration: Netherlands Trial Register NTR2268

Funding: Stichting Achmea Gezondheidszorg (SAG) and the Netherlands Organisation for Health Research and Development (Zon-MW).

Strengths and limitations of this study

- It is the largest and most pragmatic Dutch RCT trial to date assessing the cost-effectiveness of COPD disease management in primary care.
- The 2-year follow-up period, the broad range of health outcomes and costs (including program costs) measured and the statistically sophisticated analyses ensure the robustness of the results.
- The uncertainty in the cost-effectiveness of the disease management programs is adequately estimated and illustrated enabling the appropriate interpretation of the results.
- The control group was likely to be exposed to quality improvement initiatives as part of usual care.

Introduction

Disease management programs for Chronic Obstructive Pulmonary Disease (herein, COPD-DM) have been developed to change COPD care from acute, reactive and one-size-fits-all into integrated, pro-active and tailor-made. To stimulate the implementation of such programs in the Netherlands, a new payment policy (i.e. bundled payment) was recently implemented.[1] However, the wide implementation of these programs in the Netherlands, as is currently ongoing would benefit by a justification from a cost-effectiveness perspective.

Recent systematic literature reviews of COPD-DM programs showed favourable effects on both health outcomes and costs (mainly due to decreased hospitalization).[2,3] However, previous economic studies had poor methodological quality.[2,4] Most studies did not measure all relevant costs and health outcomes and did not perform incremental cost-effectiveness analyses.[2] For instance, there is little knowledge on the required investments in implementation of these programs. Furthermore, the generalizability of the outcomes of these studies was low, due to the inclusion of mainly severe COPD patients and the exclusion of patients with multi-morbidity.[2,5,6]

We aimed to conduct a comprehensive cost-effectiveness analysis (CEA) of a COPD-DM program in primary care compared to usual care in the Netherlands. This CEA was performed as part of a two-year cluster randomized controlled trial (RCT) evaluating the clinical effects of this RECODE program (acronym for Randomized clinical trial on Effectiveness of integrated COPD management in primary carE). [7,8]

In the clinical paper we concluded that, after 12 months, the RECODE program did not significantly improve the score on the Clinical COPD Questionnaire (CCQ) compared to usual care, despite an improved level of integrated care and a higher degree of self-reported physical activity.[7] Our current paper includes additional outcome measures not reported in the clinical paper and it reports 24-months results. This is important because it is often argued that it takes time before the effect of DM programs become clearly visible. The added value of a cost-effectiveness analysis is that we report the joint uncertainty in both effects and costs, allowing us to report the probability that the RECODE program would be cost-effective at various threshold values of the maximum acceptable costs per quality-adjusted life year (QALY) gained. Moreover, the publication of results in terms of cost-effectiveness is important to avoid selective reporting of positive studies. The published evidence is used to inform decision makers all across developed countries about whether and which COPD-DM programs to reimburse on a wider scale.

Methods

This study was approved by the medical ethics committee, performed according to the study protocol[8], national[9] and international[10] guidelines for pharmaco-economic research, and reported according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).[11]

Design and Intervention

RECODE is a 2-year cluster randomized trial in which 40 clusters of primary care teams were randomized to the COPD-DM program or usual care. The 20 teams of the intervention group were trained in essential components of effective COPD-DM: proper diagnosis, optimizing medication adherence, motivational interviewing, smoking cessation counselling, applying self-management plans including early recognition and treatment of exacerbations, physical (re)activation, and nutritional support. In addition, the teams learned the details of a web-based computer program for measuring and reporting process and outcome performance indicators, named ZORGDRAAD. This Information and Communications Technologies (ICT) application included a patient and provider portal that facilitated the communication within the multi-disciplinary teams as well as between care providers and patients. At the end of the 2-day course, each team developed a plan with steps to be taken in order to redesign the care process and integrate the COPD-DM program into their daily practice. After the course, the teams were invited to join refresher courses, received regular feedback reports on patients' outcomes and had access to ZORGDRAAD. The local healthcare insurer reimbursed physical reactivation for patients with a Medical Research Council (MRC) dyspnoea score >2, also if these patients had no supplementary insurance. All practices were flexible in determining and following their individual plans. Therefore, the mix and intensity of interventions for individual patients depended upon their health status, personal needs and preferences, as well as the actions taken by the team. Healthcare providers in the usual care group were asked to continue providing care as usually. Indicators of care as usual are reported before.[8]

Target population

The enrolment of primary care teams and their COPD patients took place between September 2010 and September 2011. Participating teams included at least one general practitioner (GP), one practice nurse and one physiotherapist. Patients had physician-diagnosed COPD according to GOLD guidelines.[12] Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion criterion. The GPs verified that the included patients fulfilled the inclusion and exclusion

criteria. All participating GPs and COPD patients provided written informed consent before participation.

