



HAL
open science

COST-EFFECTIVENESS OF A 3-MONTH INTERVENTION WITH ORAL NUTRITIONAL SUPPLEMENTS IN DISEASE RELATED MALNUTRITION: A RANDOMIZED CONTROLLED PILOT STUDY

Kristina Norman, Matthias Pirlich, Christine Smoliner, Anne Kilbert, Jörg-Dieter Schulzke, Johann Ockenga, Herbert Lochs, Thomas Reinhold

► **To cite this version:**

Kristina Norman, Matthias Pirlich, Christine Smoliner, Anne Kilbert, Jörg-Dieter Schulzke, et al.. COST-EFFECTIVENESS OF A 3-MONTH INTERVENTION WITH ORAL NUTRITIONAL SUPPLEMENTS IN DISEASE RELATED MALNUTRITION: A RANDOMIZED CONTROLLED PILOT STUDY. *European Journal of Clinical Nutrition*, 2011, 10.1038/ejcn.2011.31 . hal-00624167

HAL Id: hal-00624167

<https://hal.science/hal-00624167>

Submitted on 16 Sep 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 COST-EFFECTIVENESS OF A 3-MONTH INTERVENTION WITH ORAL
2 NUTRITIONAL SUPPLEMENTS IN DISEASE RELATED
3 MALNUTRITION: A RANDOMIZED CONTROLLED PILOT STUDY

4
5 Kristina Norman¹ PhD, Matthias Pirlich¹ MD, Christine Smoliner¹ Msc, Anne Kilbert¹
6 MD, Jörg Dieter Schulzke² MD, Johann Ockenga³ MD, Herbert Lochs¹ MD, Thomas
7 Reinhold⁴ PhD

8
9
10 ¹Dept. of Gastroenterology, Hepatology and Endocrinology, CHARITE UNIVERSITY MEDICINE, Berlin,
11 Germany

12 ²Dept. of General Medicine, CHARITE UNIVERSITY MEDICINE, Berlin, Germany

13 ³Dept. of Gastroenterology, Endocrinology and Clinical Nutrition, KLINIKUM BREMEN MITTE, Germany

14 ⁴Institute for Social Medicine, Epidemiology and Health Economics, CHARITE UNIVERSITY
15 MEDICINE, Berlin, Germany

16
17
18 Running title:

19 COST-EFFECTIVENESS OF ORAL NUTRITIONAL SUPPLEMENTS IN DISEASE RELATED
20 MALNUTRITION

21 Registered at Clinical Trials.gov: NCT00168935

22
23 Corresponding author:

24 Dr. Kristina Norman
25 Medizinische Klinik für Gastroenterologie, Hepatologie und Endokrinologie,
26 Charité Universitätsmedizin Berlin CCM,
27 Charitéplatz 1,
28 10117 Berlin, Germany.
29 Tel.: þ49 30 450 514 139
30 Fax: þ49 30 450 514 923

31

32 **Abstract**

33 Background: Nutritional intervention with oral nutritional supplements (ONS) has been
34 shown to increase quality of life in malnourished patients. We investigated whether
35 post-hospital supplementation with ONS is cost-effective according to international
36 benchmarks in malnourished patients.

37 Methods: 114 malnourished patients (50.6 ± 16.1 years, 57 female) with benign
38 gastrointestinal disease were included and randomised to receive either ONS for three
39 months and dietary counselling at discharge (intervention, $n=60$) or only dietary
40 counselling at discharge (control group, $n=54$). Nutritional status was assessed with
41 Subjective Global Assessment. Intervention patients documented daily intake of ONS,
42 quality of life was assessed with SF-36 Health Survey and SF-36 values were
43 transformed into health-status utilities. Quality-adjusted life years (QALYs) were
44 calculated by adopting the area-under-the-curve method. We used 2 different pricing
45 scenarios for ONS (minimum price: 2.30€ and maximum: 2.93€/tetra pack). The
46 incremental cost-effectiveness ratio (ICER) of supplementation with ONS was
47 calculated for both price scenarios. All analyses were corrected for age and gender.

48 Results: Intervention patients consumed 2.4 ± 0.8 ONS per day. Intervention and
49 control patients did not differ in their health-status utilities at baseline (0.594 ± 0.017 vs.
50 0.619 ± 0.018), but after three months the health-status utilities were significantly higher
51 in intervention patients than control patients (0.731 ± 0.015 vs. 0.671 ± 0.016 , $p=0.028$).

52 Intervention was associated with significantly higher costs (ICER: €9,497 and €12,099
53 /additional QALY, respectively) but deemed cost-effective according to international
54 thresholds ($<€50,000/\text{QALY}$).

55 Conclusions: Three month intervention with ONS increases quality of life in
56 malnourished patients. This treatment appears to be cost-effective according to
57 international benchmarks.

58 **Keywords**

59 Disease-related malnutrition, cost-effectiveness, quality of life, nutritional supplements,

60 quality of life adjusted life years

61

62

63

64

65

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84 **Introduction**

85 Disease related malnutrition remains a major challenge in hospital despite the growing
86 body of evidence demonstrating both its clinical and economical consequences.
87 Depending on the population, malnutrition affects approximately 25 to 50% of
88 hospitalized patients (Norman et al. 2008b) and is associated with higher in-hospital
89 and post-hospital mortality as well as increased morbidity. This is reflected by longer
90 length of stay in hospital, more in-hospital complications, longer convalescence
91 periods and higher non-elective readmission rates which invariably results in
92 increased costs for the health care system (Norman et al. 2008b; Russell, 2007).

93 However, although malnutrition undeniably promotes morbidity and appropriate
94 nutritional therapy is available in affluent countries, there is evidence that only a small
95 percentage of malnourished patients is receiving nutritional support (McWhirter et al.,
96 1994). Moreover, disease related malnutrition is frequently already present on
97 admission and nutritional status deteriorates further during hospital stay due to
98 progression of disease, lack of awareness or education of attending staff or simply
99 adverse clinical routines (McWhirter et al., 1994). Consequently, patients are often
100 discharged in even worse nutritional or functional status than when admitted to
101 hospital. Malnutrition itself is therefore clearly associated with increased costs for the
102 health care system; hospitalized patients suffer more infectious and non-infectious
103 complications, exhibit longer stay in and more frequent readmissions to hospitals
104 whereas malnourished patients in the community have increased use of health care
105 resources (Russell et al., 2007).

