

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

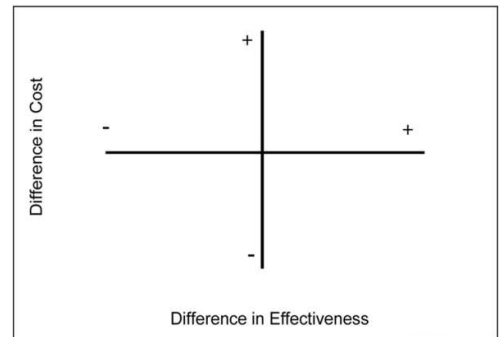
Bootstrapping means repeatedly drawing samples with replacement from the original dataset.¹ That is to say the same record can occur more than once in a given bootstrap sample. Each sample has the same size as the trial and for each sample the difference in costs and QALYs between RECODE and usual care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

References

1. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997; 6(4): 327-40.
2. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Econ* 1998; 7(8): 723-40.
3. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ* 1994; 3(5): 309-19.

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

		Costs			Effect			CE-planes				
		RECODE	usual Care	Difference (95% CI)	RECODE	usual Care	Difference (95% CI)	ICER	NW	SW	NE	SE
With intervention costs												
<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

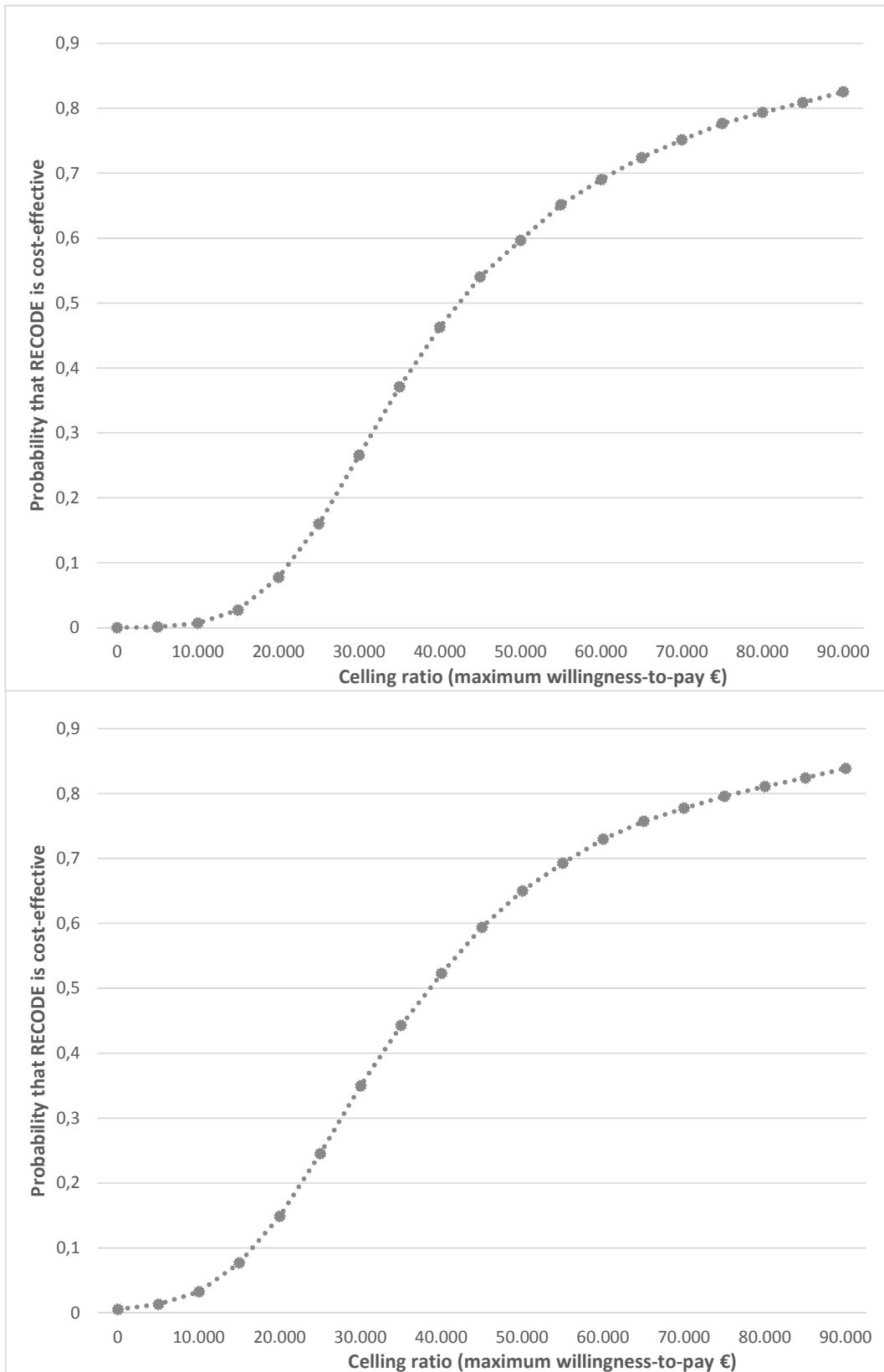
* Significant ($p < 0.05$), ** Significant ($p < 0.01$), QALY=quality-adjusted life years, CCQ=Clinical COPD Questionnaire, SGRQ=St. George's Respiratory Questionnaire, HP= healthcare perspective, SP=societal perspective, CI=confidence interval, ICER=incremental cost-effectiveness ratio, NW=north-west, 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															
<i>HP</i>	<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
<i>SP</i>	<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															
<i>HP</i>	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
<i>SP</i>	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															
<i>HP</i>	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
<i>SP</i>	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.