Outcomes

Costs were related to the following outcome measures:

I. QALYs based on the EuroQol-5D (EQ-5D) utility values using the Dutch value set[13,14];
II. proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement ≥ 0.4) on the CCQ[15,16];
III. proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory Questionnaire(SGRQ)[17,18];
IV. total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic corticosteroids and/or antibiotics, but did not require hospitalization. This information was extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as a worsening of symptoms that required a hospital admission. Hospital admissions were obtained from the resource use questionnaires and the EMR.

The EQ-5D, CCQ, SGRQ, and resource use questionnaire were administered at baseline, 6, 9, 12, 18, and 24 months.

Costs

Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a societal perspective. The healthcare perspective included all costs covered by the healthcare budget, i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse, physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions, emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective additionally included travel costs and costs of productivity loss due to absence from paid work.

Patients reported the healthcare utilization (excluding medication), travel costs, days of absence from paid work due to illness (absenteeism) and lost productivity while being at work (presenteeism) in a resource use questionnaire with a recall period of three months.

The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs were obtained from the Dutch manual for costing research[9] and inflated to 2013 using the general consumer price index.[19] The costs of medications were obtained from the GIP-Databank and included value added tax and pharmacist dispensing fees.[20] The productivity costs were estimated

using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick employee is not replaced (the friction period).[21] We used a friction period of 115 days, i.e. the average duration of vacancies (87 days) increased with the expected number of weeks employers need before taking the decision to place a vacancy for temporary or permanent replacement of the worker (28 days).[22]

The intervention costs, defined as costs of training the teams, costs of the ICT support, and costs of the monitoring reports, were calculated based on course attendance (initial 2-day course and refresher courses), computer-documented ICT-use, and time involved in producing monitoring reports (for each practice, the estimated labour time was 2.5, 0.5, and 1 hour to produce the reports at baseline, 6 months and 12 months, respectively).

Statistical analysis

Data analysis was performed according to the intention-to-treat principle. Data from patients who discontinued the trial prematurely were included in the analysis up to the point of drop-out. Additionally, patients that dropped-out during the first year were asked to fill in a CCQ questionnaire at 12 months, if possible.

We used repeated measures models to assess differences between RECODE and usual care, correcting for time, age, gender, MRC dyspnoea score >2, baseline score and clustering of patients. The distribution and link function for each outcome was selected after comparing the goodness-of-fit of models with different specifications of the distribution and link functions. Models that had the lowest Akaike's Information Criterion were selected.

EQ-5D utilities were analysed using linear mixed models with a normal distribution and identity link. We calculated the number of QALY's for each patient as the area under the predicted utility curve, using linear interpolation between two utility measurements. Generalized linear mixed models with a binary distribution and logit link were used to analyse the proportion of patients with a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated using generalized linear mixed models with negative binomial distribution and log link. Costs were analysed with generalized linear mixed models using a log-normal distribution and identity link. The cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly extrapolated to include month 0 to 3.[23] The same was done for the cost estimate of month 15 to 18 and 21 to 24.

Cost-effectiveness

Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented. Taking a multi-outcome approach is in line with recent guidelines.[24]

Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times. Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[25] Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs. The 5,000 ICERs were plotted on cost-effectiveness planes.[26] In a cost-effectiveness plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs. The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 1). Finally, the probability that the RECODE program is cost-effective using different thresholds for the monetary value of a QALY was shown in cost-effectiveness acceptability curves.[27] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

Sensitivity and subgroup analyses

Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other with a one year instead of a two year time horizon. Five subgroup analyses were performed to study the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-specified in the study protocol and the power calculation was based on the subgroup analyses by MRC dyspnoea score>2.[8]

Results

Patients

The flowchart of patient inclusion has been presented elsewhere.[7] In total, we included 1086 COPD patients from 40 teams in the trial, 554 in the RECODE group and 532 in the usual care group. The baseline characteristics of the patients in the RECODE and usual care group are summarized in Table 1. The only statistically significant difference was a higher percentage of males in the usual care group (51 vs. 57%).

The proportion of patients who completed the trial was 76% in the RECODE group and 74% in the usual care group. Length of follow-up among the drop-outs was not significantly different between groups, with a mean (±sd) follow-up of 20.5 (±0.29) and 20.0 (±0.33) months, respectively. Patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ, SGRQ, MRC-dyspnoea, and EQ-5D. Baseline characteristics between the drop-outs of the RECODE group and the usual care group were not significantly different.

[TABLE 1]

Costs

The intervention costs are presented in Table 2. The total intervention costs per patient ranged from €103 to €587 across clusters, with a mean (±sd) of €324 (±156) per patient. This variation is explained by the number of COPD patients per team, the use of the ICT system, the number of healthcare providers participating in the courses, and the different locations of the courses. The labour costs of the attendees of the RECODE courses were the main driver of the intervention costs (54%).

Complete 2-year medication data of 500 patients (90%) in the RECODE group and 478 (90%) in the usual care group were extracted from the EMRs. More than 85% of the participants used medication for obstructive airway diseases in the 2-year trial period (Table 3).

