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

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Running title:

COST-EFFECTIVENESS OF ORAL NUTRITIONAL SUPPLEMENTS IN DISEASE RELATED MALNUTRITION

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Abstract

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

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

Results: Intervention patients consumed 2.4±0.8 ONS per day. Intervention and control patients did not differ in their health-status utilities at baseline (0.594±0.017 vs. 0.619±0.018), but after three months the health-status utilities were significantly higher in intervention patients than control patients (0.731±0.015 vs. 0.671±0.016, p=0.028). Intervention was associated with significantly higher costs (ICER: €9,497 and €12,099 /additional QALY, respectively) but deemed cost-effective according to international thresholds (<€50,000/QALY).

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

Keywords

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

Introduction

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

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

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

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

Methods

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

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

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

Nutritional status

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

Supplementation and dietary counselling

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

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

Quality of life

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

Economic analyses

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

Effectiveness measurement

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

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

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

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

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

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

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

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

Cost measurement

We employed two different pricing scenarios for ONS, using high and low prices (2.93€ and 2.30€ per tetra pack, respectively) which are based on research of the assortment of German online pharmacies representing the highest and the lowest price per tetrapack at the time of searching (2010). The total costs of ONS were calculated by multiplying number of packages used during the study period and the price per unit in both pricing scenarios. Resource consumption in other areas was not collected within this pilot study. Data on acute readmissions to hospital were collected from our hospital system or from the patients themselves if admitted to other hospitals as dichotomous variable only (yes/no). We were therefore not able to include the readmission days in the cost analysis,

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

Cost-effectiveness

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

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

The ICER can be interpreted as additional costs associated with realizing one additional QALY compared to the control patients. In the UK, a threshold of 30,000 GBP per QALY gained is found to be consistent with decisions of adopting new technologies by NICE (National Institute for Clinical Excellence) (Raftery et al.,2001). In Germany, such a threshold does not yet exist, so we used a hypothetical threshold of max. €50,000 per QALY originally suggested by health care economists and in accordance with other German studies (Willich et al., 2006; Witt et al., 2009), due to comparability within one health care system.

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

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

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

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

Statistical analyses

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

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

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

Results

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

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

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

<u>Quality of life</u>

Information on quality of life, costs and ICER is given in Table 2. Health status utilities were not different at baseline between intervention and control patients, but increased in both groups during the study. The mean improvement was significantly higher in intervention patients (0.128 (CI: 0.095-0.161) vs. 0.067 (CI: 0.031-0.103)), resulting in significantly higher health status utilities than control patients after three months. As shown in Figure 2, the resulting difference in QALYs (0.045) was in favour of intervention patients. This gain can be interpreted as additional 16 days of full quality of life per year.

<u>Costs</u>

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

<u>Cost-effectiveness</u>

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

Discussion

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

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

Russell et al summarized results of studies on costs of ONS in hospital and community. Pooled results from the studies in abdominal and orthopaedic surgery as well as elderly revealed net cost savings per patient both in term of inpatient stay and complications (Russell 2007). Enteral and oral immunonutrition has also been associated with reduced postoperative complication rates and thus substantially reduced treatment costs in patients undergoing major abdominal surgery (Senkal et al., 1999) or cancer surgery (Braga et al., 2005) despite higher costs of the product. In nursing homes, offering snacks has been shown to be associated with greater cost-effectiveness than intervention with ONS (Simmons et al., 2010). In patients with cerebrovascular events, long term home enteral tube feeding was also shown to be cost-effective (Elia & Stratton, 2008). Varying but mostly high cost-effectiveness has also been demonstrated in the field of life style intervention and obesity and diabetes prevention programmes as summarized by Dalziel et al (Dalziel & Segal, 2007). Different settings and specific forms of nutritional therapy are prone to be associated with different cost-effectiveness scenarios. In our malnourished study population with benign gastrointestinal disease, nutritional therapy was a supportive measure in order to accelerate improvement of nutritional and functional status. The intervention was found to be cost-effective from the point of view of the German statutory health insurance systems; nevertheless, some potential limitations resulting from the design of economic evaluation must be kept in mind while interpreting the results of our study. Since we only considered direct costs of the intervention, the intervention was associated with significantly higher costs than the control arm. Further costs such as medication, rehospitalisation, use of other health care resources or indirect costs were not included in the pilot study design. Our findings do therefore not allow conclusions about potential additional expenses in other areas of health care. However, considering the significantly higher readmission rate in the control group, it is likely that cost-impact in favour of ONS would have been greater if all costs had been included. Another uncertainty arises from the methodology of QALY calculation: in consistency with other studies (Willich et al., 2006; Witt et al., 2009) we conservatively assumed that quality of life would decrease in a linear way after nutritional intervention returning to baseline level 12 months after study onset. Data on quality of life was only available at month 6 in 60% of patients after study intervention, due to loss of follow up. Patients were asked to send in the questionnaires at month 6, but not all questionnaires were correctly filled out and could be evaluated. Sum scales of the SF 36 quality of life questionnaire, however, did not differ significantly between month 3 (end of intervention period) and month 6 (data not shown) in intervention and control patients. We still used a very cautious approach to interpret the further development of quality of life in order not to overestimate effects. Theoretically, quality of life could however have remained stable throughout the subsequent six months or immediately dropped to baseline, which would affect the area-under-the-curve and thus the QALY calculation.