106 Despite the cost burden of malnutrition and despite the growing body of evidence of
107 the clinical benefit of nutritional intervention, there is still very limited evidence of
108 economic benefit of nutritional therapy.

109 We attempted to assess the costs and the cost-effectiveness of three month
110 intervention with oral nutritional supplements in malnourished patients in a prospective
111 randomised controlled trial.

112

113

114

115

116

117

118

119

120

121

122

123

124

125

126

127

128

129

130

131

132

133

134

135 **Methods**

136 This study was conducted at the Department of Gastroenterology, Hepatology and
137 Endocrinology, Charite University Medicine between March 2004 and July 2007.
138 Patients classified malnourished according to the Subjective Global Assessment
139 (Detsky et al., 1987) (SGA B or C) and suffering from a benign gastrointestinal disease
140 were recruited and randomised to either dietary counselling alone (control group) or
141 oral nutritional supplements (ONS) in addition to dietary counselling for three months
142 after hospital discharge (intervention patients). The study protocol was approved by
143 the Ethics Committee of the University Medicine Berlin, Charite. All patients signed
144 written informed consent. The results of the study concerning impact on body
145 composition and muscle function in 80 of the study patients are published elsewhere
146 (Norman et al. 2008a), this paper focuses on the cost-effectiveness of the study; for
147 this, the original study was continued to reach a total of 120 patients.

148 Exclusion criteria were malignant disease, renal insufficiency (serum creatinine > 1.3
149 mg/dl), and life expectancy less than three months or age under 18 years.

150 Patients were randomised according to a computer generated randomisation list kept
151 by a co-worker not involved in the study. Quality of life at discharge (baseline) and
152 after three months was investigated; intake of ONS during the study period was
153 documented by the patients; non elective readmissions during the study period were
154 also recorded.

155 Nutritional status

156 Nutritional status was assessed according to the Subjective Global Assessment (SGA)
157 using the protocol developed by Detsky et al. (Detsky et al., 1987). Patients were
158 classified well nourished (A), moderately (B) or severely malnourished (C). Weight and
159 height were documented and used to calculate BMI (weight [kg] / height [m]²).

160 Supplementation and dietary counselling

161 Both intervention and control patients received a standard dietary counselling session
162 (45 minutes) by a registered dietician. The patients were advised how to improve their
163 protein and energy intake with normal food. The session took place in hospital within
164 48 h before hospital discharge. Intervention patients were asked to consume up to 3
165 ONS (à 200 ml) per day (Fresubin Protein Energy DRINK, Fresenius Kabi) according
166 to possibility and to record their daily intake. Patients were told to drink their
167 supplements slowly and in between meals, but were not prescribed individual ONS
168 amounts according to nutritional intake.

169 During the study period, all patients were provided with a contact person (study
170 assistant) and were actively contacted once a month.

171 Quality of life

172 *Quality of life* was assessed employing the validated Medical Outcomes Study 36-item
173 Short-Form General Health Survey described in detail elsewhere (Ware et al., 1987).
174 The questionnaire consists of 36 questions, is self administered and assesses quality
175 of life and wellbeing in 8 multi item scales regarding physical functioning and
176 perception of physical role, vitality, general and mental health, perception of emotional
177 role, social functioning and bodily pain.

178 Economic analyses

179 The effectiveness level was measured as changes in quality of life and related to the
180 costs of the intervention with ONS.

181 *Effectiveness measurement*

182 SF-36 quality of life values were transformed into a single mean values, i.e. health
183 state utilities, by using an algorithm developed by Brazier (Brazier et al., 2002). In a
184 hypothetical framework, the health state utility can range from 1 (complete health) to 0
185 (death). In addition to the time a person lives in a specific health state, it is possible to
186 calculate quality adjusted life years (quality of life adjusted life years, QALYs). The

187 QALYs gained were calculated by employing the area-under-the-curve method using
 188 the following formula for all patients who survived during the year after study onset:

$$189 \text{ QALYs}_{\text{gained for intervention group}} = \left(\frac{\alpha_{\text{Intervention}} + \beta_{\text{Intervention}}}{2} \right) - \left(\frac{\alpha_{\text{Control}} + \beta_{\text{Control}}}{2} \right)$$

190 The analysis is based on utility values at each time point (α = baseline utility, β = utility
 191 after three months) and uses the common assumption of a linear change over time
 192 (Richardson et al. 2004) (Figure2). After the intervention period of three months, we
 193 conservatively assumed a linear decrease of intervention effects returning to baseline
 194 level 12 months after study onset.

195 During the three month intervention period; no fatal casualties were observed. One
 196 intervention and three control patients died after study intervention, for these patients
 197 we assumed a linear decrease in health state utilities reaching zero at the month of
 198 death. The following calculation was used for these patients (i = month of death after
 199 baseline):

$$200 \text{ QALYs}_{\text{deceased patients}} = \frac{3\alpha + \frac{3(\beta - \alpha)}{2} + \frac{\beta(i-3)}{2}}{12}$$

201 For all patients, the respective area-under-the-curve reflects the quality life years
 202 experienced during the one-year period. QALYs gained for intervention group was
 203 calculated as QALY-group differences:

$$204 \text{ QALYs}_{\text{gained for intervention group}} = \text{QALYs}_{\text{Intervention}} - \text{QALYs}_{\text{Control}}$$

205

206 *Cost measurement*

207 We employed two different pricing scenarios for ONS, using high and low prices
 208 (2.93€ and 2.30€ per tetra pack, respectively) which are based on research of the
 209 assortment of German online pharmacies representing the highest and the lowest
 210 price per tetrapack at the time of searching (2010). The total costs of ONS were

211 calculated by multiplying number of packages used during the study period and the
 212 price per unit in both pricing scenarios. Resource consumption in other areas was not
 213 collected within this pilot study. Data on acute readmissions to hospital were collected
 214 from our hospital system or from the patients themselves if admitted to other hospitals
 215 as dichotomous variable only (yes/no). We were therefore not able to include the
 216 readmission days in the cost analysis,

217 There was no need to discount any costs or effects, because the observation period
 218 was shorter than one year. The study is focused on direct intervention costs; the
 219 economic perspective taken in this study is that of German statutory health insurance
 220 systems.