Of the 1086 patients 93% had complete health care utilization data at 6 months, 79% at 9 months, 88% at 12 months, 73% at 18 months, and 75% at 24 months. This was similar for both groups. The unit costs, observed mean use of resources, and associated costs, as reported by the patients are presented in Table 3. In both groups, important cost drivers were hospital admissions, home care, and productivity loss. Excluding intervention costs, the adjusted mean total 2-year costs (estimated from the generalized linear mixed model) were significant higher in the RECODE group

than in the usual care group by €584 from the healthcare perspective and €645 from the societal perspective (Table 4).

[TABLE 2]

[TABLE 3]

[TABLE 4]

Outcomes

Over a two year period, the number of QALYs was 0.04 (p=0.02) lower in the RECODE group than in the usual care group while there was no significant difference in percentage of patients with a MCID in CCQ, nor in any of the other outcomes (Table 4).

Cost-effectiveness

From a healthcare and societal perspective, the point-estimates of costs and effects pointed towards higher costs and lower effects of the RECODE program, resulting in negative ICERs for all outcome measures (QALYs, exacerbation avoided, additional patient with a MCID in the CCQ score, and additional patient with a MCID in the SGRQ score). The CE-planes of the different outcomes showed that the majority of the bootstrap replications (>98%) had higher costs. Furthermore, more than half of the bootstrap replications fell within the north-west quadrant of the plane indicating that RECODE was dominated by the usual care group, e.g. more costs and less effects.

Sensitivity analyses

When including the intervention costs, the cost difference, which favoured usual care, further increased to a difference of €883 from the healthcare perspective and €1,005 from the societal perspective (Appendix 2).

Using a 12-month instead of a 24 month time horizon, the costs per patient were significantly higher in the RECODE group in comparison with the usual care group by €408 from the healthcare perspective and €370 from the societal perspective (Appendix 3). After 12 months, there was no significant difference in QALYs, or any of the other outcomes, except for the percentage of patients improving at least the MCID in CCQ, which was 7% less in the RECODE group than in the usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was

8% and 79%, respectively (Appendix 4). From a societal perspective these probabilities were slightly higher, i.e. 15% and 81%.

Subgroup analyses

Only age showed a significant interaction with the effect of RECODE on costs (Appendix 5,6). The difference in costs (healthcare and societal perspective) between RECODE and usual care was significantly lower in patients younger than 65 years, than in patients above 65 years. There was also a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that RECODE is cost-effective within the subgroup of patients <65 years.

Discussion

This study compared the costs and health effects of a COPD-DM program in primary care (RECODE) with usual care in the Netherlands. Our results show that RECODE is not cost-effective from a healthcare as well as a societal perspective. The point-estimates of costs and effects pointed towards higher costs and no significant difference in effects, except for 0.04 less QALYs. The majority of bootstrap replications in the CE-planes showed that RECODE was dominated by usual care. The decrease in utility, especially in the second year, might be explained by the consistent pattern of no effect or a worse effect on the outcomes. The reduction in utility might also result from the increased awareness by patients of their health problems as an effect of being enrolled in the RECODE program.

These unexpected findings cannot be related to weaknesses in the research design. The strength of our study lies in the inclusion of a large and representative group of COPD patients recruited in primary care. To avoid contamination, randomization was performed at cluster level. Since blinding of participants and clinicians was impossible, blinded research nurses collected the data, while patients were instructed not to report back on their type of intervention. Additional strengths of this study are the 2-year follow-up period, the broad range of health outcomes and costs categories included and the sophisticated analyses that took into account the hierarchical nature of the data. A limitation of our study is that we collected healthcare resource utilization at baseline, 6, 12, 18 and 24 months using a questionnaire with a 3-months recall period, necessitating the extrapolation of the 3-month data to 6 months to estimate the costs of month 3 to 6, 15 to 18 and 21 to 24. We chose to collect intermittent data for two reasons. The first was to avoid study drop-outs resulting from endless questionnaires or daily diaries over a long follow-up period. The second reason was that evidence from the literature suggests that intermittent data provides reliable estimates of total annual health expenditures.[23] A second limitation is that patients who dropped out were significantly older and had a significantly worse baseline score on the CCQ, SGRQ, MRC-dyspnoea, and EQ-5D, thus potentially jeopardizing the generalizability of the results. However, baseline characteristics of the drop-outs in the RECODE group and the drop-outs in the usual care group were not significantly different. Moreover, after correction for baseline scores no evidence of benefits of the intervention were found, indicating that dropout is unlikely to have biased the results.

There are several possible explanations for the finding that the RECODE intervention was not cost-effective. Firstly, it may be due to the relatively low intensity of our pragmatic intervention. The RECODE program did not require the teams to implement all elements of effective COPD-DM that

they learned during the courses. Instead, each team made their own plan to redesign the care process and implement COPD-DM. Consequently, the mixture and intensity of interventions for individual patients was not only dependent upon health status, personal needs and preferences of the individual patients, but also on the specific focus that a team may have chosen, the level of implementation of the DM interventions and the context within which each team operates. As an example of an area that may not have been sufficiently addressed during the courses we should mention interventions to improve psychological health.[28] However, only 10% of the patients in the RECODE trial suffered from a depression at baseline. Although this has probably influenced their motivation to change their health behaviour and may have increased unscheduled care,[29] it is unlikely to be a major explanation for the lack of effect. Obviously, further research is required to understand the conditions for a successful implementation and thus cost-effectiveness of a COPD-DM program.