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

When considering economic benefit of nutritional therapy, economic perspective has to be taken into account. Restricted to direct intervention costs, we concluded ONS to be a cost-effective intervention from the German statutory health insurance perspective. This conclusion is further supported by the reduced rehospitalisation rate in our intervention patients. Whereas reducing the number of inpatient stays is attractive from the point of health insurance systems, for a single hospital centre artificial nutrition might, however, be considered a potential economic burden through increased resource consumption. These different viewpoints reveal a basic problem in health policies. It seems necessary to find incentives for inpatient care providers to decide on a special treatment, although this might not appear to be economically useful from their point of view.

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

Acknowledgements

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Conflict of interest

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

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Figure legends

Figure 1: Trial diagram of patients from inclusion to analysis

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

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

Figure 3: Cost-effectiveness acceptability curves

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

	Intervention group	Control group	P-value
Age [years]	50.6±15.3	50.9±15.9	n.s.
Diagnoses			
IBD Liver disease Biliary disease Pancreatic disease Gastritis others	21 16 6 4 4 9	17 16 3 4 7 7	n.s.
BMI [kg/m²]	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

Abbr. IBD: inflammatory bowel disease, SGA : subjective global assessment, CRP: C-reactive Protein

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

<table>
<tr><th></th><th>High price scenario</th><th>Low price scenario</th></tr>
<tr><td colspan="2">Costs (Euro)</td><td></td></tr>
<tr><td>Intervention</td><td>561.42 (513.77 to 609.08)</td><td>440.71 (403.30 to 478.12)</td></tr>
<tr><td>Control</td><td>21.56 (0 to 72.70)</td><td>16.89 (0 to 57.07)</td></tr>
<tr><td>Difference</td><td>540.16 (468.39 to 611.94)</td><td>424.02 (367.68 to 480.36)</td></tr>
<tr><td>P-value</td><td>≤0.001</td><td>≤0.001</td></tr>
<tr><td colspan="3">Utilties</td></tr>
<tr><td colspan="3">baseline</td></tr>
<tr><td>Intervention</td><td colspan="2">0.594 (0.556 to 0.632)</td></tr>
<tr><td>Control</td><td colspan="2">0.619 (0.579 to 0.659)</td></tr>
<tr><td>P-value</td><td colspan="2">n.s.</td></tr>
<tr><td colspan="3">3 months after study onset</td></tr>
<tr><td>Intervention</td><td colspan="2">0.731 (0.698 to 0.764)</td></tr>
<tr><td>Control</td><td colspan="2">0.671 (0.635 to 0.706)</td></tr>
<tr><td>P-value</td><td colspan="2">0.022</td></tr>
<tr><td colspan="3">Quality of Life adjusted Life Years</td></tr>
<tr><td>Intervention</td><td colspan="2">0.659 (0.643 to 0.676)</td></tr>
<tr><td>Control</td><td colspan="2">0.615 (0.597 to 0.633)</td></tr>
<tr><td>Difference</td><td colspan="2">0.045 (QALYs gained for intervention)</td></tr>
<tr><td>P-value</td><td colspan="2">0.003</td></tr>
<tr><td colspan="3">ICER (costs to reach one QALY gained due to the intervention) (Euro)</td></tr>
<tr><td></td><td>12,099</td><td>9,497</td></tr>
</table>