221 *Cost-effectiveness*

222 We calculated the incremental cost-effectiveness ratio (ICER, cost/QALY), by using
 223 the following relation (Claxton et al., 1999).

$$224 \text{ ICER} = \frac{\text{mean costs}_{\text{Intervention}} - \text{mean costs}_{\text{Control}}}{\text{QALYs}_{\text{gained for intervention group}}}$$

225

226 The ICER can be interpreted as additional costs associated with realizing one
 227 additional QALY compared to the control patients. In the UK, a threshold of 30,000
 228 GBP per QALY gained is found to be consistent with decisions of adopting new
 229 technologies by NICE (National Institute for Clinical Excellence) (Raftery et al., 2001).

230 In Germany, such a threshold does not yet exist, so we used a hypothetical threshold
 231 of max. €50,000 per QALY originally suggested by health care economists and in
 232 accordance with other German studies (Willich et al., 2006; Witt et al., 2009), due to
 233 comparability within one health care system.

234 Further, the net benefit approach (Zethraeus et al., 2003) was used to measure the
235 incremental cost-effectiveness against a societal threshold value λ , that is often
236 described as society's willingness to pay for one extra QALY gained.

$$237 \text{ Net benefit} = (\text{QALYs}_{\text{gained for intervention group}} * \lambda) - (\text{mean costs}_{\text{Intervention}} - \text{mean costs}_{\text{Control}})$$

238 For a given value of λ , an intervention would be considered cost-effective if its net
239 benefit is greater than zero or in other words, the ICER lies below λ . Thus, a new
240 treatment should replace the existing one when the net benefit under λ is greater than
241 zero (Lothgren et al., 2000).

242 To reach information on the probability of cost-effectiveness, 1,000 bootstrapped cost-
243 effectiveness results (see statistical analyses) were transformed into net benefit values
244 under varying threshold values and then plotted in a cost-effectiveness acceptability
245 curve.

246 Statistical analyses

247 Student t-test and Pearson's chi-square test was used for comparisons on socio-
248 demographic baseline characteristics. Analysis of covariance (ANCOVA) was used for
249 health state utilities data as well as costs. The analysis was adjusted for age and
250 gender. Three month data were further adjusted for differences in baseline health
251 state utilities.

252 To derive cost-effectiveness acceptability curves, we used non-parametric
253 bootstrapping (Efron et al., 1979). The original sample was bootstrapped 1,000 times
254 to obtain 1,000 means for cost and effect differences and the resulting ICERs. These
255 bootstrap results were used to build the cost-effectiveness acceptability curves as
256 described above. The analysis was based on intention to treat approach.

257 For inferential statistics, we used PASW statistics version 18.0. Bootstrap-analyses
258 were applied using MS EXCEL[®] 2007. The predefined significance level was $P < 0.05$.

259 **Results**

260 644 consecutively admitted patients of the Dept. of Gastroenterology, Hepatology and
261 Endocrinology, Charite University Medicine were screened, whereof 201 were eligible
262 for the study. 160 patients were recruited for the study, whereof 120 patients
263 completed the study, but only 114 patients (60 intervention) also provided complete
264 SF 36 quality of life questionnaires and could therefore be included in the cost analysis
265 (see Figure 1 for trial diagram).

266 Average intake was 2.4 ± 0.8 ONS per day; three intervention patients discontinued use
267 of ONS and two control patients reported consumption of ONS during the study
268 period.

269 Clinical characteristics and diagnoses are given in Table 1. At baseline, intervention
270 and control patients did not differ significantly in regard to age, gender distribution, and
271 nutritional status as defined by SGA or BMI. Length of stay, co-morbidity count and
272 number of drugs on discharge were comparable between the groups. Acute
273 readmission rate during study period was significantly higher in control patients
274 compared to intervention patients. One intervention patient died six months after the
275 intervention period and three control patients died at one, five and nine months after
276 the intervention period.

277 Quality of life

278 Information on quality of life, costs and ICER is given in Table 2. Health status utilities
279 were not different at baseline between intervention and control patients, but increased
280 in both groups during the study. The mean improvement was significantly higher in
281 intervention patients (0.128 (CI: 0.095-0.161) vs. 0.067 (CI: 0.031-0.103)), resulting in
282 significantly higher health status utilities than control patients after three months. As
283 shown in Figure 2, the resulting difference in QALYs (0.045) was in favour of

284 intervention patients. This gain can be interpreted as additional 16 days of full quality
285 of life per year.

286 Costs

287 The mean costs were calculated for both price scenarios and are presented in Table
288 2. The mean costs in our intervention group were €561.42 in the high price and
289 €440.71 in the low price scenario. Since two control patients also received oral
290 nutritional supplements, the costs in this group were between €21.56 and €16.89,
291 respectively. The additional costs were between €540.16 and €424.02 according to
292 cost scenario.

293

294 Cost-effectiveness

295 Depending on the price scenario the calculation is based on, the ICER was between
296 €9,497 (low price scenario) and €12,099 per additional QALY (high price scenario).
297 Figure 3 shows the results of our 1,000 bootstrap samples. Approximately 95% of the
298 results are located in the upper right hand quadrant of the cost-effectiveness-plane,
299 showing intervention with ONS is more effective and more costly than dietary
300 counselling alone. Otherwise, the bootstrap results further indicate the remaining
301 bootstrap-samples (5%) as more expensive but not more effective. The overall
302 probability that the intervention is cost-effective (cost per additional QALY lower than
303 the society's willingness to pay) was approximating 89.9% (high price scenario) resp.
304 91.5% for the assumed threshold value of €50,000 (Figure 4). Assuming the
305 willingness to pay would be lower than the assumed €50,000, the probability of cost-
306 effectiveness will also decrease.