Secondly, it is questionable whether the pragmatic provider-oriented interventions of the RECODE program (e.g. training and education, support in writing practice reform plans, ICT system Zorgdraad) were optimally translated into patient-oriented interventions. This is important because it has been shown that successful COPD-DM programs mainly include patient-oriented interventions.[2,3] Literature showed that exercise is an important success factor of a COPD-DM program[3] and education, exercise and relaxation are important factors for reducing the use of urgent and unscheduled healthcare among people with COPD.[30] In our study, physical exercise was not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

Thirdly, there was limited room for improvement in comparison with previous studies due to the relatively high standard of COPD care in the Netherlands[31] and the low proportion of severe COPD patients in this study.[2,3] It could be that a program like RECODE would have led to more positive results in settings where the COPD care is less advanced. For instance, in 2005, when the standards of good COPD care in developed countries were less well developed, a Spanish study did find that a community-based integrated care program in frail COPD patients improved clinical outcomes including survival and decreased the emergency department visits.[32] Moreover, Bourbeau and collegues[33,34] demonstrated positive results of a COPD-DM program in patients recruited from 7 hospitals in Canada in 1999, while a similar program in 15 general practices in the Netherlands in 2006[31] found no long-term benefits and a study in the US in 2009 did even find negative results in patients recruited from 20 hospital-based outpatient clinics.[35] It might well be that as time passes and quality of COPD care improves, there is less room for improvement. However, even in the presence of incentivised quality improvement programs like the Quality and Outcome Framework in England, hospital admissions for COPD still occur more frequently among the least well served such

as those in deprived areas.[36] So there is still room for improvement among certain sub-groups of COPD patients and it might be a question of targeting DM programs at those most likely to benefit.

Fourthly, changes in healthcare occurred during the study period that affected COPD care in the RECODE as well as the usual care group. Since July 2010, a new bundled payment scheme for COPD patients has been introduced in the Netherlands to stimulate the integration of care.[37] In this scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes secondary care and medications, it primarily stimulates the cooperation between different providers in the primary care setting. This increased attention for integrated chronic care and the ability to reimburse COPD interventions such as smoking cessation and nutritional counselling could have stimulated integrated care in the usual care group too.

Future research should determine the cost-effectiveness of more intensive COPD-DM programs in primary care using a long(er) time horizon. Hence, the gains from preventing patients with moderate COPD to progress to severe COPD are likely to be detected only in the long run.

In conclusion, this comprehensive economic evaluation of an integrated care program in primary care showed that the program increased costs but did not improve health outcomes. It even reduced QALYs. This is most likely due to the sub-optimal translation of the provider-oriented interventions of the RECODE program into patient-oriented interventions, the suboptimal implementation of the interventions, the relatively mild COPD population, and the national reforms in COPD care.

TRIAL REGISTRATION: Netherlands Trial Register (NTR): NTR2268.

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CONTRIBUTORSHIP : MPHMR, WJJA, JG, and NHC conceived and designed the study. MRSB, ALK, AT, and CB acquired the data. MRSB, AT, and MPHMR analysed and interpreted the data. MRSB drafted the manuscript. ALK, NHC, AT, JG, WJJA, and MPHMR advised on the preparation of the manuscript. All authors read, edited, and approved the final version of the manuscript.

CONFLICT OF INTEREST: There are no competing interests.

ETHICAL APPROVAL: The study was reviewed and approved by the medical ethical committee of the Leiden University Medical Centre, the Netherlands. All general practitioners and participants gave written informed consent.

DATA SHARING: No additional data available.

DECLERATION OF TRANSPARENCY: The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Table of content

Table 1. Baseline characteristics

	RECODE (n=554)	usual care (n=532)
Age (years), mean (SD)	68.2±11.3	68.4±11.1
Male sex (%)	50.5	57.3*
Employment (%)	27.7	28.8
Low education/ low Social Economic Status (%)	39.2	41.5
Marital status: Single (%)	37.0	38.3
FEV1% predicted , mean (SD)	67.7 (20.3)	67.9 (20.5)
Current smoker (%)	34.8	38.7
Former smoker (%)	53.8	52.6
Moderate exacerbation in the last year, mean (SD)	0.36 (0.83)	0.33 (0.78)
Severe exacerbation in the last three months, mean (SD)	0.02 (0.18)	0.02 (0.17)
Charlson comorbidity index	2.35 (1.26)	2.32 (1.27)
Major cardiovascular disease (%)	14.6	17.7
Hypertension (%)	35.4	38.3
Diabetes (%)	14.6	14.8
Depression (%)	9.8	10.1
MRC score, mean (SD)	2.06 (1.30)	1.95 (1.26)
MRC score > 2 (%)	35.1	31.6
CCQ score, mean (SD)	1.54 (0.98)	1.46 (0.96)
SGRQ total score, mean (SD)	36.7 (21.1)	34.5 (19.8)
EQ-5D score, mean (SD)	0.74 (0.25)	0.73 (0.28)

