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ORIGINAL ARTICLE

Cost-effectiveness of a 3-month intervention with oral nutritional supplements in disease-related malnutrition: a randomised controlled pilot study

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Background/Objectives: 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.
Subjects/Methods: In total, 114 malnourished patients (50.6 ± 16.1 years, 57 female) with benign gastrointestinal disease were included and randomised to receive either ONS for 3 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 Short-Form (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 two different pricing scenarios for ONS (minimum price: €2.30 and maximum: €2.93/tetrapack). 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 3 months, the health status utilities were significantly higher in intervention patients than in control patients (0.731 ± 0.015 vs 0.671 ± 0.016, $P = 0.028$). Intervention was associated with significantly higher costs (ICER: €9497 and €12 099/additional QALY, respectively) but deemed cost-effective according to international thresholds (<€50 000/QALY).
Conclusions: A 3-month intervention with ONS increases quality of life in malnourished patients. This treatment appears to be cost-effective according to international benchmarks.
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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 25–50% of hospitalised 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 (Russell, 2007; Norman *et al.* 2008b).

However, although malnutrition undeniably promotes morbidity, and appropriate nutritional therapy is available

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in affluent countries, there is evidence that only a small percentage of malnourished patients is receiving nutritional support (McWhirter and Pennington, 1994). Moreover, disease-related malnutrition is frequently already present on admission and nutritional status deteriorates further during hospital stay because of progression of disease, lack of awareness or education of attending staff or simply adverse clinical routines (McWhirter and Pennington, 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; hospitalised 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, 2007).

Despite the cost burden of malnutrition and 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 a 3-month intervention with oral nutritional supplements (ONS) 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 as 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 ONS in addition to dietary counselling for 3 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 regarding the affect 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 <3 months or age <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 3 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 using the protocol developed by 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 body mass index (weight (kg)/height (m^2)).

Supplementation and dietary counselling

Both intervention and control patients received a standard dietary counselling session (45 min) 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 three ONS (~ 200 ml) per day (Fresubin Protein Energy DRINK, Fresenius Kabi, Bad Homburg, Germany) 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 using the validated Medical Outcomes Study 36-item Short-Form (SF) General Health Survey described in detail elsewhere (Ware and Sherbourne, 1992; Ware *et al*., 1998). The questionnaire consists of 36 questions, is self-administered and assesses quality of life and well-being in eight 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 single mean values, that is, health state utilities, by using an algorithm developed by 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 (QALYs). The QALYs gained were calculated by using the area under the curve method, using the following formula for all patients who survived during the year after study onset:

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

The analysis is based on utility values at each time point (α = baseline utility, β = utility after 3 months) and uses the common assumption of a linear change over time (Thompson and Barber, 2000; Richardson and Manca, 2004) (Figure 2). After the intervention period of 3 months, we conservatively assumed a linear decrease of intervention effect returning to baseline level 12 months after study onset.

During the 3-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):

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

For all patients, the respective area under the curve reflects the quality life years experienced during the 1-year period. QALYs gained for intervention group was calculated as QALY-group differences:

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

Cost measurement. We used two different pricing scenarios for ONS, using high and low prices (€2.93 and €2.30 per tetrapack, respectively), which are based on research of the assortment of the 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 of the 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 1 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, 1999).

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

The ICER can be interpreted as additional costs associated with realising one additional QALY compared with 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 National Institute for Clinical Excellence (Raftery, 2001). In Germany, such a threshold does not yet exist, so we used a hypothetical threshold of maximum €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), because of 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.

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

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 and Zethraeus, 2000).

To reach information on the probability of cost-effectiveness, 1000 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 χ^2-test were used for comparisons on sociodemographic baseline characteristics. Analysis of covariance was used for health state utilities data as well as for costs. The analysis was adjusted for age and gender. A 3-month data were further adjusted for differences in baseline health state utilities.

To derive cost-effectiveness acceptability curves, we used non-parametric bootstrapping (Efron, 1979). The original sample was bootstrapped 1000 times to obtain 1000 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 (Chicago, IL, USA). Bootstrap-analyses were applied using MS EXCEL 2007. The predefined significance level was $P<0.05$.