307

308 **Discussion**

309

310 In this prospective pilot study, we have shown that three month nutritional
311 supplementation with ONS increases quality of life in malnourished patients with
312 benign gastrointestinal disease and that the intervention appears to be cost-effective
313 according to international thresholds.

314 There is evidence that early and adequate treatment of malnutrition is fundamental for
315 improving patients' prognosis and wellbeing and international evidence-based
316 guidelines have been developed to standardize nutritional therapy (Lochs et al., 2006).
317 Several clinical trials have shown that supplementation with oral nutritional
318 supplements are beneficial in the perioperative setting (Beattie et al. 2000; Smedley et
319 al. 2004). However, the impact on clinical routine still remains moderate. This has
320 been attributed to low awareness and poor education (McWhirter et al., 1994) as well
321 as resistance to change, high workload, limited resources and slow administrative
322 processes (Jones et al., 2007) Although various studies have demonstrated that
323 disease related malnutrition is associated with major costs for the health care system,
324 few studies have investigated cost-effectiveness of nutritional therapy (Darmon et al.,
325 2008; Russell, 2009). Within the current climate of cost constraint in health care,
326 however, evidence of economic benefit of nutritional interventions is necessary to
327 convince health administrators and thereby contribute to promote and implement
328 nutritional therapy in clinical routine.

329 Russell et al summarized results of studies on costs of ONS in hospital and
330 community. Pooled results from the studies in abdominal and orthopaedic surgery as
331 well as elderly revealed net cost savings per patient both in term of inpatient stay and
332 complications (Russell 2007). Enteral and oral immunonutrition has also been
333 associated with reduced postoperative complication rates and thus substantially
334 reduced treatment costs in patients undergoing major abdominal surgery (Senkal et

335 al., 1999) or cancer surgery (Braga et al., 2005) despite higher costs of the product. In
336 nursing homes, offering snacks has been shown to be associated with greater cost-
337 effectiveness than intervention with ONS (Simmons et al., 2010). In patients with
338 cerebrovascular events, long term home enteral tube feeding was also shown to be
339 cost-effective (Elia & Stratton, 2008). Varying but mostly high cost-effectiveness has
340 also been demonstrated in the field of life style intervention and obesity and diabetes
341 prevention programmes as summarized by Dalziel et al (Dalziel & Segal, 2007).
342 Different settings and specific forms of nutritional therapy are prone to be associated
343 with different cost-effectiveness scenarios. In our malnourished study population with
344 benign gastrointestinal disease, nutritional therapy was a supportive measure in order
345 to accelerate improvement of nutritional and functional status. The intervention was
346 found to be cost-effective from the point of view of the German statutory health
347 insurance systems; nevertheless, some potential limitations resulting from the design
348 of economic evaluation must be kept in mind while interpreting the results of our study.
349 Since we only considered direct costs of the intervention, the intervention was
350 associated with significantly higher costs than the control arm. Further costs such as
351 medication, rehospitalisation, use of other health care resources or indirect costs were
352 not included in the pilot study design. Our findings do therefore not allow conclusions
353 about potential additional expenses in other areas of health care. However,
354 considering the significantly higher readmission rate in the control group, it is likely that
355 cost-impact in favour of ONS would have been greater if all costs had been included.
356 Another uncertainty arises from the methodology of QALY calculation: in consistency
357 with other studies (Willich et al., 2006; Witt et al., 2009) we conservatively assumed
358 that quality of life would decrease in a linear way after nutritional intervention returning
359 to baseline level 12 months after study onset. Data on quality of life was only available
360 at month 6 in 60% of patients after study intervention, due to loss of follow up. Patients

361 were asked to send in the questionnaires at month 6, but not all questionnaires were
362 correctly filled out and could be evaluated. Sum scales of the SF 36 quality of life
363 questionnaire, however, did not differ significantly between month 3 (end of
364 intervention period) and month 6 (data not shown) in intervention and control patients.
365 We still used a very cautious approach to interpret the further development of quality
366 of life in order not to overestimate effects. Theoretically, quality of life could however
367 have remained stable throughout the subsequent six months or immediately dropped
368 to baseline, which would affect the area-under-the-curve and thus the QALY
369 calculation.

370 In general, a number of factors can further limit the transferability of cost-of-illness
371 study results from one country to another (Reinhold et al., 2010). It is well known that
372 e.g. individual patient characteristics have at least indirect influence on resource use
373 and induced costs. Examples include socioeconomic or demographic factors, both of
374 which may exhibit systematic country-specific differences. Differences in design and
375 organisation of healthcare systems are further factors that may limit the transferability
376 of study results. It is important to keep in mind that problems related to transferability
377 affect the interpretation of international health economic findings. Since our results
378 cannot indiscriminately be translated into other settings and other countries, further
379 studies are needed to contribute to the evidence of cost utility of nutritional therapy.

380 When considering economic benefit of nutritional therapy, economic perspective has
381 to be taken into account. Restricted to direct intervention costs, we concluded ONS to
382 be a cost-effective intervention from the German statutory health insurance
383 perspective. This conclusion is further supported by the reduced rehospitalisation rate
384 in our intervention patients. Whereas reducing the number of inpatient stays is
385 attractive from the point of health insurance systems, for a single hospital centre
386 artificial nutrition might, however, be considered a potential economic burden through

387 increased resource consumption. These different viewpoints reveal a basic problem in
388 health policies. It seems necessary to find incentives for inpatient care providers to
389 decide on a special treatment, although this might not appear to be economically
390 useful from their point of view.

391 In conclusion, we have shown that nutritional intervention with ONS increases quality
392 of life in malnourished patients and, for the German health care system, our study
393 provides evidence that use of ONS in malnourished patients is a cost-effective
394 investment resulting in good value for money.

395

396 Acknowledgements

397 This study was financially supported by a grant from Fresenius Kabi, Bad Homburg,
398 Germany.

399 Conflict of interest

400 The authors declare that they have no conflict of interest concerning this paper.

401

402

403

404 **References**

405

406

407 Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial
408 evaluating the use of enteral nutritional supplements postoperatively in malnourished
409 surgical patients. *Gut*. 2000 Jun;46(6):813-8.