**Significant (p<0.05), FEV1= forced expiratory volume in 1 second, MRC=Medical Research Council, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire,EQ-5D=EuroQoL-5D ,*

Table 2. Intervention costs (in euros, 2013)

DM intervention	Cost description	% teams with any use of	Mean cost per team ± SD (€)	Mean cost per patient ± SD (€)
RECODE Course	*Catering*	100	119 ± 56	4.78 ± 2.45
	Location	100	3 ± 4	0.15 ± 0.21
	Presenters	100	84 ± 37	50.9 ± 36.31
	*Other costs**	100	1,174 ± 587	3.63 ± 2.39
	Labour costs attendees	100	4,008 ± 1,683	163.72 ± 87.65
	Travel	100	48 ± 30	1.94 ± 1.24
Refresher course	*Catering*	70	29 ± 25	1.1 ± 0.97
	Location	70	-	-
	Presenters	70	146 ± 123	5.94 ± 6.63
	*Other costs**	70	-	-
	Labour costs attendees	70	273 ± 273	10.84 ± 11.69
	Travel	70	7 ± 6	0.25 ± 0.23
ICT system ZORGDRAAD	*Labour costs of ICT use*	50	42 ± 86	1.45 ± 2.65
	Labour costs of ICT support	100	1,354 ± 0	57.80 ± 24.07
Monitoring reports	*Labour costs of feedback report at baseline*	100	333 ± 141	13.56 ± 6.2
	Labour costs of feedback report at 6 months	100	67 ± 28	2.71 ± 1.24
	Labour costs of feedback report at 12 months	100	133 ± 57	5.42 ± 2.48
Total			7,862 ± 2,543	324 ± 156

** Other costs includes material and equipment used during the course*

Table 3. Unit costs, data sources, mean use of resources and associated costs over the 2-years, as reported by the patients (unadjusted)

	Unit cost (€)	Source*	RECODE			usual care		
			Any use (%)	Mean use	Mean cost ± SD (€)	Any use (%)	Mean use	Mean cost ± SD (€)
Costs from healthcare perspective								
GP, (home) visits, phone contacts	15-46	a	91	16.23	476 ± 504	89	14.02	401 ± 450
Practice nurse, visits	23	b	74	5.51	131 ± 277	75	5.18	109 ± 166
Specialist, visits	78	a	78	10.05	784 ± 1,037	78	9.84	768 ± 973
Emergency department, visits	163	a	26	0.78	127 ± 284	23	0.79	129 ± 346
Physiotherapist, visits	39	a	53	25.82	1,007 ± 1,770	45	16.33	637 ± 1,260
Dietician, visits	29	a	21	1.45	42 ± 141	19	1.21	35 ± 148
Podiatrist, visits	32	b	43	3.78	121 ± 203	40	3.27	105 ± 167
Speech therapist, visits	36	a	3	0.12	4 ± 42	2	0.28	10 ± 158
Occupational therapy, visits	24	a	4	0.29	7 ± 76	3	0.32	8 ± 83
Rehabilitation centre, visits	78	a	12	3.86	459 ± 2,157	12	3.01	358 ± 1,731
Home care, hours of household help	26	a	22	34.42	895 ± 2,287	20	31.01	806 ± 2,171
Home care, hours of personal care	47	a	9	8.28	389 ± 1,995	8	9.49	446 ± 2,327
Home care, hours of nursing	70	a	6	2.11	148 ± 1,108	6	2.39	167 ± 1,064
Home care, other, hours	48	a	1	0.47	22 ± 262	2	0.65	31 ± 309
Hospital stay, days	493	a	25	4.65	2,293 ± 5,915	25	4.84	2,388 ± 7,522
Intensive care unit, days	2,356	a	5	0.49	1,161 ± 11,316	2	0.14	328 ± 2,658
Drugs for obstructive airway diseases	-	c	84	-	945 ± 814	84	-	934 ± 1,024
Other medication	-	c	91	-	1,367 ± 3,421	90	-	1,131 ± 2,506
Costs from societal perspective								
Travel expenses, public transport/car, KM	0.22	a	94	189.00	42 ± 56	92	174.43	38 ± 59
Productivity loss, absenteeism hours	31-43	a	11	47.74	1,698 ± 8,344	11	42.89	1,649 ± 8,448
Productivity loss, presenteeism hours	31-43		8	10.38	376 ± 2,304	9	10.92	374 ± 1,774

** Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research[9], (b) The Dutch Healthcare Authority NZA (c) GIP Databank [20]*

Table 4. Results from the cost-utility and cost-effectiveness analysis from the base case (in euros, 2013)

