

BMJ Open

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Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007284
Article Type:	Research
Date Submitted by the Author:	24-Nov-2014
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Health economics, Respiratory medicine
Keywords:	HEALTH ECONOMICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE, RESPIRATORY MEDICINE (see Thoracic Medicine)

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Manuscripts

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

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Keywords: COPD, cost effectiveness, integrated care, primary care

Words: 3080

28 Abstract

29 Background

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

35 Methods

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

38 Results

39 The intervention costs were €324 per patient. Excluding these costs, the intervention group had
40 €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI €28
41 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both groups,
42 except for 0.04 (95% CI -0.07 to -0.01) less quality-adjusted life-years in the intervention group.

43 Conclusion

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

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47 Strengths and limitations of this study

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

57

58 Introduction

59

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

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

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

77

78 **Methods**

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80 This study was approved by the medical ethics committee, performed according to the study
81 protocol⁷, national⁹ and international¹⁰ guidelines for pharmaco-economic research, and reported
82 according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).¹¹

83

84 *Design and Intervention*

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

104

105 *Target population*

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

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3 112 criteria. All participating GPs and COPD patients provided written informed consent before
4 113 participation.

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8 115 *Outcomes*

9 116 Costs were related to the following outcome measures:

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11 117 I. quality-adjusted life years(QALYs) based on the EuroQol-5D (EQ-5D) utility values using the
12 118 Dutch value set^{13,14};
- 13
14 119 II. proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement
15 120 ≥ 0.4) on the Clinical COPD Questionnaire(CCQ)^{15,16};
- 16
17 121 III. proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory
18 122 Questionnaire(SGRQ)^{17,18};
- 19
20 123 IV. total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was
21 124 defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic
22 125 corticosteroids and/or antibiotics, but did not require hospitalization. This information was
23 126 extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as
24 127 a worsening of symptoms that required a hospital admission. Hospital admissions were
25 128 obtained from the resource use questionnaires and the EMR.

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27 129
28 130 The EQ-5D, CCQ, SGRQ, and resource use questionnaire were administered at baseline, 6, 9, 12, 18,
29 131 and 24 months.

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31 132

32 133 *Costs*

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34 134 Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a
35 135 societal perspective. The healthcare perspective included all costs covered by the healthcare budget,
36 136 i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse,
37 137 physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions,
38 138 emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective
39 139 additionally included travel costs and costs of productivity loss due to absence from paid work.

40
41 140 Patients reported the healthcare utilization (excluding medication), travel costs, days of
42 141 absence from paid work due to illness (absenteeism) and lost productivity while being at work
43 142 (presenteeism) in a resource use questionnaire with a recall period of three months.

44
45 143 The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs
46 144 were obtained from the Dutch manual for costing research⁹ and inflated to 2013 using the general
47 145 consumer price index.¹⁹ The costs of medications were obtained from the GIP-Databank and

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3 146 included value added tax and pharmacist dispensing fees.²⁰ The productivity costs were estimated
4 147 using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick
5 148 employee is not replaced (the friction period).²¹ We used a friction period of 115 days.⁹

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8 149 The intervention costs, defined as costs of training the teams, costs of the ICT support, and
9 150 costs of the monitoring reports, were calculated based on (refresher) course attendance, computer-
10 151 documented ICT-use, and estimated time involved in producing monitoring reports.

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14 153 *Statistical analysis*

15 154 Data analysis was performed according to the intention-to-treat principle. Data from patients who
16 155 discontinued the trial prematurely were included in the analysis up to the point of drop-out.
17 156 Additionally, patients that dropped-out during the first year were asked to fill in a CCQ questionnaire
18 157 at 12 months, if possible.

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22 158 We used repeated measures models to assess differences between RECODE and usual care,
23 159 correcting for time, age, gender, MRC dyspnoea score >2, baseline score and clustering of patients.
24 160 The distribution and link function for each outcome was selected after comparing the goodness-of-
25 161 fit of models with different specifications of the distribution and link functions. Models that had the
26 162 lowest Akaike's Information Criterion were selected.

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30 163 EQ-5D utilities were analysed using linear mixed models with a normal distribution and
31 164 identity link. We calculated the number of QALY's for each patient as the area under the predicted
32 165 utility curve, using linear interpolation between two utility measurements. Generalized linear mixed
33 166 models with a binary distribution and logit link were used to analyse the proportion of patients with
34 167 a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated
35 168 using generalized linear mixed models with negative binomial distribution and log link. Costs were
36 169 analysed with generalized linear mixed models using a log-normal distribution and identity link. The
37 170 cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly
38 171 extrapolated to include month 0 to 3.²² The same was done for the cost estimate of month 15 to 18
39 172 and 21 to 24.

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48 174 *Cost-effectiveness*

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50 175 Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental
51 176 cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the
52 177 CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented.
53 178 Taking a multi-outcome approach is in line with recent guidelines.²³

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3 179 Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times.
4 180 Bootstrapping means repeatedly drawing samples with replacement from the original dataset.²⁴
5 181 Each sample has the same size as the trial and for each sample the difference in costs and QALYs
6 182 between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the
7 183 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs.
8 184 The 5,000 ICERs were plotted on cost-effectiveness planes.²⁵ In a cost-effectiveness plane, the
9 185 horizontal axis displays the difference in effects and the vertical axis displays the difference in costs.
10 186 The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant
11 187 (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant
12 188 (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 1). Finally,
13 189 the probability that the RECODE program is cost-effective using different thresholds for the
14 190 monetary value of a QALY was shown in cost-effectiveness acceptability curves.²⁶ This probability
15 191 equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.
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193 *Sensitivity and subgroup analyses*

194 Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other
195 with a one year instead of a two year time horizon. Five subgroup analyses were performed to study
196 the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-
197 specified in the study protocol and the power calculation was based on the subgroup analyses by
198 MRC dyspnoea score >2.⁷

199

200 Results

201

202 *Patients*

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

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

214

215

[TABLE 1]

216

217 *Costs*

218 The intervention costs are presented in Table 2. The total intervention costs per patient ranged from
219 €103 to €587 across clusters, with a mean (\pm sd) of €324 (\pm 156) per patient. This variation is
220 explained by the number of COPD patients per team, the use of the ICT system, the number of
221 healthcare providers participating in the courses, and the different locations of the courses. The
222 labour costs of the attendees of the RECODE courses were the main driver of the intervention costs
223 (54%).

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

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

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3 233 than in the usual care group by €584 from the healthcare perspective and €645 from the societal
4 234 perspective (Table 4).

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6 236 [TABLE 2]

7 237 [TABLE 3]

8 238 [TABLE 4]

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11 241 *Outcomes*

12 242 Over a two year period, the number of QALYs was 0.04 ($p=0.02$) lower in the RECODE group than in
13 243 the usual care group while there was no significant difference in percentage of patients with a MCID
14 244 in CCQ, nor in any of the other outcomes (Table 4).

15 245

16 246 *Cost-effectiveness*

17 247 From a healthcare and societal perspective, the point-estimates of costs and effects pointed towards
18 248 higher costs and lower effects of the RECODE program, resulting in negative ICERs. The CE-planes of
19 249 the different outcomes showed that the majority of the bootstrap replications (>98%) had higher
20 250 costs. Furthermore, more than half of the bootstrap replications fell within the north-west quadrant
21 251 of the plane indicating that RECODE was dominated by the usual care group, e.g. more costs and less
22 252 effects.

23 253

24 254 *Sensitivity analyses*

25 255 When including the intervention costs, the cost difference, which favoured usual care, further
26 256 increased to a difference of €883 from the healthcare perspective and €1,005 from the societal
27 257 perspective (Appendix 2).

28 258 Using a 12-month instead of a 24 month time horizon, the costs per patient were
29 259 significantly higher in the RECODE group in comparison with the usual care group by €408 from the
30 260 healthcare perspective and €370 from the societal perspective (Appendix 3). After 12 months, there
31 261 was no significant difference in QALYs, or any of the other outcomes, except for the percentage of
32 262 patients improving at least the MCID in CCQ, which was 7% less in the RECODE group than in the
33 263 usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was
34 264 €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that
35 265 RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was

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3 266 8% and 79%, respectively (Appendix 4). From a societal perspective these probabilities were slightly
4 267 higher, i.e. 15% and 81%.