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

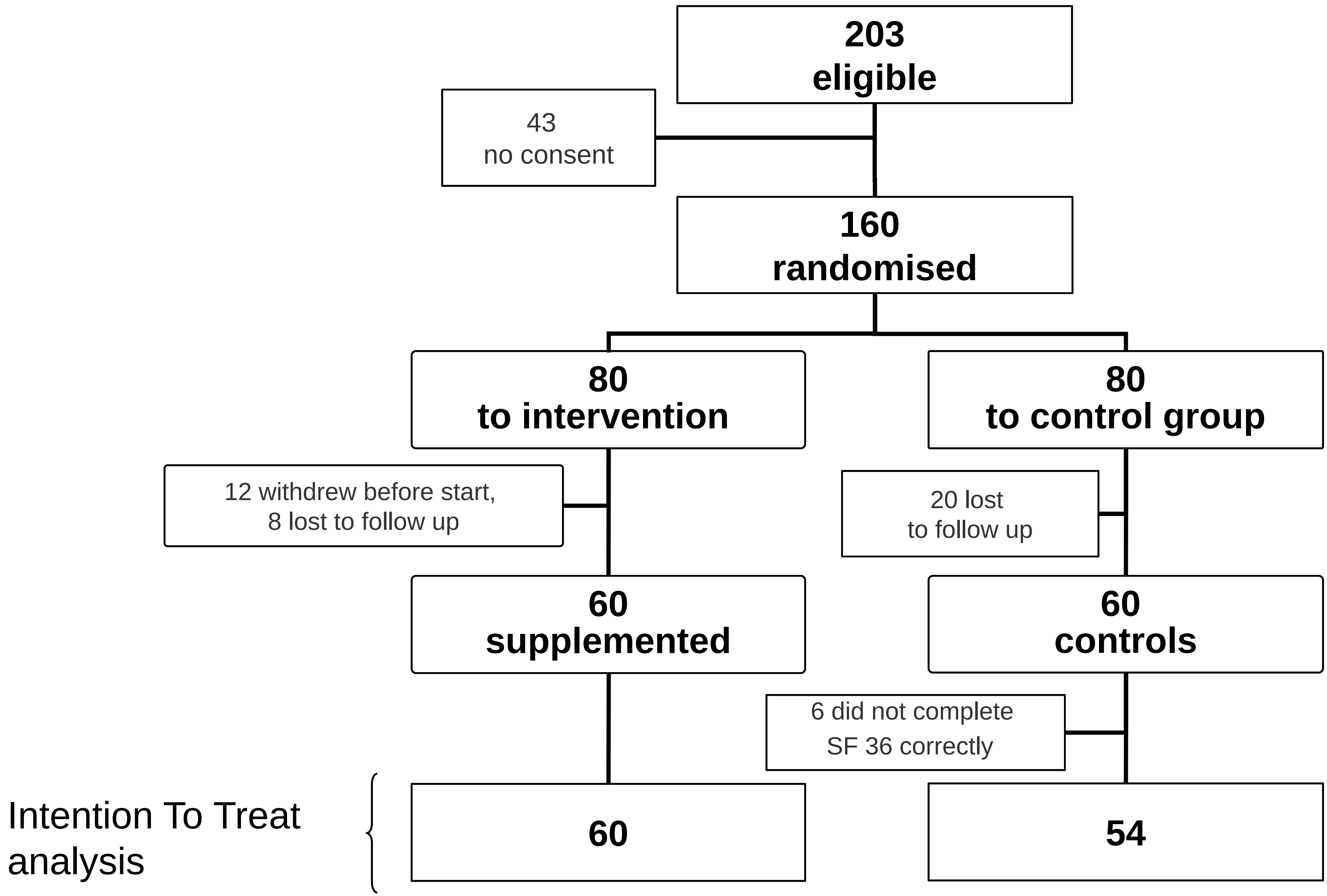
203
eligible
43
no consent
160
randomised
80
to intervention
80
to control group
12 withdrew before start,
8 lost to follow up
20 lost
to follow up
60
supplemented
60
controls
6 did not complete
SF 36 correctly
Intention To Treat
analysis
60
54