		Costs			Effect			cost-effectiveness planes				
		RECODE	Usual Care	Difference (95% CI)	RECODE	Usual Care	Difference (95% CI)	ICER	NW C↑E↓	SW C↓E↓	NE C↑E↑	SE C↓E↑
Cost per QALY	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-15,720**	97.9	1.3	0.8	0.0
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-17,358**	97.3	1.9	0.8	0.0
Cost per exacerbation avoided	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-4,211**	91.3	1.2	7.4	0.1
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-4,650**	90.7	1.8	7.4	0.1
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-35,772**	75.2	1.0	23.5	0.3
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-39,498**	74.8	1.4	23.3	0.5
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5.119	€ 4.535	€ 584* (86 – 1,046)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-46,508**	66.5	0.9	32.3	0.4
	SP	€ 5.750	€ 5.105	€ 645* (28 – 1,190)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-51,353**	66.1	1.3	32.0	0.6

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west (more cost and less effects), SW=south-west (less cost and less effects), NE=north-east (more cost and more effects) , SE=south-east (more cost and less effects), C= difference in costs, E=difference in effects.*

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Appendix 1. Health economic terms

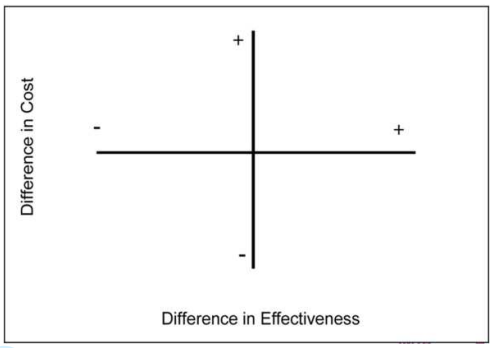
Incremental costs
= Difference in costs between the intervention and usual care group
= $\text{Costs}_{\text{intervention group}} - \text{Costs}_{\text{usual care group}}$

Incremental effects
= Difference in effects between the intervention and usual care group
= $\text{Effect}_{\text{intervention group}} - \text{Effect}_{\text{usual care group}}$

Incremental cost-effectiveness ratios (ICERs)
= Incremental costs / Incremental effects
= $(\text{Costs}_{\text{intervention group}} - \text{Costs}_{\text{usual care group}}) / (\text{Effect}_{\text{intervention group}} - \text{Effect}_{\text{usual care group}})$

Bootstrapping
Bootstrapping means repeatedly drawing samples with replacement from the original dataset.[1] That is to say the same record can occur more than once in a given bootstrap sample. Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs.

Cost-effectiveness plane
We plot the uncertainty around the difference in costs and effects in a cost-effectiveness plane (CE-plane). In a CE-plane, the horizontal axis displays the difference in effects and the vertical axis displays the difference in costs.[2] The results of the bootstrap replications fall into one of four quadrants:



- North-east quadrant: more cost and more effects;
- South-east quadrant: less cost and more effects (intervention is dominant);
- South-west quadrant: less cost and less effects;
- North-west quadrant: more cost and less effects (intervention is dominated).

In the most ideal situation, all the results of the bootstraps lay in lower-right corner of the plane, indicating lower costs and improved outcomes.

Cost-effectiveness acceptability curves
The cost-effectiveness acceptability curve shows the probability that the RECODE program is cost-effective using different thresholds for the willingness to pay for a quality adjusted life year.[3] This probability equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

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Appendix 2. Sensitivity analyses: impact on cost-utility and cost-effectiveness, with intervention costs

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
With intervention costs												
Cost per QALY	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-23,792**	99.1	0.0	0.9	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	1.40	1.44	-0.04* (-0.07 – -0.01)	**-27,053**	99.0	0.2	0.9	0.0
Cost per exacerbation avoided	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-6,373**	92.5	0.0	7.5	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.78	0.65	-0.14 (-0.30 – 0.06)	**-7,247**	92.4	0.2	7.5	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-54,139**	76.2	0.0	23.8	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.11	0.12	-0.02 (-0.06 – 0.02)	**-61,559**	76.1	0.1	23.8	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 5,528	€ 4,644	€ 883** (375 – 1,353)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-70,388**	67.4	0.0	32.6	0.0
	SP	€ 6,211	€ 5,206	€ 1,005** (381 –1,570)	0.26	0.27	-0.01 (-0.07 – 0.04)	**-80,035**	67.3	0.1	32.6	0.1