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8 269 *Subgroup analyses*

9 270 Only age showed a significant interaction with the effect of RECODE on costs (Appendix 5,6). The
10 271 difference in costs (healthcare and societal perspective) between RECODE and usual care was
11 272 significantly lower in patients younger than 65 years, than in patients above 65 years. There was also
12 273 a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below
13 274 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients
14 275 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that
15 276 RECODE is cost-effective within the subgroup of patients <65 years.
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277 Discussion

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

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

296 There are several possible explanations why the RECODE intervention was not found to be
297 cost-effective. Firstly, it may be due to the relatively low intensity of our pragmatic intervention. The
298 RECODE program did not require the teams to implement all elements of the program. For instance,
299 70% of the intervention teams attended the refresher courses and 50% actively used the ICT system
300 ZORGDRAAD. Consequently, the intensity of the intervention for individual patients was not only
301 dependent upon health status, personal needs and preferences of the individual patients, but also
302 on the level of implementation of the DM interventions and the context within which each team
303 operates. Further research is required to understand the conditions for a successful implementation
304 and thus cost-effectiveness of a DM program.

305 Secondly, it is questionable whether the pragmatic provider-oriented interventions of the
306 RECODE program were optimally translated into patient-oriented interventions. This is important
307 because it has been shown that successful COPD-DM programs mainly include patient-oriented
308 interventions.^{2,3} Literature showed that exercise is an important success factor of a COPD-DM
309 program³ and education, exercise and relaxation are important factors for reducing the use of

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3 310 urgent and unscheduled healthcare among people with COPD.²⁷ In our study, physical exercise was
4 311 not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

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6 312 Thirdly, there was limited room for improvement in comparison with previous studies due to
7
8 313 the relatively high standard of COPD care in the Netherlands²⁸, the low proportion of severe COPD
9 314 patients in this study^{2,3} and the selective drop-out of patients who are more severely ill and thus had
10 315 the greatest potential for improvement.²⁹

11
12 316 Fourthly, changes in healthcare occurred during the study period that affected COPD care in
13 317 the RECODE as well as the usual care group. Since July 2010, a new bundled payment scheme for
14 318 COPD patients has been introduced in the Netherlands to stimulate the integration of care.³⁰ In this
15 319 scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price
16 320 per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes
17 321 secondary care and medications, it primarily stimulates the cooperation between different providers
18 322 in the primary care setting. This increased attention for integrated chronic and the ability to
19 323 reimburse COPD interventions such as smoking cessation and nutritional counselling could have
20 324 stimulated integrated care in the usual care group too.

21
22 325 In conclusion, this comprehensive economic evaluation of an integrated care program in
23 326 primary care showed that the program increased costs but did not improve health outcomes. It even
24 327 reduced QALYs. This is most likely due to the fact that the interventions targeted professionals
25 328 instead of patients and were sub-optimally implemented, the relatively mild COPD population, and
26 329 the national reforms in COPD care.

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3 330 **TRIAL REGISTRATION:** Netherlands Trial Register (NTR): NTR2268.
4 331

5 332 **FUNDING:** This study was supported by grants from Stichting Achmea Gezondheidszorg (SAG), a
6
7 333 research fund of a Dutch Healthcare insurance company, and the Netherlands Organisation for
8
9 334 Health Research and Development (Zon-MW). The funding agencies (SAG and Zon-MW) have no
10
11 335 influence on the analysis and writing of the paper.
12 336

13 337 **CONTRIBUTORSHIP :** MPHMR, WJJA, JG, and NHC conceived and designed the study. MRSB, ALK, AT,
14
15 338 and CB acquired the data. MRSB, AT, and MPHMR analysed and interpreted the data. MRSB drafted
16
17 339 the manuscript. ALK, NHC, AT, JG, WJJA, and MPHMR advised on the preparation of the manuscript.
18
19 340 All authors read, edited, and approved the final version of the manuscript.
20 341

21 342 **CONFLICT OF INTEREST:** There are no competing interests.
22 343

23 344 **ETHICAL APPROVAL:** The study was reviewed and approved by the medical ethical committee of the
24
25 345 Leiden University Medical Centre, the Netherlands. All general practitioners and participants gave
26
27 346 written informed consent.
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29 348 **DATA SHARING:** No additional data available.
30 349

31 350 **DECLARATION OF TRANSPARENCY:** The authors affirm that this manuscript is an honest, accurate,
32
33 351 and transparent account of the study being reported; that no important aspects of the study have
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35 352 been omitted; and that any discrepancies from the study as planned (and, if relevant, registered)
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37 353 have been explained.
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3 354 **Table of content**
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6 356 **Table 1.** Baseline characteristics
7 357 **Table 2.** Intervention costs (in euros, 2013)
8 358 **Table 3.** Unit costs, data sources, mean use of resources and associated costs over the 2-
9 359 years, as reported by the patients (unadjusted)
10 360 **Table 4.** Results from the cost-utility and cost-effectiveness analysis from the base case (in
11 361 euros, 2013)
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14 **Appendix 1.** Health economic terms
15 364 **Appendix 2.** Sensitivity analyses: impact on cost-utility and cost-effectiveness, with intervention
16 365 costs
17 366 **Appendix 3.** Sensitivity analyses: impact on cost-utility and cost-effectiveness, 12 months' time
18 367 horizon
19 368 **Appendix 4.** Cost-effectiveness acceptability curves, healthcare (upper) and societal perspective
20 369 (lower) with a 12 months' time horizon
21 370 **Appendix 5.** Subgroup analyses (age, gender MRC)
22 371 **Appendix 6.** Subgroup analyses (FEV1, SES)
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372 **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)

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

375 **Table 2.** Intervention costs (in euros, 2013)

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

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

377 **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								
<i>GP, (home) visits, phone contacts</i>	15-46	a	91	16.23	476 ± 504	89	14.02	401 ± 450
<i>Practice nurse, visits</i>	23	b	74	5.51	131 ± 277	75	5.18	109 ± 166
<i>Specialist, visits</i>	78	a	78	10.05	784 ± 1,037	78	9.84	768 ± 973
<i>Emergency department, visits</i>	163	a	26	0.78	127 ± 284	23	0.79	129 ± 346
<i>Physiotherapist, visits</i>	39	a	53	25.82	1,007 ± 1,770	45	16.33	637 ± 1,260
<i>Dietician, visits</i>	29	a	21	1.45	42 ± 141	19	1.21	35 ± 148
<i>Podiatrist, visits</i>	32	b	43	3.78	121 ± 203	40	3.27	105 ± 167
<i>Speech therapist, visits</i>	36	a	3	0.12	4 ± 42	2	0.28	10 ± 158
<i>Occupational therapy, visits</i>	24	a	4	0.29	7 ± 76	3	0.32	8 ± 83
<i>Rehabilitation centre, visits</i>	78	a	12	3.86	459 ± 2,157	12	3.01	358 ± 1,731
<i>Home care, hours of household help</i>	26	a	22	34.42	895 ± 2,287	20	31.01	806 ± 2,171
<i>Home care, hours of personal care</i>	47	a	9	8.28	389 ± 1,995	8	9.49	446 ± 2,327
<i>Home care, hours of nursing</i>	70	a	6	2.11	148 ± 1,108	6	2.39	167 ± 1,064
<i>Home care, other, hours</i>	48	a	1	0.47	22 ± 262	2	0.65	31 ± 309
<i>Hospital stay, days</i>	493	a	25	4.65	2,293 ± 5,915	25	4.84	2,388 ± 7,522
<i>Intensive care unit, days</i>	2,356	a	5	0.49	1,161 ± 11,316	2	0.14	328 ± 2,658
<i>Drugs for obstructive airway diseases</i>	-	c	84	-	945 ± 814	84	-	934 ± 1,024
<i>Other medication</i>	-	c	91	-	1,367 ± 3,421	90	-	1,131 ± 2,506
Costs from societal perspective								
<i>Travel expenses, public transport/car, KM</i>	0.22	a	94	189.00	42 ± 56	92	174.43	38 ± 59
<i>Productivity loss, absenteeism hours</i>	31-43	a	11	47.74	1,698 ± 8,344	11	42.89	1,649 ± 8,448
<i>Productivity loss, presenteeism hours</i>	31-43		8	10.38	376 ± 2,304	9	10.92	374 ± 1,774

378 * Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research⁹, (b) The Dutch Healthcare Authority NZA (c) GIP Databank²⁰

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

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	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↑	
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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

382 * 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,
 383 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-
 384 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												
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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