410 Braga M, Gianotti L. Preoperative immunonutrition: cost-benefit analysis. *JPEN J*
411 *Parenter Enteral Nutr* 2005;2:S57-S61.

412 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of
413 health from the SF-36. *J Health Econ* 2002;21:271-92.

414 Claxton K. The irrelevance of inference: a decision-making approach to the stochastic
415 evaluation of health care technologies. *J Health Econ* 1999;18:341-64.

416 Dalziel K, Segal L. Time to give nutrition interventions a higher profile: cost-
417 effectiveness of 10 nutrition interventions. *Health Promot Int* 2007;22:271-83.

418 Darmon P, Lochs H, Pichard C. Economic impact and quality of life as endpoints of
419 nutritional therapy. *Curr Opin Clin Nutr Metab Care* 2008;11:452-8.

420 Detsky AS, McLaughlin JR, Baker JP, Johnston, N., Whittaker, S., Mendelson, R.
421 A., Jeejeebhoy, K. N.) What is subjective global assessment of nutritional status?
422 *JPEN J Parenter Enteral Nutr* 1987;11:8-13.

423 Efron B. Bootstrap methods: another look at the jackknife. *Ann Statist* 1979;7:1-26.

424 Elia M, Stratton RJ. A cost-utility analysis in patients receiving enteral tube feeding at
425 home and in nursing homes. *Clin Nutr* 2008;27:416-23.

426 Gianotti L, Braga M, Frei A, Greiner R, Di C, V. Health care resources consumed to
427 treat postoperative infections: cost saving by perioperative immunonutrition. *Shock*
428 2000;14:325-30.

429 Jones NE, Suurdt J, Ouelette-Kuntz H, Heyland DK. Implementation of the Canadian
430 Clinical Practice Guidelines for Nutrition Support: a multiple case study of barriers and
431 enablers. *Nutr Clin Pract* 2007;22:449-57.

432 Lochs H. ESPEN Guidelines on adult enteral nutrition *Clinical Nutrition* 2006;25:177-
433 360

434 Lothgren M, Zethraeus N. Definition, interpretation and calculation of cost-
435 effectiveness acceptability curves. *Health Econ* 2000;9:623-30.

436 McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital.
437 *Bmj* 1994;308:945-8.

438 Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month
439 intervention with protein and energy rich supplements improve muscle function and
440 quality of life in malnourished patients with non-neoplastic gastrointestinal disease--a
441 randomized controlled trial. *Clin Nutr* 2008a;27:48-56.

442 Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related
443 malnutrition. *Clin Nutr* 2008b;27:5-15.

- 444 Raftery J. NICE: faster access to modern treatments? Analysis of guidance on health
445 technologies. *BMJ* 2001;323:1300-3.
- 446 Reinhold T, Bruggenjürgen B, Schlander M, Rosenfeld S, Hessel F, Willich SN.
447 Economic Analysis Based on Multinational Studies – Methods for Adapting Findings to
448 National Contexts. *J Public Health* 2010;18.
- 449 Richardson G, Manca A. Calculation of quality adjusted life years in the published
450 literature: a review of methodology and transparency. *Health Econ* 2004;13:1203-10.
- 451 Russell C. The impact of malnutrition on healthcare costs and economic
452 considerations for the use of oral nutritional supplements. *Clinical Nutrition*
453 *Supplements* 2007;2:25-32.
- 454 Senkal M, Zumtobel V, Bauer KH, Marpe, B., Wolfram, G., Frei, A. et al. Outcome and
455 cost-effectiveness of perioperative enteral immunonutrition in patients undergoing
456 elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch*
457 *Surg* 1999;134:1309-16.
- 458 Simmons SF, Zhuo X, Keeler E. Cost-effectiveness of nutrition interventions in nursing
459 home residents: a pilot intervention. *J Nutr Health Aging* 2010;14:367-72.
- 460 Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, Oldale C, Jones
461 P, Silk D. Randomized clinical trial of the effects of preoperative and postoperative oral
462 nutritional supplements on clinical course and cost of care. *Br J Surg.* 2004
463 Aug;91(8):983-90.
- 464 Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be
465 analysed? *BMJ* 2000;320:1197-200.
- 466 Ware JE, Jr., Gandek B, Kosinski M, Aaronson, N. K., Apolone, G., Brazier, J. et al.
467 The equivalence of SF-36 summary health scores estimated using standard and
468 country-specific algorithms in 10 countries: results from the IQOLA Project.
469 International Quality of Life Assessment. *J Clin Epidemiol* 1998;51:1167-70.
- 470 Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I.
471 Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- 472 Willich SN, Reinhold T, Selim D, Jena S, Brinkhaus B, Witt CM. Cost-effectiveness of
473 acupuncture treatment in patients with chronic neck pain. *Pain* 2006;125:107-13.
- 474 Witt CM, Reinhold T, Jena S, Brinkhaus B, Willich SN. Cost-effectiveness of
475 acupuncture in women and men with allergic rhinitis: a randomized controlled study in
476 usual care. *Am J Epidemiol* 2009;169:562-71.
- 477 Zethraeus N, Johannesson M, Jonsson B, Lothgren M, Tambour M. Advantages of
478 using the net-benefit approach for analysing uncertainty in economic evaluation
479 studies. *Pharmacoeconomics* 2003;21:39-48.
- 480
481
482
483
484
485

486 Figure legends

487

488 Figure 1: Trial diagram of patients from inclusion to analysis

489

490 Figure 2: Concept of quality adjusted life years (the area-under-the-curves can be
491 interpreted as the quality adjusted life years associated with intervention or control
492 strategy)

493

494 Figure 2: Cost-effectiveness plane of n=1,000 bootstrap samples (each for both
495 scenarios)

496

497 Figure 3: Cost-effectiveness acceptability curves

498

499

500

501

502

503

504

505

506

507

508

509

510

511

512

513

514

515

516

517

518

519

520

521

522

523

524

525

526

527

528

529

530

531

532

533

534 Table 1: Clinical characteristics of study patients at baseline and readmissions during
 535 the intervention period
 536