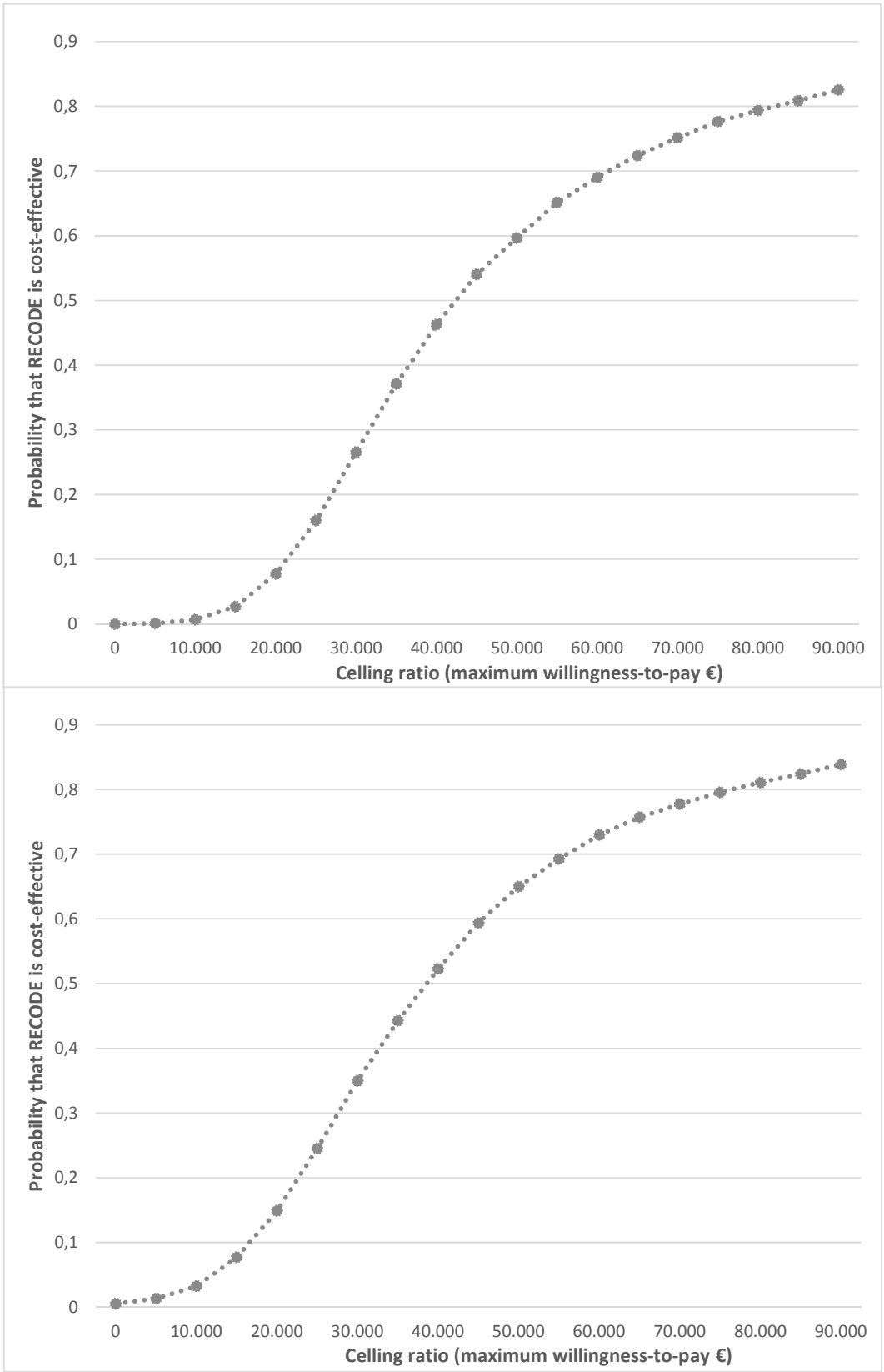
** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 3. Sensitivity analyses: impact on cost-utility and cost-effectiveness, 12 months' time horizon

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
12 months' time horizon												
Cost per QALY	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.71	0.70	0.01 (-0.001 – 0.02)	**42,458**	3.6	0.0	96.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.71	0.70	0.01 (-0.001 – 0.02)	**38,471**	3.6	0.0	95.8	0.6
Cost per exacerbation avoided	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.38	0.32	-0.06 (-0.14 – 0.05)	**-7,401**	87.3	0.0	12.7	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.38	0.32	-0.06 (-0.14 – 0.05)	**-6,706**	86.8	0.5	12.7	0.0
Cost per additional patient with a clinical relevant improvement in CCQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.19	0.26	-0.07** (-0.14 – -0.02)	**-5,582**	99.6	0.0	0.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.19	0.26	-0.07** (-0.14 – -0.02)	**-5,058**	99.0	0.6	0.4	0.0
Cost per additional patient with a clinical relevant improvement in SGRQ score	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.36	0.37	-0.01 (-0.05 – 0.03)	**-36,869**	69.4	0.0	30.6	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.36	0.37	-0.01 (-0.05 – 0.03)	**-33,408**	69.1	0.3	30.3	0.2

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 4. Cost-effectiveness acceptability curves, healthcare (upper) and societal perspective (lower) with a 12 months' time horizon