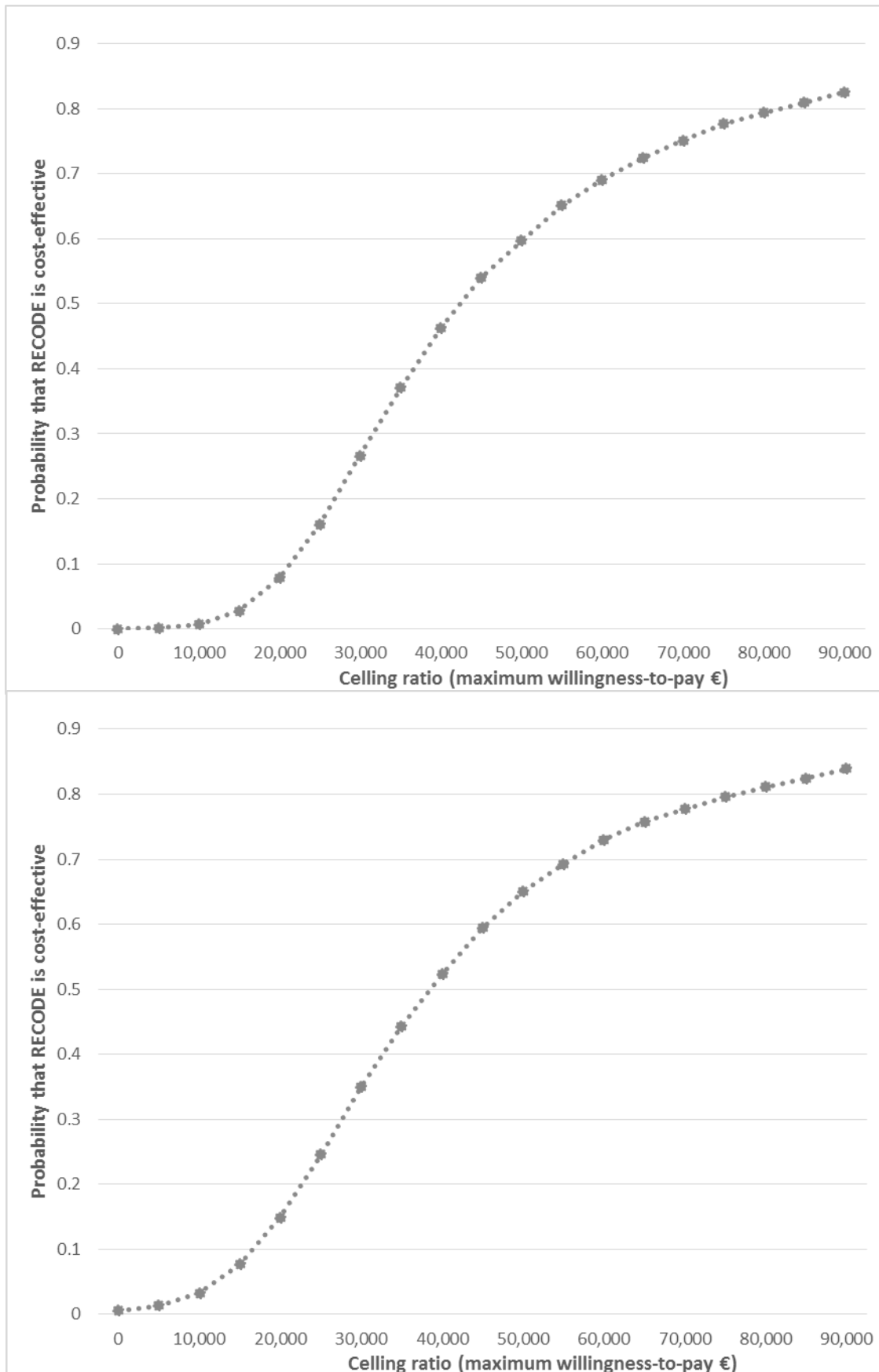
	RECODE	Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
12 months' time horizon												
<i>Cost per QALY</i>	HP	€ 2,622	€ 2,214	€ 408** (193 – 607)	0.71	0.70	0.01 (-0.001 – 0.02)	42,458	3.6	0.0	96.4	0.0
	SP	€ 2,955	€ 2,585	€ 370* (90 – 206)	0.71	0.70	0.01 (-0.001 – 0.02)	38,471	3.6	0.0	95.8	0.6
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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.

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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)	0.1	-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)	0.1	-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)	0.4	-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)	0.4	-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.

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Appendix 5. Subgroup analyses (FEV1, SES)

			Costs				Effect (QALY's)				CE-planes				
			RECODE	usual Care	Difference	P-value Interaction	RECODE	usual Care	Difference	P-value Interaction	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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007284.R1
Article Type:	Research
Date Submitted by the Author:	28-May-2015
Complete List of Authors:	<p>Boland, Melinde; Erasmus University Rotterdam, Institute for Medical Technology Assessment; Easmus University Rotterdam, Department of Health Policy and Management</p> <p>Kruis, Annemarije; Leiden University Medical Center, Department of Public Health and Primary Care</p> <p>Tsiachristas, Apostolos; Erasmus University Rotterdam, Institute for Medical Technology Assessment, Department of Health Policy and Management; Health Economics Research Centre, University of Oxford, Department of Population Health</p> <p>Assendelft, Willem; Leiden University Medical Centre, Department of Public Health and Primary Care; Radboud University Nijmegen Medical Centre, Department of Primary and Community Care</p> <p>Gussekloo, Jacobijn; Leiden University Medical Center, Department of Public Health and Primary Care</p> <p>Blom, Coert; Stichting Zorgdraad Foundation,</p> <p>Chavannes, Niels; Leiden University Medical Center, Public Health and Primary Care</p> <p>Rutten-van Mólken, Maureen; Erasmus University Rotterdam, Institute for Medical Technology Assessment; Easmus University Rotterdam, Department of Health Policy and Management</p>
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Health economics, Respiratory medicine
Keywords:	HEALTH ECONOMICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE, RESPIRATORY MEDICINE (see Thoracic Medicine)

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Manuscripts

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

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Keywords: COPD, cost effectiveness, integrated care, primary care

Words: 3080

30 Abstract

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

33
34 **Design:** two-year, cluster-randomised controlled trial

35
36 **Setting:** 40 general practices in the western part of the Netherlands

37
38 **Participants:** 1086 patients with COPD according to GOLD (Global Initiative for COPD) criteria.
39 Exclusion criteria were terminal illness, cognitive impairment, alcohol or drug misuse, and inability to
40 fill in Dutch questionnaires. Practices were included if they were willing to create a multidisciplinary
41 COPD team.

42
43 **Interventions:** A multidisciplinary team of caregivers was trained in motivational interviewing,
44 setting-up individual care plans, exacerbation management, implementing clinical guidelines and
45 redesigning the care process. In addition, clinical decision making was supported by feedback
46 reports provided by an ICT program.

47
48 **Main outcome measures:** We investigated impact on health outcomes (quality-adjusted life years
49 (QALYs), Clinical COPD Questionnaire, St. George's Respiratory Questionnaire, and exacerbations)
50 and costs (healthcare and societal perspective).

51 **Results:** The intervention costs were €324 per patient. Excluding these costs, the intervention group
52 had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI
53 €28 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both
54 groups, except for 0.04 (95% CI -0.07 to -0.01) less QALYs in the intervention group.

55
56 **Conclusions:** This integrated care program for COPD patients that mainly included professional-
57 directed interventions was not cost-effective in primary care.

58
59 **Trial registration:** Netherlands Trial Register NTR2268

60
61 **Funding:** Stichting Achmea Gezondheidszorg (SAG) and the Netherlands Organisation for Health
62 Research and Development (Zon-MW).

63 Strengths and limitations of this study

- 64
- 65 • It is the largest and most pragmatic Dutch RCT trial to date assessing the cost-effectiveness
66 of COPD disease management in primary care.
 - 67 • The 2-year follow-up period, the broad range of health outcomes and costs (including
68 program costs) measured and the statistically sophisticated analyses ensure the robustness
69 of the results.
 - 70 • The uncertainty in the cost-effectiveness of the disease management programs is
71 adequately estimated and illustrated enabling the appropriate interpretation of the results.
 - 72 • The control group was likely to be exposed to quality improvement initiatives as part of
73 usual care.
- 74

75 Introduction

76

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

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

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

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

107 **Methods**

108

109 This study was approved by the medical ethics committee, performed according to the study
110 protocol⁸, national⁹ and international¹⁰ guidelines for pharmaco-economic research, and reported
111 according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).¹¹

112

113 *Design and Intervention*

114 RECODE is a 2-year cluster randomized trial in which 40 clusters of primary care teams were
115 randomized to the COPD-DM program or usual care. The 20 teams of the intervention group were
116 trained in essential components of effective COPD-DM: proper diagnosis, optimizing medication
117 adherence, motivational interviewing, smoking cessation counselling, applying self-management
118 plans including early recognition and treatment of exacerbations, physical (re)activation, and
119 nutritional support. In addition, the teams learned the details of a web-based computer program for
120 measuring and reporting process and outcome performance indicators, named ZORGDRAAD. This
121 Information and Communications Technologies (ICT) application included a patient and provider
122 portal that facilitated the communication within the multi-disciplinary teams as well as between care
123 providers and patients. At the end of the 2-day course, each team developed a plan with steps to be
124 taken in order to redesign the care process and integrate the COPD-DM program into their daily
125 practice. After the course, the teams were invited to join refresher courses, received regular
126 feedback reports on patients' outcomes and had access to ZORGDRAAD. The local healthcare insurer
127 reimbursed physical reactivation for patients with a Medical Research Council (MRC) dyspnoea score
128 >2, also if these patients had no supplementary insurance. All practices were flexible in determining
129 and following their individual plans. Therefore, the mix and intensity of interventions for individual
130 patients depended upon their health status, personal needs and preferences, as well as the actions
131 taken by the team. Healthcare providers in the usual care group were asked to continue providing
132 care as usually. Indicators of care as usual are reported before.⁸

133

134 *Target population*

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

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3 141 criteria. All participating GPs and COPD patients provided written informed consent before
4 142 participation.