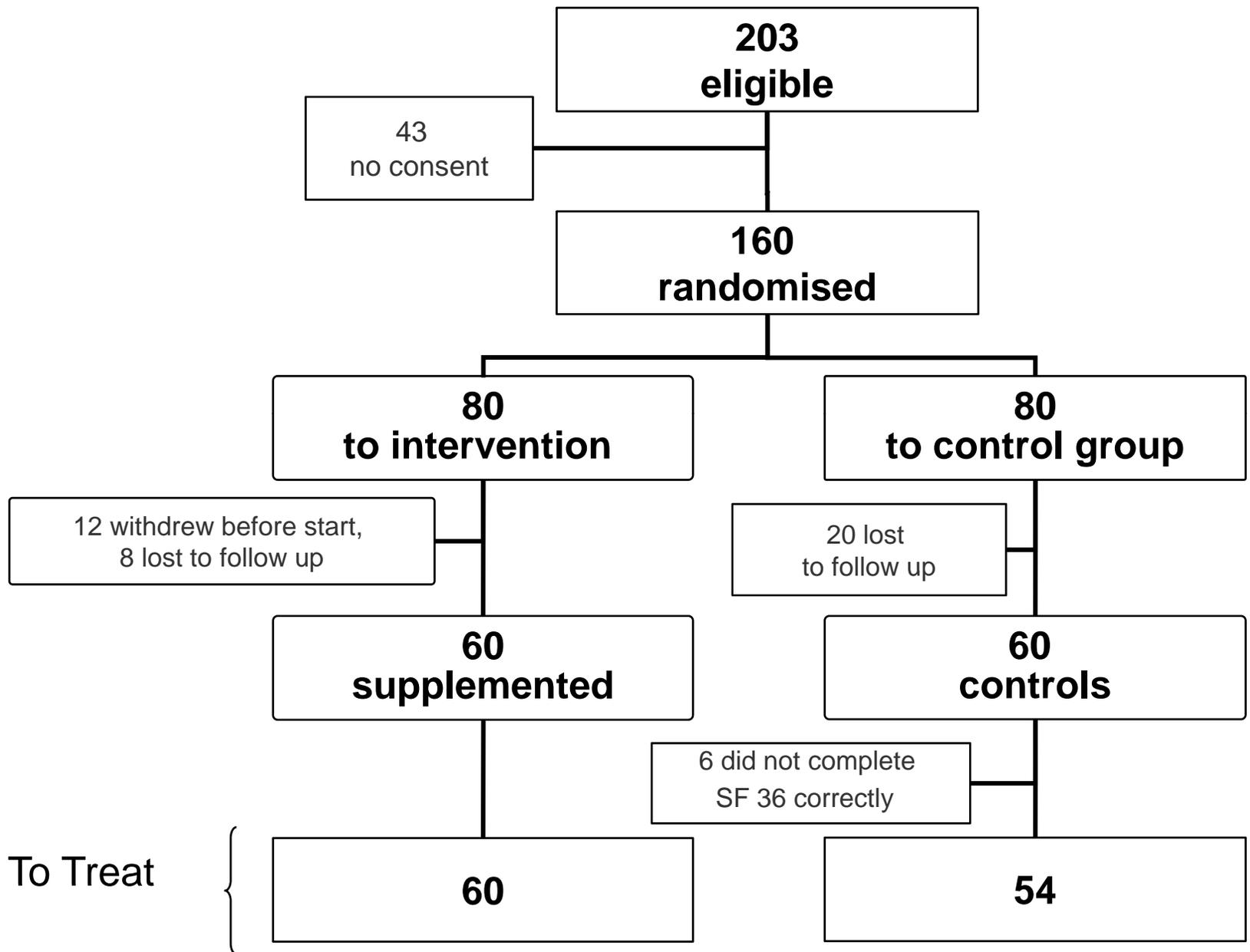
	Intervention group	Control group	P-value
Age [years]	50.6±15.3	50.9±15.9	n.s.
Diagnoses			
IBD	21	17	n.s.
Liver disease	16	16	
Biliary disease	6	3	
Pancreatic disease	4	4	
Gastritis	4	7	
others	9	7	
BMI [kg/m ²]	21±3.9	21.9±3.7	n.s.
Gender distribution [m/f]	27/33	30/24	n.s.
Severity of malnutrition (SGA B/SGA C)	29/31	34/20	n.s.
Length of hospital stay [days]	17.2±14.8	14±9.6	n.s.
Comorbidity count [n]	5±3.6	4.6±3.1	n.s.
Number of drugs/d	5±2.8	3.9±2.4	n.s.
CRP [mg/dl]	2.63±3.50	2.27±2.54	n.s.
Readmissions within intervention period	17	26	0.029

537 Abbr. IBD: inflammatory bowel disease, SGA : subjective global assessment, CRP: C-reactive
 538 Protein
 539
 540
 541
 542
 543
 544
 545
 546
 547
 548

549 Table 2: Costs, quality of life and incremental cost effectiveness in the study
 550 population
 551

	High price scenario	Low price scenario
Costs (Euro)		
Intervention	561.42 (513.77 to 609.08)	440.71 (403.30 to 478.12)
Control	21.56 (0 to 72.70)	16.89 (0 to 57.07)
Difference	540.16 (468.39 to 611.94)	424.02 (367.68 to 480.36)
P-value	≤0.001	≤0.001
Utilities		
baseline		
Intervention	0.594 (0.556 to 0.632)	
Control	0.619 (0.579 to 0.659)	
P-value	n.s.	
3 months after study onset		
Intervention	0.731 (0.698 to 0.764)	
Control	0.671 (0.635 to 0.706)	
P-value	0.022	
Quality of Life adjusted Life Years		
Intervention	0.659 (0.643 to 0.676)	
Control	0.615 (0.597 to 0.633)	
Difference	0.045 (QALYs gained for intervention)	
P-value	0.003	
ICER (costs to reach one QALY gained due to the intervention) (Euro)		
	12,099	9,497