Appendix 5. Subgroup analyses (age, gender, Medical Research Council (MRC) Dyspnoea scale)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY age subgroups															
HP	<65 years	N=411	€ 3,975	€ 3,801	€ 174 (-434 – 711)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-9,820**	58.0	20.4	15.8	5.9
	≥65 years	N=675	€ 6,029	€ 5,028	€ 1,001* (248 – 1,701)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,698**	98.8	0.5	0.7	0.0
SP	<65 years	N=411	€ 5,374	€ 5,158	€ 216 (-737 – 1,035)	0.03*	1.57	1.58	-0.02 (-0.06 – 0.03)	0.04*	**-12,171**	54.1	24.2	15.1	6.5
	≥65 years	N=675	€ 6,064	€ 5,079	€ 985* (224 – 1,679)		1.55	1.60	-0.05* (-0.10 – -0.01)		**-18,409**	98.7	0.6	0.7	0.0
Cost per QALY gender subgroups															
HP	Men	N=585	€ 4,725	€ 4,344	€ 381 (-250 – 963)	0.92	1.53	1.57	-0.04* (-0.08 – -0.01)	0.16	**-8,951**	88.4	10.5	1.1	0.1
	Women	N=501	€ 5,527	€ 4,756	€ 771 (-44 – 1,472)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-35,680**	80.4	2.7	16.4	0.4
SP	Men	N=585	€ 5,226	€ 4,924	€ 302 (-502 – 1,000)	0.75	1.53	1.57	-0.04* (-0.08 – -0.01)	0.16	**-7,090**	78.2	20.7	0.9	0.2
	Women	N=501	€ 6,302	€ 5,331	€ 971* (106–1,748)		1.35	1.37	-0.02 (-0.07 – 0.02)		**-44,939**	81.8	1.4	16.7	0.2
Cost per QALY MRC subgroups															
HP	MRC≤2	N=725	€ 3,927	€ 3,500	€ 427 (-29– 821)	0.67	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,060**	99.5	2.9	1.5	0.1
	MRC>2	N=361	€ 8,721	€ 7,231	€ 1,489 (-164 – 2,881)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-42,301**	81.2	2.8	15.5	0.5
SP	MRC≤2	N=725	€ 4,543	€ 4,101	€ 443 (-191 – 1,029)	0.52	1.57	1.61	-0.04* (-0.07 – -0.003)	0.41	**-11,464**	90.8	7.6	1.3	0.2
	MRC>2	N=361	€ 9,358	€ 7,744	€ 1,614 (-161 – 3,115)		0.66	0.69	-0.04 (-0.10 – 0.03)		**-45,846**	81.0	3.0	15.5	0.5

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, MRC=Medical Research Council, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

Appendix 5. Subgroup analyses (FEV1, SES)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Inter-action	RECODE	usual Care	Difference	P-value Inter-action	ICER	NW	SW	NE	SE
Cost per QALY lung function subgroups															
HP	FEV1≥50	N=674	€ 4,797	€ 4,025	€ 773** (198 – 1,287)	0.85	1.47	1.51	-0.04 (-0.07 – 0.003)	0.15	**-21,762**	96.0	0.5	3.5	0.0
	FEV1<50	N=193	€ 7,744	€ 7,415	€ 329 (-1,499 – 1,837)		1.39	1.34	-0.05 (-0.12 – 0.03)		**-10,044**	60.3	29.4	6.9	3.4
SP	FEV1≥50	N=674	€ 5,359	€ 4,537	€ 822* (159 – 1,420)	0.82	1.47	1.51	-0.04 (-0.07 – 0.003)	0.15	**-23,155**	95.5	1.0	3.5	0.0
	FEV1<50	N=193	€ 8,622	€ 8,170	€ 452 (-1,536 –2,139)		1.39	1.34	-0.05 (-0.12 – 0.03)		**-7,310**	63.3	26.5	7.2	3.1
Cost per QALY Social economic status (SES) subgroups															
HP	Low SES	N=399	€ 5,124	€ 4,562	€ 562 (-434 – 1,423)	0.46	1.04	1.09	-0.05 (-0.11 – 0.01)	0.15	**-11,505**	84.2	10.8	4.4	0.5
	Moderate/ high SES	N=590	€ 5,347	€ 4,598	€ 749 (74 – 1,362)		1.54	1.57	-0.03 (-0.07 – 0.01)		**-24,627**	91.9	1.5	6.5	0.1
SP	Low SES	N=399	€ 5,534	€ 4,859	€ 675 (-415 – 1,632)	0.49	1.04	1.09	-0.05 (-0.11 – 0.01)	0.15	**-13,801**	85.3	9.7	4.4	0.6
	Moderate/ high SES	N=590	€ 6,089	€ 5,372	€ 717 (-125 – 1,459)		1.54	1.57	-0.03 (-0.07 – 0.01)		**-23,560**	89.1	4.3	6.2	0.4

** Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, FEV1= forced expiratory volume in 1 second, SES=Social Economic Status, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, NE=north-east, SE=south-east, CE-planes=cost-effectiveness planes.*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N.A.
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5,6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N.A.
Sample size	7a	How sample size was determined	Details in published protocol paper
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N.A.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Details in published protocol paper
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details in

			published protocol paper
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Details in published protocol paper
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Details in published protocol paper
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Details in published protocol paper
	11b	If relevant, description of the similarity of interventions	N.A.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6,7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	N.A.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8-10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8-10

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11,12
Other information			
Registration	23	Registration number and name of trial registry	Details in published protocol paper
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.