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8 144 *Outcomes*

9 145 Costs were related to the following outcome measures:

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11 146 I. QALYs based on the EuroQol-5D (EQ-5D) utility values using the Dutch value set^{13,14};
12 147 II. proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement
13 148 ≥ 0.4) on the CCQ^{15,16};
14 149 III. proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory
15 150 Questionnaire(SGRQ)^{17,18};
16 151 IV. total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was
17 152 defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic
18 153 corticosteroids and/or antibiotics, but did not require hospitalization. This information was
19 154 extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as
20 155 a worsening of symptoms that required a hospital admission. Hospital admissions were
21 156 obtained from the resource use questionnaires and the EMR.

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24 158 The EQ-5D, CCQ, SGRQ, and resource use questionnaire were administered at baseline, 6, 9, 12, 18,
25 159 and 24 months.

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28 161 *Costs*

29 162 Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a
30 163 societal perspective. The healthcare perspective included all costs covered by the healthcare budget,
31 164 i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse,
32 165 physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions,
33 166 emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective
34 167 additionally included travel costs and costs of productivity loss due to absence from paid work.

35 168 Patients reported the healthcare utilization (excluding medication), travel costs, days of
36 169 absence from paid work due to illness (absenteeism) and lost productivity while being at work
37 170 (presenteeism) in a resource use questionnaire with a recall period of three months.

38 171 The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs
39 172 were obtained from the Dutch manual for costing research⁹ and inflated to 2013 using the general
40 173 consumer price index.¹⁹ The costs of medications were obtained from the GIP-Databank and
41 174 included value added tax and pharmacist dispensing fees.²⁰ The productivity costs were estimated

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

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

185

186 *Statistical analysis*

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

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

196 EQ-5D utilities were analysed using linear mixed models with a normal distribution and
197 identity link. We calculated the number of QALY's for each patient as the area under the predicted
198 utility curve, using linear interpolation between two utility measurements. Generalized linear mixed
199 models with a binary distribution and logit link were used to analyse the proportion of patients with
200 a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated
201 using generalized linear mixed models with negative binomial distribution and log link. Costs were
202 analysed with generalized linear mixed models using a log-normal distribution and identity link. The
203 cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly
204 extrapolated to include month 0 to 3.²³ The same was done for the cost estimate of month 15 to 18
205 and 21 to 24.

206

207 *Cost-effectiveness*

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3 208 Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental
4 209 cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the
5 210 CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented.
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8 211 Taking a multi-outcome approach is in line with recent guidelines.²⁴

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10 212 Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times.
11 213 Bootstrapping means repeatedly drawing samples with replacement from the original dataset.²⁵
12 214 Each sample has the same size as the trial and for each sample the difference in costs and QALYs
13 215 between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the
14 216 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs.
15 217 The 5,000 ICERs were plotted on cost-effectiveness planes.²⁶ In a cost-effectiveness plane, the
16 218 horizontal axis displays the difference in effects and the vertical axis displays the difference in costs.
17
18 219 The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant
19 220 (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant
20 221 (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 1). Finally,
21 222 the probability that the RECODE program is cost-effective using different thresholds for the
22 223 monetary value of a QALY was shown in cost-effectiveness acceptability curves.²⁷ This probability
23 224 equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.
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32 226 *Sensitivity and subgroup analyses*

33 227 Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other
34 228 with a one year instead of a two year time horizon. Five subgroup analyses were performed to study
35 229 the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-
36 230 specified in the study protocol and the power calculation was based on the subgroup analyses by
37 231 MRC dyspnoea score >2.⁸
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233 Results

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235 Patients

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

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

247

248 [TABLE 1]

249

250 Costs

251 The intervention costs are presented in Table 2. The total intervention costs per patient ranged from
252 €103 to €587 across clusters, with a mean (\pm sd) of €324 (\pm 156) per patient. This variation is
253 explained by the number of COPD patients per team, the use of the ICT system, the number of
254 healthcare providers participating in the courses, and the different locations of the courses. The
255 labour costs of the attendees of the RECODE courses were the main driver of the intervention costs
256 (54%).

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

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

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

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269 [TABLE 2]

270 [TABLE 3]

271 [TABLE 4]

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274 *Outcomes*

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

278

279 *Cost-effectiveness*

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

287

288 *Sensitivity analyses*

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

292 Using a 12-month instead of a 24 month time horizon, the costs per patient were
293 significantly higher in the RECODE group in comparison with the usual care group by €408 from the
294 healthcare perspective and €370 from the societal perspective (Appendix 3). After 12 months, there
295 was no significant difference in QALYs, or any of the other outcomes, except for the percentage of
296 patients improving at least the MCID in CCQ, which was 7% less in the RECODE group than in the
297 usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was
298 €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that
299 RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was

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3 300 8% and 79%, respectively (Appendix 4). From a societal perspective these probabilities were slightly
4 301 higher, i.e. 15% and 81%.

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8 303 *Subgroup analyses*

9 304 Only age showed a significant interaction with the effect of RECODE on costs (Appendix 5,6). The
10 305 difference in costs (healthcare and societal perspective) between RECODE and usual care was
11 306 significantly lower in patients younger than 65 years, than in patients above 65 years. There was also
12 307 a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below
13 308 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients
14 309 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that
15 310 RECODE is cost-effective within the subgroup of patients <65 years.
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311 Discussion

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

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

341 There are several possible explanations why the RECODE intervention was not found to be
342 cost-effective. Firstly, it may be due to the relatively low intensity of our pragmatic intervention. The
343 RECODE program did not require the teams to implement all elements of the program. For instance,
344 70% of the intervention teams attended the refresher courses and 50% actively used the ICT system

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3 345 ZORGDRAAD. Consequently, the intensity of the intervention for individual patients was not only
4 346 dependent upon health status, personal needs and preferences of the individual patients, but also
5 347 on the level of implementation of the DM interventions and the context within which each team
6 348 operates. Further research is required to understand the conditions for a successful implementation
7 349 and thus cost-effectiveness of a DM program.

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11 350 Secondly, it is questionable whether the pragmatic provider-oriented interventions of the
12 351 RECODE program were optimally translated into patient-oriented interventions. This is important
13 352 because it has been shown that successful COPD-DM programs mainly include patient-oriented
14 353 interventions.^{2,3} Literature showed that exercise is an important success factor of a COPD-DM
15 354 program³ and education, exercise and relaxation are important factors for reducing the use of
16 355 urgent and unscheduled healthcare among people with COPD.²⁸ In our study, physical exercise was
17 356 not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

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22 357 Thirdly, there was limited room for improvement in comparison with previous studies due to
23 358 the relatively high standard of COPD care in the Netherlands²⁹ and the low proportion of severe
24 359 COPD patients in this study.^{2,3} It could be that a program like RECODE would have led to more
25 360 positive results in settings where the COPD care is less advanced. For instance, in 2005, when the
26 361 standards of good COPD care in developed countries were less well developed, a Spanish study did
27 362 find that a community-based integrated care program in frail COPD patients improved clinical
28 363 outcomes including survival and decreased the emergency department visits.³⁰ Moreover, Bourbeau
29 364 and colleagues^{31,32} demonstrated positive results of a COPD-DM program in patients recruited from 7
30 365 hospitals in Canada in 1999, while a similar program in 15 general practices in the Netherlands in
31 366 2006²⁹ found no long-term benefits and a study in the US in 2009 did even find negative results in
32 367 patients recruited from 20 hospital-based outpatient clinics.³³ It might well be that as time passes
33 368 and quality of COPD care improves, there is less room for improvement.

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42 369 Fourthly, changes in healthcare occurred during the study period that affected COPD care in
43 370 the RECODE as well as the usual care group. Since July 2010, a new bundled payment scheme for
44 371 COPD patients has been introduced in the Netherlands to stimulate the integration of care.³⁴ In this
45 372 scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price
46 373 per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes
47 374 secondary care and medications, it primarily stimulates the cooperation between different providers
48 375 in the primary care setting. This increased attention for integrated chronic care and the ability to
49 376 reimburse COPD interventions such as smoking cessation and nutritional counselling could have
50 377 stimulated integrated care in the usual care group too.