552 Abbr. QALY: quality of life adjusted life year, ICER: incremental cost effectiveness ratio
 553 Values are portrayed as mean and 95 % CI
 554



Intention To Treat analysis

Figure 1

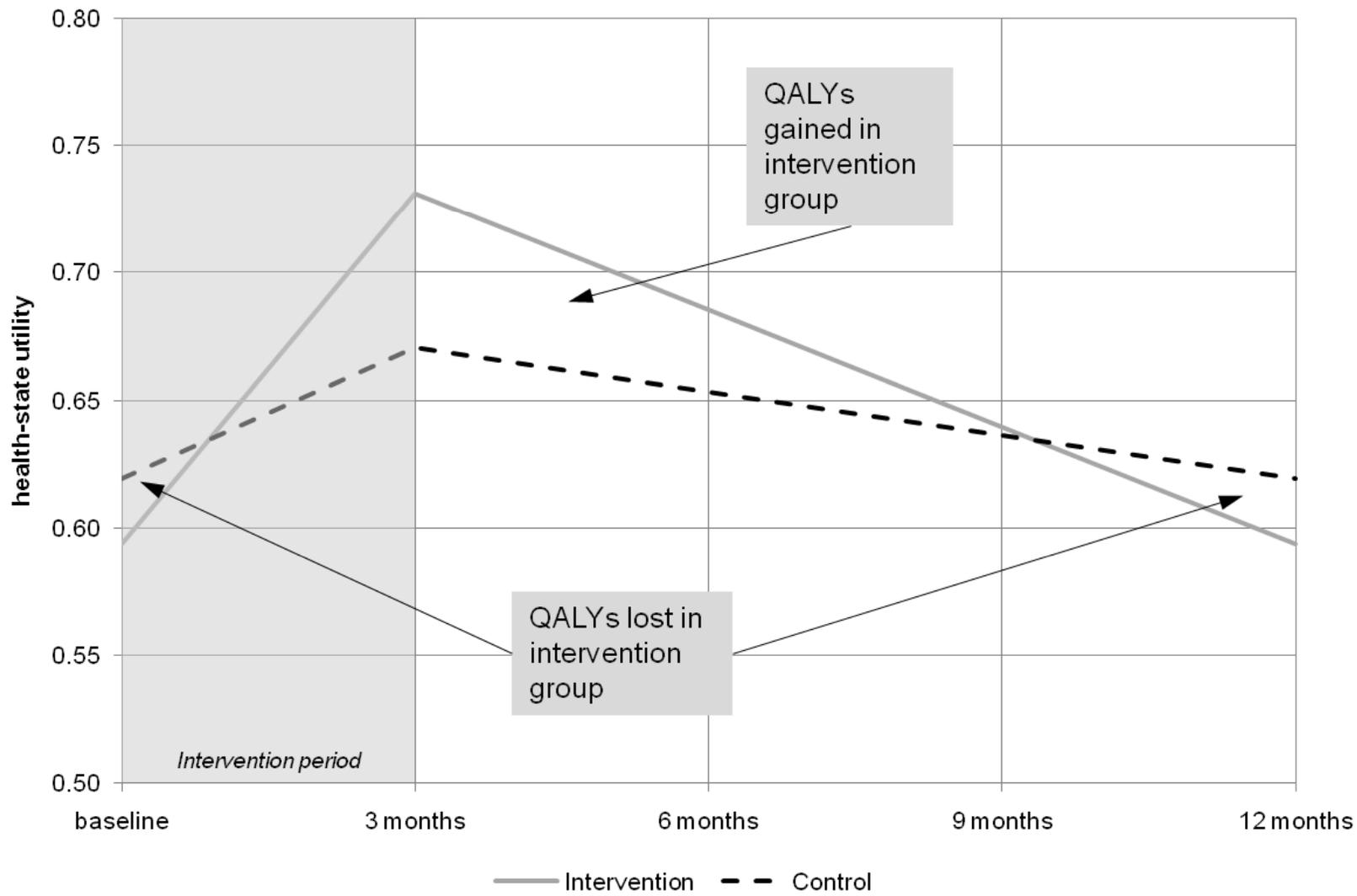


Figure 2

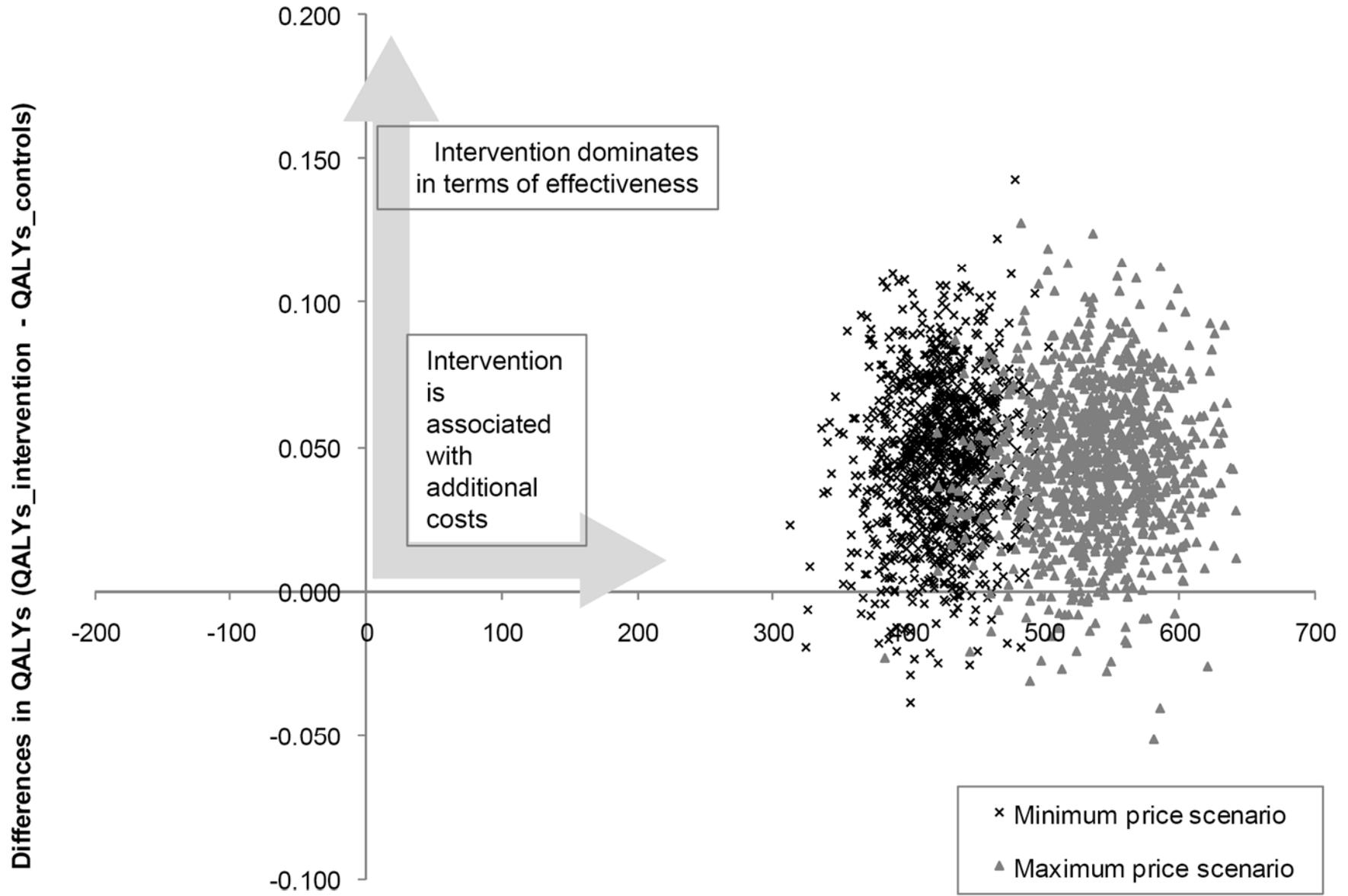


Figure 3

Cost differences in Euro (costs_intervention - costs_controls)

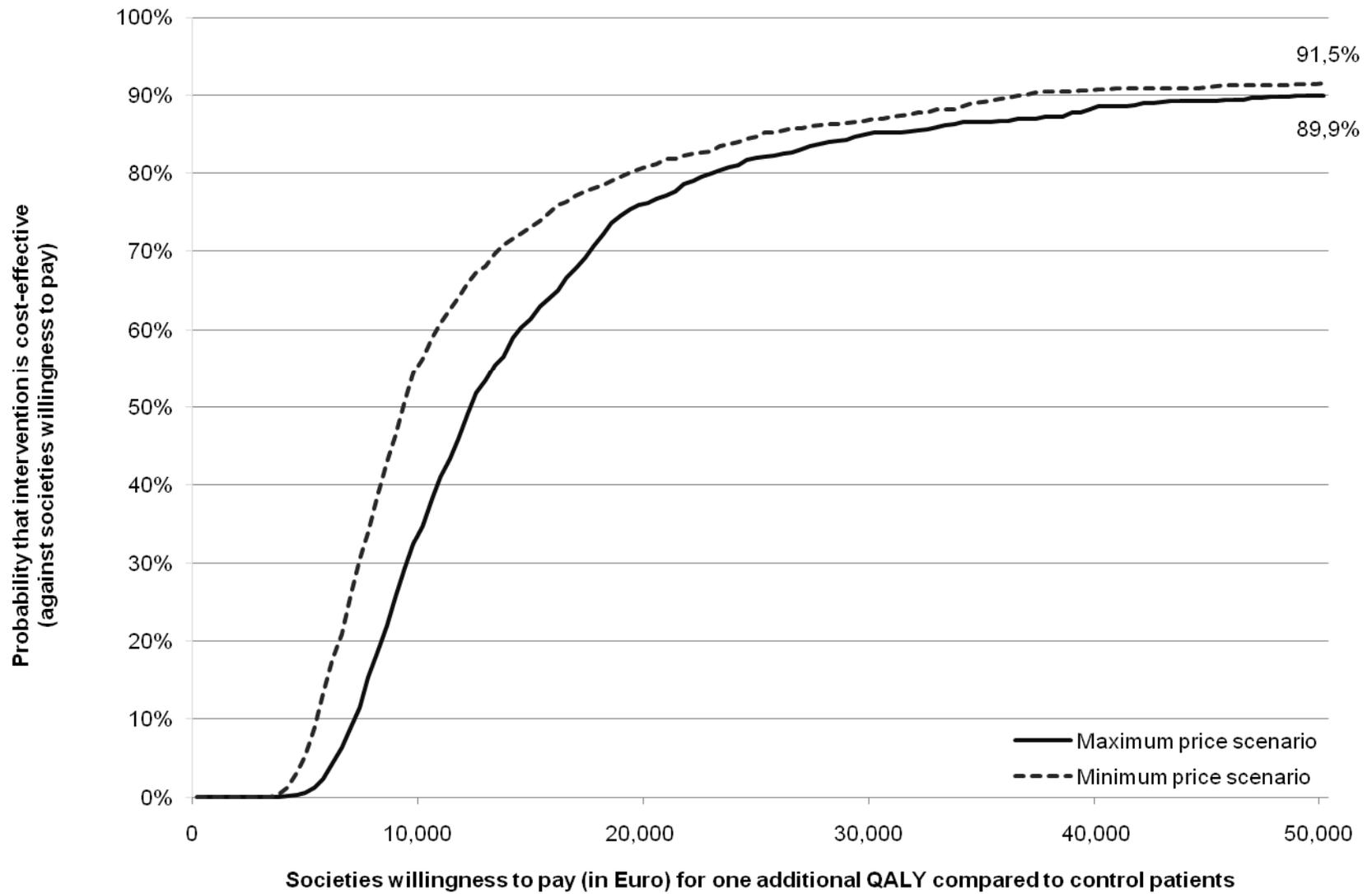


Figure 4