Figure 1

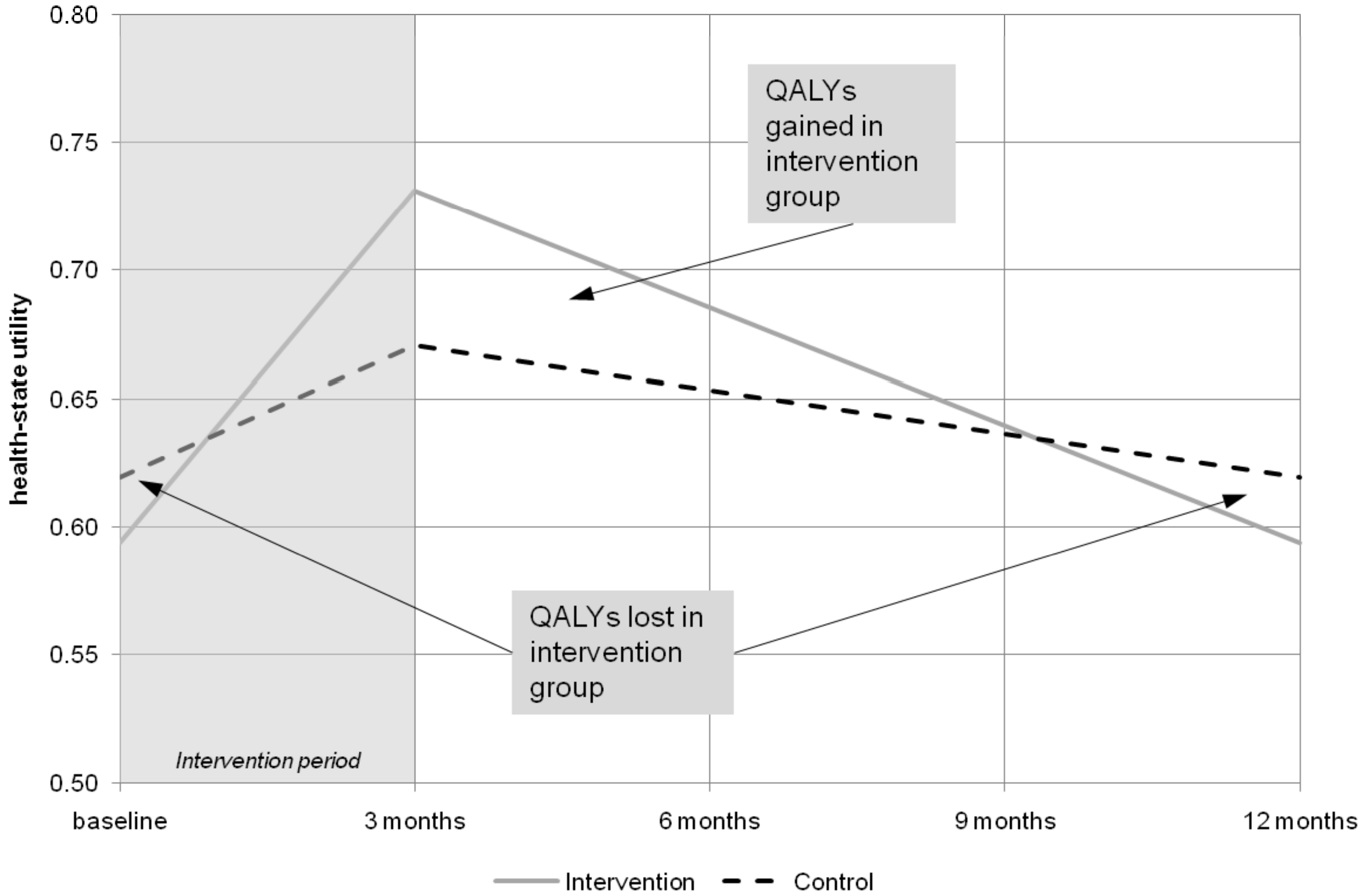
0.80
0.75
0.70
0.65
0.60
0.55
0.50
health-state utility
QALYs gained in intervention group
QALYs lost in intervention group
Intervention period
baseline
3 months
6 months
9 months
12 months
Intervention
Control