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3 378 Future research should determine the cost-effectiveness of more intensive COPD-DM
4 379 programs in primary care using a long(er) time horizon. Hence, the gains from preventing patients
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6 380 with moderate COPD to progress to severe COPD are likely to be detected only in the long run.
7

8 381 In conclusion, this comprehensive economic evaluation of an integrated care program in
9
10 382 primary care showed that the program increased costs but did not improve health outcomes. It even
11 383 reduced QALYs. This is most likely due to the fact that the interventions targeted professionals
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13 384 instead of patients and were sub-optimally implemented, the relatively mild COPD population, and
14 385 the national reforms in COPD care.
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For peer review only

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3 386 **TRIAL REGISTRATION:** Netherlands Trial Register (NTR): NTR2268.
4 387

5 388 **FUNDING:** This study was supported by grants from Stichting Achmea Gezondheidszorg (SAG), a
6
7 389 research fund of a Dutch Healthcare insurance company, and the Netherlands Organisation for
8
9 390 Health Research and Development (Zon-MW). The funding agencies (SAG and Zon-MW) have no
10
11 391 influence on the analysis and writing of the paper.
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14 393 **CONTRIBUTORSHIP :** MPHMR, WJJA, JG, and NHC conceived and designed the study. MRSB, ALK, AT,
15 394 and CB acquired the data. MRSB, AT, and MPHMR analysed and interpreted the data. MRSB drafted
16 395 the manuscript. ALK, NHC, AT, JG, WJJA, and MPHMR advised on the preparation of the manuscript.
17 396 All authors read, edited, and approved the final version of the manuscript.
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19 397

20 398 **CONFLICT OF INTEREST:** There are no competing interests.
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22 399

23 400 **ETHICAL APPROVAL:** The study was reviewed and approved by the medical ethical committee of the
24 401 Leiden University Medical Centre, the Netherlands. All general practitioners and participants gave
25 402 written informed consent.
26
27 403

28 404 **DATA SHARING:** No additional data available.
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30 405

31 406 **DECLARATION OF TRANSPARENCY:** The authors affirm that this manuscript is an honest, accurate,
32 407 and transparent account of the study being reported; that no important aspects of the study have
33 408 been omitted; and that any discrepancies from the study as planned (and, if relevant, registered)
34 409 have been explained.
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9	415	years, as reported by the patients (unadjusted)
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11	417	euros, 2013)
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428 **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)

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

431 **Table 2.** Intervention costs (in euros, 2013)

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

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

433 **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								
<i>GP, (home) visits, phone contacts</i>	15-46	a	91	16.23	476 ± 504	89	14.02	401 ± 450
<i>Practice nurse, visits</i>	23	b	74	5.51	131 ± 277	75	5.18	109 ± 166
<i>Specialist, visits</i>	78	a	78	10.05	784 ± 1,037	78	9.84	768 ± 973
<i>Emergency department, visits</i>	163	a	26	0.78	127 ± 284	23	0.79	129 ± 346
<i>Physiotherapist, visits</i>	39	a	53	25.82	1,007 ± 1,770	45	16.33	637 ± 1,260
<i>Dietician, visits</i>	29	a	21	1.45	42 ± 141	19	1.21	35 ± 148
<i>Podiatrist, visits</i>	32	b	43	3.78	121 ± 203	40	3.27	105 ± 167
<i>Speech therapist, visits</i>	36	a	3	0.12	4 ± 42	2	0.28	10 ± 158
<i>Occupational therapy, visits</i>	24	a	4	0.29	7 ± 76	3	0.32	8 ± 83
<i>Rehabilitation centre, visits</i>	78	a	12	3.86	459 ± 2,157	12	3.01	358 ± 1,731
<i>Home care, hours of household help</i>	26	a	22	34.42	895 ± 2,287	20	31.01	806 ± 2,171
<i>Home care, hours of personal care</i>	47	a	9	8.28	389 ± 1,995	8	9.49	446 ± 2,327
<i>Home care, hours of nursing</i>	70	a	6	2.11	148 ± 1,108	6	2.39	167 ± 1,064
<i>Home care, other, hours</i>	48	a	1	0.47	22 ± 262	2	0.65	31 ± 309
<i>Hospital stay, days</i>	493	a	25	4.65	2,293 ± 5,915	25	4.84	2,388 ± 7,522
<i>Intensive care unit, days</i>	2,356	a	5	0.49	1,161 ± 11,316	2	0.14	328 ± 2,658
<i>Drugs for obstructive airway diseases</i>	-	c	84	-	945 ± 814	84	-	934 ± 1,024
<i>Other medication</i>	-	c	91	-	1,367 ± 3,421	90	-	1,131 ± 2,506
Costs from societal perspective								
<i>Travel expenses, public transport/car, KM</i>	0.22	a	94	189.00	42 ± 56	92	174.43	38 ± 59
<i>Productivity loss, absenteeism hours</i>	31-43	a	11	47.74	1,698 ± 8,344	11	42.89	1,649 ± 8,448
<i>Productivity loss, presenteeism hours</i>	31-43		8	10.38	376 ± 2,304	9	10.92	374 ± 1,774

434 * Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research⁹, (b) The Dutch Healthcare Authority NZA (c) GIP Databank²⁰

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

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	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↑	
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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

438 * 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,
 439 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-
 440 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

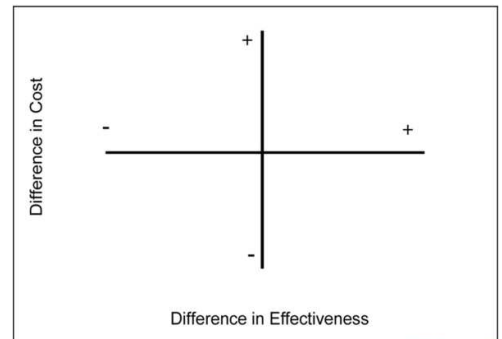
Bootstrapping means repeatedly drawing samples with replacement from the original dataset.¹ That is to say the same record can occur more than once in a given bootstrap sample. Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care 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

	RECODE	Costs			Effect			CE-planes				
		usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE	
With intervention costs												
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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

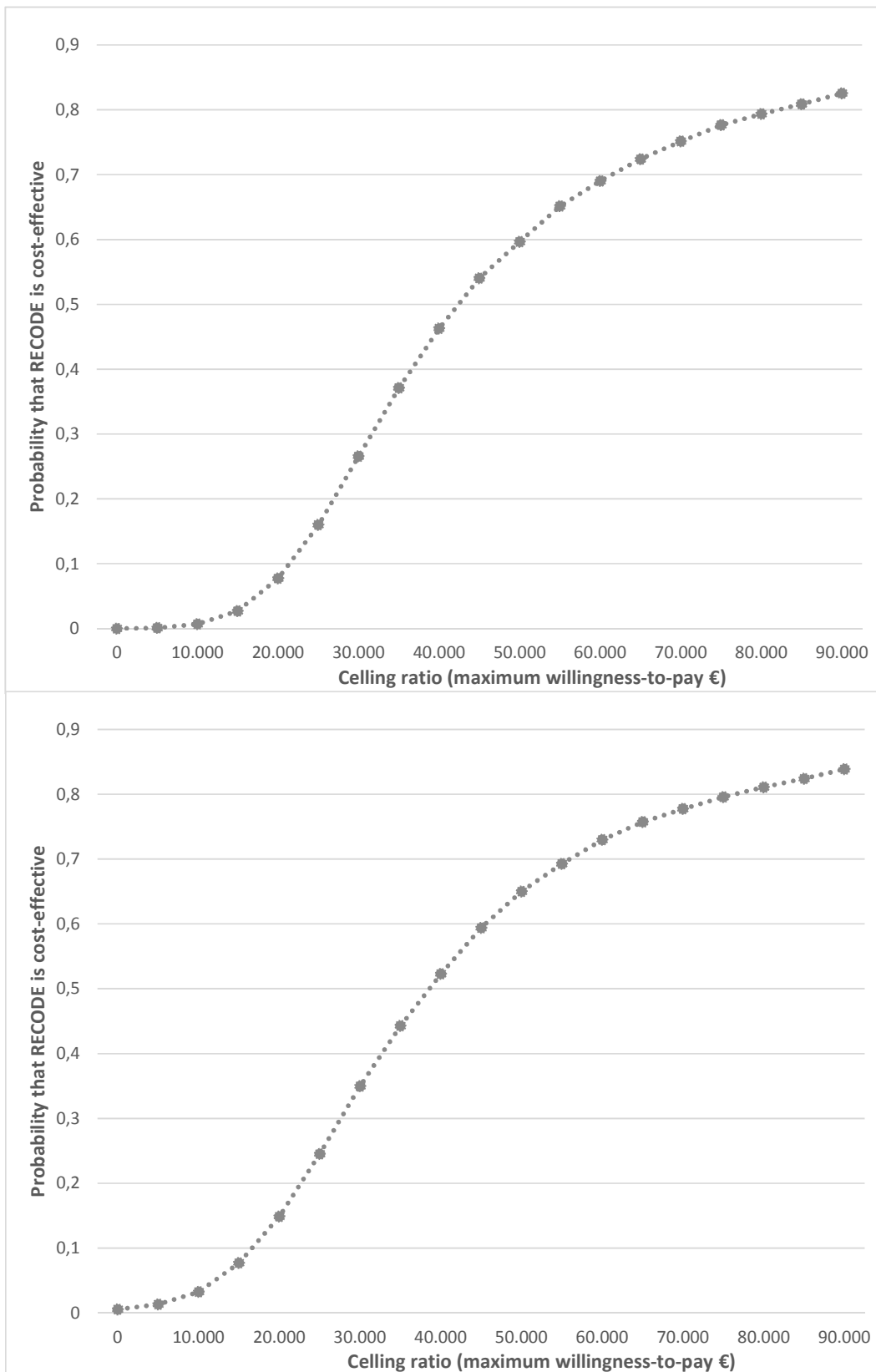
* Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, 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												
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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 Interaction	RECODE	usual Care	Difference	P-value Interaction	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 Interaction	RECODE	usual Care	Difference	P-value Interaction	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

1				
2				
3				published
4				protocol
5				paper
6	Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	Details in
7	concealment		describing any steps taken to conceal the sequence until interventions were assigned	published
8	mechanism			protocol
9				paper
10	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	Details in
11			interventions	published
12				protocol
13				paper
14				
15				
16	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Details in
17			assessing outcomes) and how	published
18				protocol
19				paper
20				
21		11b	If relevant, description of the similarity of interventions	N.A.
22	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6,7
23		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
24				
25	Results			
26	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	8
27	diagram is strongly		were analysed for the primary outcome	
28	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	8
29	Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
30		14b	Why the trial ended or was stopped	N.A.
31	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
32	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	8
33			by original assigned groups	
34				
35				
36	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	8-10
37	estimation		precision (such as 95% confidence interval)	
38		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8-10
39	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	8-10
40			pre-specified from exploratory	
41	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8-10
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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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-007284.R2
Article Type:	Research
Date Submitted by the Author:	06-Jul-2015
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Health economics, Respiratory medicine
Keywords:	HEALTH ECONOMICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE, RESPIRATORY MEDICINE (see Thoracic Medicine)

SCHOLARONE™
Manuscripts

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

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Keywords: COPD, cost effectiveness, integrated care, primary care

Words: 3867

30 Abstract

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

33
34 **Design:** two-year, cluster-randomised controlled trial

35
36 **Setting:** 40 general practices in the western part of the Netherlands

37
38 **Participants:** 1086 patients with COPD according to GOLD (Global Initiative for COPD) criteria.
39 Exclusion criteria were terminal illness, cognitive impairment, alcohol or drug misuse, and inability to
40 fill in Dutch questionnaires. Practices were included if they were willing to create a multidisciplinary
41 COPD team.

42
43 **Interventions:** A multidisciplinary team of caregivers was trained in motivational interviewing,
44 setting-up individual care plans, exacerbation management, implementing clinical guidelines and
45 redesigning the care process. In addition, clinical decision making was supported by feedback
46 reports provided by an ICT program.

47
48 **Main outcome measures:** We investigated impact on health outcomes (quality-adjusted life years
49 (QALYs), Clinical COPD Questionnaire, St. George's Respiratory Questionnaire, and exacerbations)
50 and costs (healthcare and societal perspective).

51 **Results:** The intervention costs were €324 per patient. Excluding these costs, the intervention group
52 had €584 (95% CI €86 to €1,046) higher healthcare costs than the usual care group and €645 (95% CI
53 €28 to €1,190) higher costs from the societal perspective. Health outcomes were similar in both
54 groups, except for 0.04 (95% CI -0.07 to -0.01) less QALYs in the intervention group.

55
56 **Conclusions:** This integrated care program for COPD patients that mainly included professional-
57 directed interventions was not cost-effective in primary care.

58
59 **Trial registration:** Netherlands Trial Register NTR2268

60
61 **Funding:** Stichting Achmea Gezondheidszorg (SAG) and the Netherlands Organisation for Health
62 Research and Development (Zon-MW).

63 Strengths and limitations of this study

- 64
- 65 • It is the largest and most pragmatic Dutch RCT trial to date assessing the cost-effectiveness
66 of COPD disease management in primary care.
 - 67 • The 2-year follow-up period, the broad range of health outcomes and costs (including
68 program costs) measured and the statistically sophisticated analyses ensure the robustness
69 of the results.
 - 70 • The uncertainty in the cost-effectiveness of the disease management programs is
71 adequately estimated and illustrated enabling the appropriate interpretation of the results.
 - 72 • The control group was likely to be exposed to quality improvement initiatives as part of
73 usual care.
- 74

75 Introduction

76

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

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

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

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

107 **Methods**

108

109 This study was approved by the medical ethics committee, performed according to the study
110 protocol⁸, national⁹ and international¹⁰ guidelines for pharmaco-economic research, and reported
111 according to the Consolidated Health Economic Evaluation Reporting Standard(CHEERS).¹¹

112

113 *Design and Intervention*

114 RECODE is a 2-year cluster randomized trial in which 40 clusters of primary care teams were
115 randomized to the COPD-DM program or usual care. The 20 teams of the intervention group were
116 trained in essential components of effective COPD-DM: proper diagnosis, optimizing medication
117 adherence, motivational interviewing, smoking cessation counselling, applying self-management
118 plans including early recognition and treatment of exacerbations, physical (re)activation, and
119 nutritional support. In addition, the teams learned the details of a web-based computer program for
120 measuring and reporting process and outcome performance indicators, named ZORGDRAAD. This
121 Information and Communications Technologies (ICT) application included a patient and provider
122 portal that facilitated the communication within the multi-disciplinary teams as well as between care
123 providers and patients. At the end of the 2-day course, each team developed a plan with steps to be
124 taken in order to redesign the care process and integrate the COPD-DM program into their daily
125 practice. After the course, the teams were invited to join refresher courses, received regular
126 feedback reports on patients' outcomes and had access to ZORGDRAAD. The local healthcare insurer
127 reimbursed physical reactivation for patients with a Medical Research Council (MRC) dyspnoea score
128 >2, also if these patients had no supplementary insurance. All practices were flexible in determining
129 and following their individual plans. Therefore, the mix and intensity of interventions for individual
130 patients depended upon their health status, personal needs and preferences, as well as the actions
131 taken by the team. Healthcare providers in the usual care group were asked to continue providing
132 care as usually. Indicators of care as usual are reported before.⁸

133

134 *Target population*

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

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3 141 criteria. All participating GPs and COPD patients provided written informed consent before
4 142 participation.

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8 144 *Outcomes*

9 145 Costs were related to the following outcome measures:

- 10
11 146 I. QALYs based on the EuroQol-5D (EQ-5D) utility values using the Dutch value set^{13,14};
12 147 II. proportion of patients with a minimal clinical important difference(MCID) (i.e. improvement
13 148 ≥ 0.4) on the CCQ^{15,16};
14 149 III. proportion of patients with a MCID (i.e. improvement ≥ 4) on the St. George's Respiratory
15 150 Questionnaire(SGRQ)^{17,18};
16 151 IV. total number of COPD-exacerbations (moderate and severe). A moderate exacerbation was
17 152 defined as a worsening of daily symptoms that led a patient's clinician to prescribe systemic
18 153 corticosteroids and/or antibiotics, but did not require hospitalization. This information was
19 154 extracted from the Electronic Medical Records (EMR). A severe exacerbation was defined as
20 155 a worsening of symptoms that required a hospital admission. Hospital admissions were
21 156 obtained from the resource use questionnaires and the EMR.

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24 158 The EQ-5D, CCQ, SGRQ, and resource use questionnaire were administered at baseline, 6, 9, 12, 18,
25 159 and 24 months.

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27 160

28 161 *Costs*

29 162 Total two-year costs (not only related to COPD) were calculated from a healthcare perspective and a
30 163 societal perspective. The healthcare perspective included all costs covered by the healthcare budget,
31 164 i.e. medication prescriptions, contact with care providers (GP, medical specialist, nurse,
32 165 physiotherapist, dietician, podiatrist, occupational therapist), home care, hospital admissions,
33 166 emergency department visits, and pulmonary rehabilitation. The costs from the societal perspective
34 167 additionally included travel costs and costs of productivity loss due to absence from paid work.