Figure 2

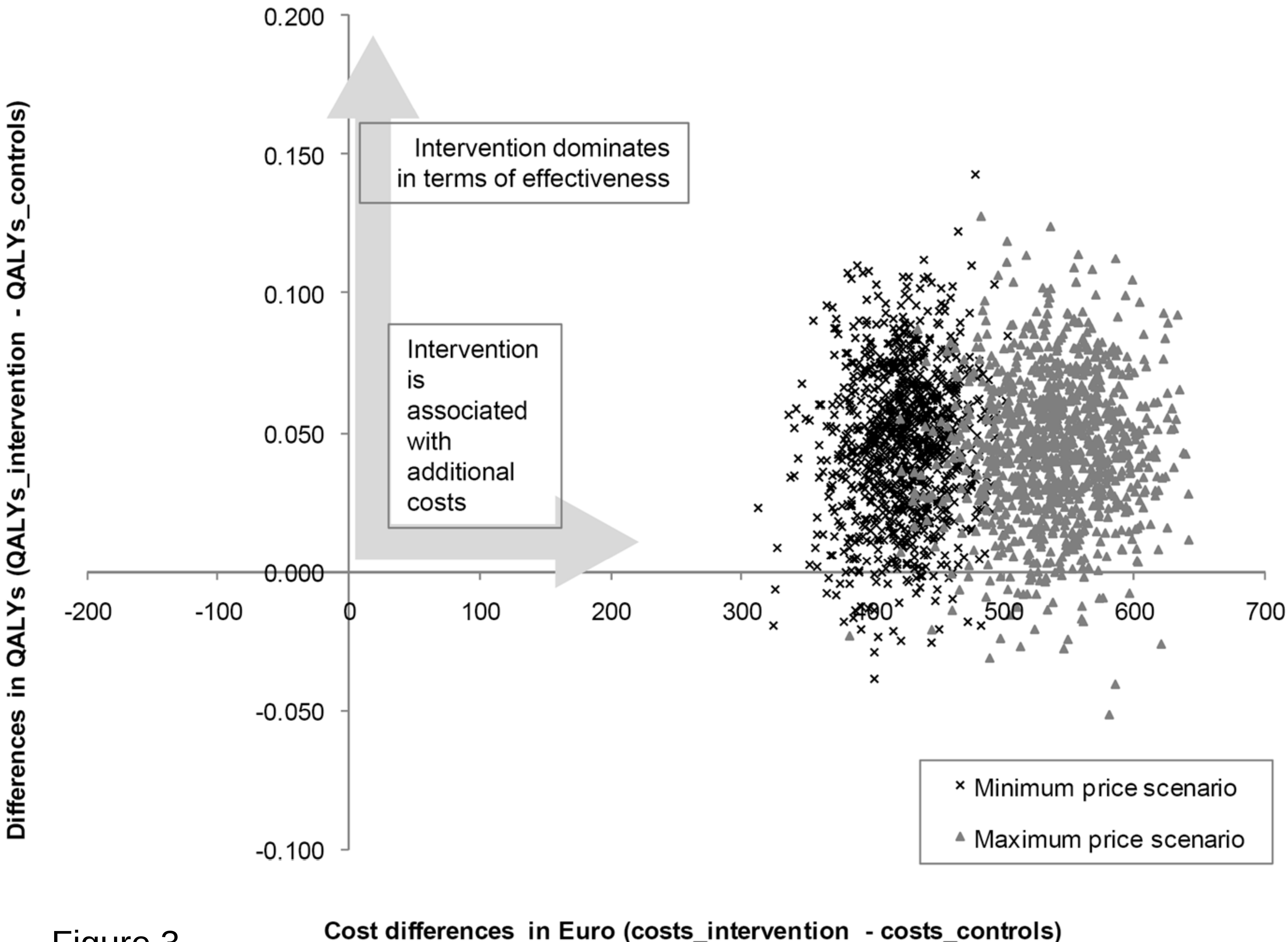
0.200
0.150
0.100
0.050
0.000
-0.050
-0.100
-200
-100
0
100
200
300
400
500
600
700
Intervention dominates
in terms of effectiveness
Intervention
is
associated
with
additional
costs
Minimum price scenario
Maximum price scenario
Differences in QALYs (QALYs_intervention - QALYs_controls)
Cost differences in Euro (costs_intervention - costs_controls)