35 168 Patients reported the healthcare utilization (excluding medication), travel costs, days of
36 169 absence from paid work due to illness (absenteeism) and lost productivity while being at work
37 170 (presenteeism) in a resource use questionnaire with a recall period of three months.

38 171 The medication prescriptions were extracted from the EMRs of the GPs. Standard unit costs
39 172 were obtained from the Dutch manual for costing research⁹ and inflated to 2013 using the general
40 173 consumer price index.¹⁹ The costs of medications were obtained from the GIP-Databank and
41 174 included value added tax and pharmacist dispensing fees.²⁰ The productivity costs were estimated

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

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

185

186 *Statistical analysis*

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

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

196 EQ-5D utilities were analysed using linear mixed models with a normal distribution and
197 identity link. We calculated the number of QALY's for each patient as the area under the predicted
198 utility curve, using linear interpolation between two utility measurements. Generalized linear mixed
199 models with a binary distribution and logit link were used to analyse the proportion of patients with
200 a MCID on the CCQ and SGRQ questionnaire. The differences in exacerbation rates were estimated
201 using generalized linear mixed models with negative binomial distribution and log link. Costs were
202 analysed with generalized linear mixed models using a log-normal distribution and identity link. The
203 cost estimate for month 3 to 6 (based on the questionnaire administered in month 6) was linearly
204 extrapolated to include month 0 to 3.²³ The same was done for the cost estimate of month 15 to 18
205 and 21 to 24.

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207 *Cost-effectiveness*

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3 208 Cost-effectiveness was reported in terms of costs per QALY. Additionally, the following incremental
4 209 cost-effectiveness ratios (ICERs) were calculated: costs per additional patient with a MCID on the
5 210 CCQ, costs per additional patient with a MCID on the SGRQ, and costs per exacerbation prevented.
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8 211 Taking a multi-outcome approach is in line with recent guidelines.²⁴

9
10 212 Uncertainty around the ICERs was handled by bootstrapping the data 5,000 times.
11 213 Bootstrapping means repeatedly drawing samples with replacement from the original dataset.²⁵
12 214 Each sample has the same size as the trial and for each sample the difference in costs and QALYs
13 215 between RECODE and usual care and the ICER is calculated. The 2,5th and the 97,5th percentile of the
14 216 5,000 bootstrap replications form the 95% uncertainty interval of the differences in costs and QALYs.
15
16 217 The 5,000 ICERs were plotted on cost-effectiveness planes.²⁶ In a cost-effectiveness plane, the
17 218 horizontal axis displays the difference in effects and the vertical axis displays the difference in costs.
18
19 219 The results of the bootstrap replications can fall into one of four quadrants: north-east quadrant
20 220 (more cost and more effects); south-east quadrant (less cost and more effects); south-west quadrant
21 221 (less cost and less effects); north-west quadrant (more cost and less effects) (Appendix 1). Finally,
22 222 the probability that the RECODE program is cost-effective using different thresholds for the
23 223 monetary value of a QALY was shown in cost-effectiveness acceptability curves.²⁷ This probability
24 224 equals the proportion of bootstrap replications in which the ICER is lower than the threshold value.

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32 226 *Sensitivity and subgroup analyses*

33 227 Two sensitivity analyses were performed: one with the inclusion of intervention costs and the other
34 228 with a one year instead of a two year time horizon. Five subgroup analyses were performed to study
35 229 the influence of age, sex, dyspnoea, lung function, and socioeconomic status. These were all pre-
36 230 specified in the study protocol and the power calculation was based on the subgroup analyses by
37 231 MRC dyspnoea score >2.⁸

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233 Results

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235 Patients

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

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

247

248 [TABLE 1]

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250 Costs

251 The intervention costs are presented in Table 2. The total intervention costs per patient ranged from
252 €103 to €587 across clusters, with a mean (\pm sd) of €324 (\pm 156) per patient. This variation is
253 explained by the number of COPD patients per team, the use of the ICT system, the number of
254 healthcare providers participating in the courses, and the different locations of the courses. The
255 labour costs of the attendees of the RECODE courses were the main driver of the intervention costs
256 (54%).

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

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

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

268

269 [TABLE 2]

270 [TABLE 3]

271 [TABLE 4]

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274 *Outcomes*

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

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279 *Cost-effectiveness*

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

287

288 *Sensitivity analyses*

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

292 Using a 12-month instead of a 24 month time horizon, the costs per patient were
293 significantly higher in the RECODE group in comparison with the usual care group by €408 from the
294 healthcare perspective and €370 from the societal perspective (Appendix 3). After 12 months, there
295 was no significant difference in QALYs, or any of the other outcomes, except for the percentage of
296 patients improving at least the MCID in CCQ, which was 7% less in the RECODE group than in the
297 usual care group. After 12 months, the costs per QALY ratio of RECODE compared to usual care was
298 €38,471 from a healthcare perspective and €42,458 from a societal perspective. The probability that
299 RECODE is cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY at 12 months was

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3 300 8% and 79%, respectively (Appendix 4). From a societal perspective these probabilities were slightly
4 301 higher, i.e. 15% and 81%.

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8 303 *Subgroup analyses*

9 304 Only age showed a significant interaction with the effect of RECODE on costs (Appendix 5,6). The
10 305 difference in costs (healthcare and societal perspective) between RECODE and usual care was
11 306 significantly lower in patients younger than 65 years, than in patients above 65 years. There was also
12 307 a significant interaction between age and the effect of RECODE in terms of QALYs. In patients below
13 308 65 there was no significant difference in QALYs between RECODE and usual care, whereas in patients
14 309 65 or over there were fewer QALYs in RECODE than in usual care (Appendix 4). It is more likely that
15 310 RECODE is cost-effective within the subgroup of patients <65 years.
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311 Discussion

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

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

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

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3 345 they learned during the courses. Instead, each team made their own plan to redesign the care
4 346 process and implement COPD-DM. Consequently, the mixture and intensity of interventions for
5 347 individual patients was not only dependent upon health status, personal needs and preferences of
6 348 the individual patients, but also on the specific focus that a team may have chosen, the level of
7 349 implementation of the DM interventions and the context within which each team operates. As an
8 350 example of an area that may not have been sufficiently addressed during the courses we should
9 351 mention interventions to improve psychological health.²⁸ However, only 10% of the patients in the
10 352 RECODE trial suffered from a depression at baseline. Although this has probably influenced their
11 353 motivation to change their health behaviour and may have increased unscheduled care,²⁹ it is
12 354 unlikely to be a major explanation for the lack of effect. Obviously, further research is required to
13 355 understand the conditions for a successful implementation and thus cost-effectiveness of a COPD-
14 356 DM program.

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22 357 Secondly, it is questionable whether the pragmatic provider-oriented interventions of the
23 358 RECODE program (e.g. training and education, support in writing practice reform plans, ICT system
24 359 Zorgdraad) were optimally translated into patient-oriented interventions. This is important because
25 360 it has been shown that successful COPD-DM programs mainly include patient-oriented
26 361 interventions.^{2,3} Literature showed that exercise is an important success factor of a COPD-DM
27 362 program³ and education, exercise and relaxation are important factors for reducing the use of
28 363 urgent and unscheduled healthcare among people with COPD.³⁰ In our study, physical exercise was
29 364 not mandatory and only patients with MRC>2 received full reimbursement of physiotherapy.

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37 365 Thirdly, there was limited room for improvement in comparison with previous studies due to
38 366 the relatively high standard of COPD care in the Netherlands³¹ and the low proportion of severe
39 367 COPD patients in this study.^{2,3} It could be that a program like RECODE would have led to more
40 368 positive results in settings where the COPD care is less advanced. For instance, in 2005, when the
41 369 standards of good COPD care in developed countries were less well developed, a Spanish study did
42 370 find that a community-based integrated care program in frail COPD patients improved clinical
43 371 outcomes including survival and decreased the emergency department visits.³² Moreover, Bourbeau
44 372 and colleagues^{33,34} demonstrated positive results of a COPD-DM program in patients recruited from 7
45 373 hospitals in Canada in 1999, while a similar program in 15 general practices in the Netherlands in
46 374 2006³¹ found no long-term benefits and a study in the US in 2009 did even find negative results in
47 375 patients recruited from 20 hospital-based outpatient clinics.³⁵ It might well be that as time passes
48 376 and quality of COPD care improves, there is less room for improvement. However, even in the
49 377 presence of incentivised quality improvement programs like the Quality and Outcome Framework in
50 378 England, hospital admissions for COPD still occur more frequently among the least well served such

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3 379 as those in deprived areas.³⁶ So there is still room for improvement among certain sub-groups of
4 380 COPD patients and it might be a question of targeting DM programs at those most likely to benefit.

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6 381 Fourthly, changes in healthcare occurred during the study period that affected COPD care in
7
8 382 the RECODE as well as the usual care group. Since July 2010, a new bundled payment scheme for
9 383 COPD patients has been introduced in the Netherlands to stimulate the integration of care.³⁷ In this
10 384 scheme, healthcare insurers purchase integrated care from care groups by negotiating a fixed price
11 385 per patient per year for all multidisciplinary COPD care required by a patient. As the bundle excludes
12 386 secondary care and medications, it primarily stimulates the cooperation between different providers
13 387 in the primary care setting. This increased attention for integrated chronic care and the ability to
14 388 reimburse COPD interventions such as smoking cessation and nutritional counselling could have
15 389 stimulated integrated care in the usual care group too.

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20 390 Future research should determine the cost-effectiveness of more intensive COPD-DM
21 391 programs in primary care using a long(er) time horizon. Hence, the gains from preventing patients
22 392 with moderate COPD to progress to severe COPD are likely to be detected only in the long run.

23
24 393 In conclusion, this comprehensive economic evaluation of an integrated care program in
25 394 primary care showed that the program increased costs but did not improve health outcomes. It even
26 395 reduced QALYs. This is most likely due to the sub-optimal translation of the provider-oriented
27 396 interventions of the RECODE program into patient-oriented interventions, the suboptimal
28 397 implementation of the interventions, the relatively mild COPD population, and the national reforms
29 398 in COPD care.
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399 **TRIAL REGISTRATION:** Netherlands Trial Register (NTR): NTR2268.

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401 **FUNDING:** This study was supported by grants from Stichting Achmea Gezondheidszorg (SAG), a
402 research fund of a Dutch Healthcare insurance company, and the Netherlands Organisation for
403 Health Research and Development (Zon-MW). The funding agencies (SAG and Zon-MW) have no
404 influence on the analysis and writing of the paper.

405

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

410

411 **CONFLICT OF INTEREST:** There are no competing interests.

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

416

417 **DATA SHARING:** No additional data available.

418

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

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441 **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)

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

444 **Table 2.** Intervention costs (in euros, 2013)

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

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

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

447 * Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research⁹, (b) The Dutch Healthcare Authority NZA (c) GIP Databank²⁰

448

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

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	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↑	
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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

451 * 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,
 452 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-
 453 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

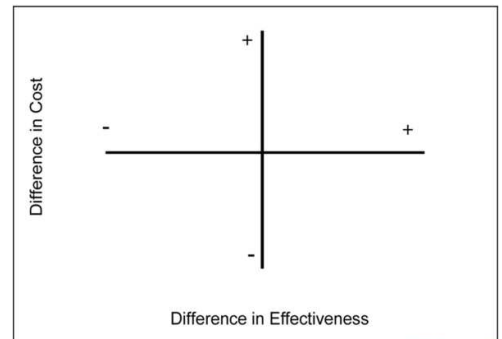
Bootstrapping means repeatedly drawing samples with replacement from the original dataset.¹ That is to say the same record can occur more than once in a given bootstrap sample. Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care 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

	RECODE	Costs			RECODE	Effect		ICER	CE-planes			
		usual Care	Difference (95% CI)	usual Care		Difference (95% CI)	NW		SW	NE	SE	
With intervention costs												
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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

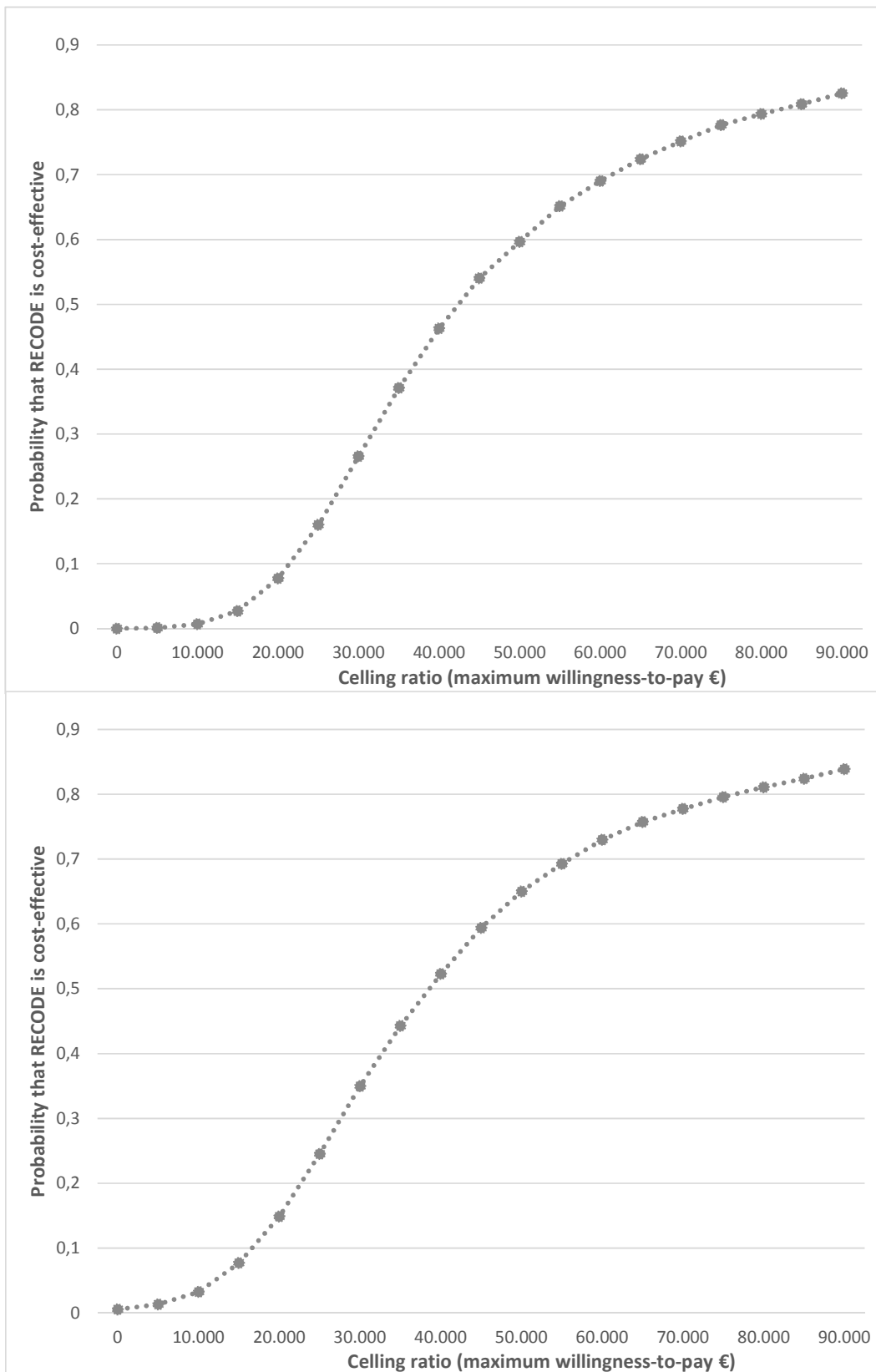
* Significant (p<0.05), ** Significant (p<0.01), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, SW=south-west, 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												
<i>Cost per QALY</i>	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
<i>Cost per exacerbation avoided</i>	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
<i>Cost per additional patient with a clinical relevant improvement in CCQ score</i>	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
<i>Cost per additional patient with a clinical relevant improvement in SGRQ score</i>	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



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

		Costs				Effect (QALY's)				CE-planes					
		RECODE	usual Care	Difference	P-value Interaction	RECODE	usual Care	Difference	P-value Interaction	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

1				
2				
3				published
4				protocol
5				paper
6	Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	Details in
7	concealment		describing any steps taken to conceal the sequence until interventions were assigned	published
8	mechanism			protocol
9				paper
10	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	Details in
11			interventions	published
12				protocol
13				paper
14				
15				
16	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Details in
17			assessing outcomes) and how	published
18				protocol
19				paper
20				
21		11b	If relevant, description of the similarity of interventions	N.A.
22	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6,7
23		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
24				
25	Results			
26	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	8
27	diagram is strongly		were analysed for the primary outcome	
28	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	8
29	Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
30		14b	Why the trial ended or was stopped	N.A.
31	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
32	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	8
33			by original assigned groups	
34				
35				
36	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	8-10
37	estimation		precision (such as 95% confidence interval)	
38		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8-10
39	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	8-10
40			pre-specified from exploratory	
41				
42	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8-10
43				

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Discussion

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	<u>11</u>
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	<u>11</u>
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	<u>11,12</u>
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	<u>3</u>
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	<u>12</u>

*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.