Figure 3

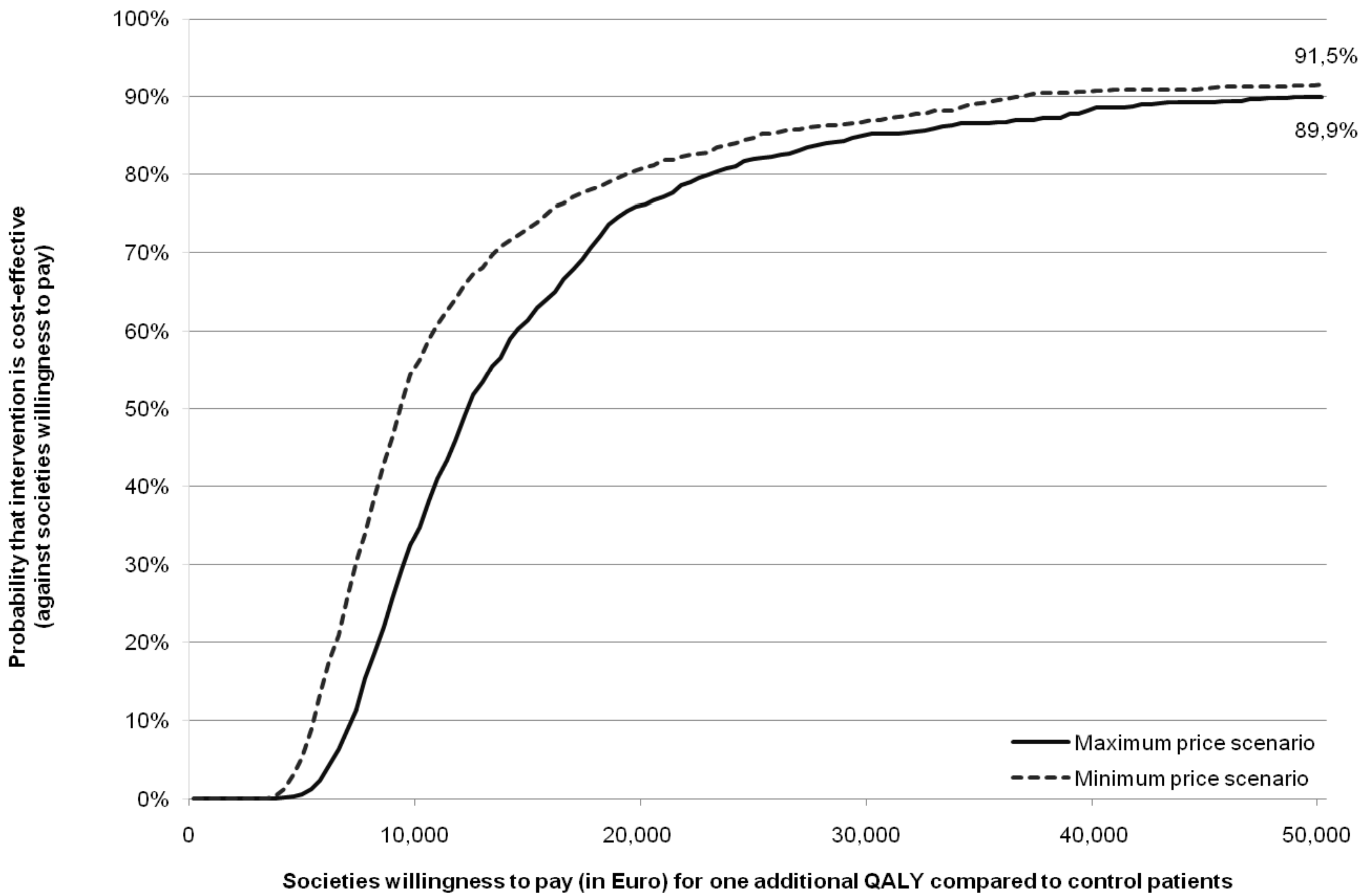
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
91,5%
89,9%
Maximum price scenario
Minimum price scenario
0
10,000
20,000
30,000
40,000
50,000
Probability that intervention is cost-effective (against societies willingness to pay)
Societies willingness to pay (in Euro) for one additional QALY compared to control patients

Figure 4