Results

A total of 644 consecutively admitted patients of the Deptartment of Gastroenterology, Hepatology and Endocrinology, Charite University Medicine were screened, whereof 201 were eligible for the study. In total, 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

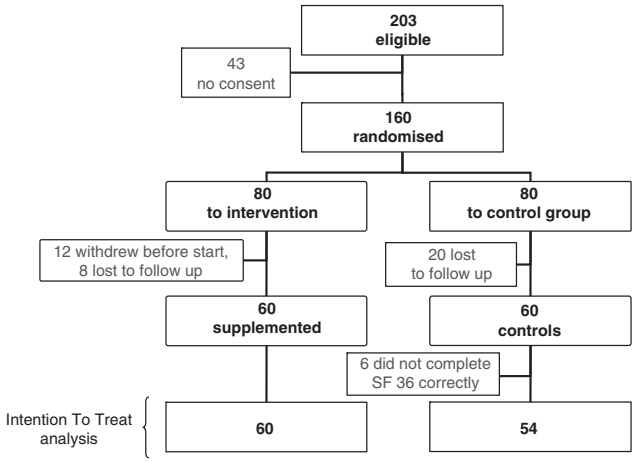

Figure 1 Trial diagram of patients from inclusion to analysis.

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	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/day	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

Abbreviation: n.s., not significant; BMI, body mass index; CRP, C-reactive protein; IBD, inflammatory bowel disease, SGA, subjective global assessment.

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 with regard to age, gender distribution and nutritional status as defined by Subjective Global Assessment or body mass index. Length of stay, comorbidity 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 with intervention patients. One intervention patient died 6 months after the intervention period and three control patients died at 1, 5 and 9 months after the intervention period.

Quality of life

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 (confidence interval: 0.095–0.161) vs 0.067 (confidence interval: 0.031–0.103)), resulting in significantly higher health status utilities than control patients after 3 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.

Costs

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. As two control patients also received ONS, 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.

Cost-effectiveness

Depending on the price scenario the ICER that was between €9497 (low-price scenario) and €12 099 per additional QALY (high-price scenario). Figure 3 shows the results of our 1000 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), and 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 3-month nutritional supplementation with ONS increases quality of life in malnourished patients with benign gastrointestinal

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

	High-price scenario	*Low-price scenario*
Costs (Euro)		
Intervention	561.42 (513.77–609.08)	440.71 (403.30–478.12)
Control	21.56 (0–72.70)	16.89 (0–57.07)
Difference	540.16 (468.39–611.94)	424.02 (367.68–480.36)
P-value	⩽0.001	⩽0.001
Utilties		
Baseline		
Intervention	0.594 (0.556–0.632)	
Control	0.619 (0.579–0.659)	
P-value	n.s.	
At 3 months after study onset		
Intervention	0.731 (0.698–0.764)	
Control	0.671 (0.635–0.706)	
P-value	0.022	
Quality-adjusted life years		
Intervention	0.659 (0.643–0.676)	
Control	0.615 (0.597–0.633)	
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	9497

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.
Values are portrayed as mean and 95% confidence interval.

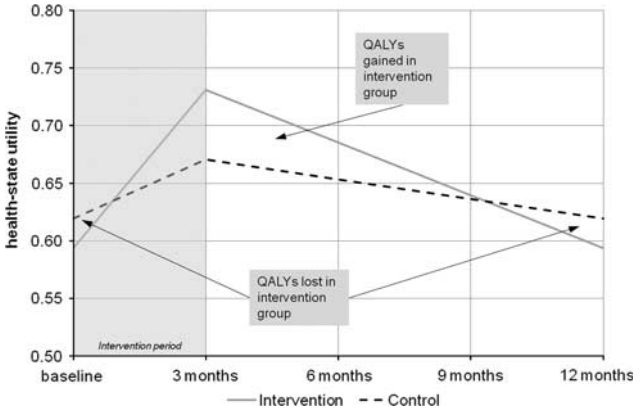

Figure 2 Concept of quality adjusted life years (the area under the curves can be interpreted as the quality-adjusted life years associated with intervention or control strategy).

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 well-being, and international evidence-based guidelines have been developed to standardise nutritional therapy (Lochs, 2006). Several clinical trials have shown that supplementation with ONS 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 and Pennington, 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 (Russell, 2007; Darmon *et al*., 2008). Within the current climate of cost constraint in healthcare, 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, (2007) summarised the results of studies on costs of ONS in hospital and community. Pooled results from the studies in abdominal and orthopaedic surgery, as well as in elderly patients revealed net cost savings per patient both in terms 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 (Gianotti *et al*., 2000; Braga and Gianotti, 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

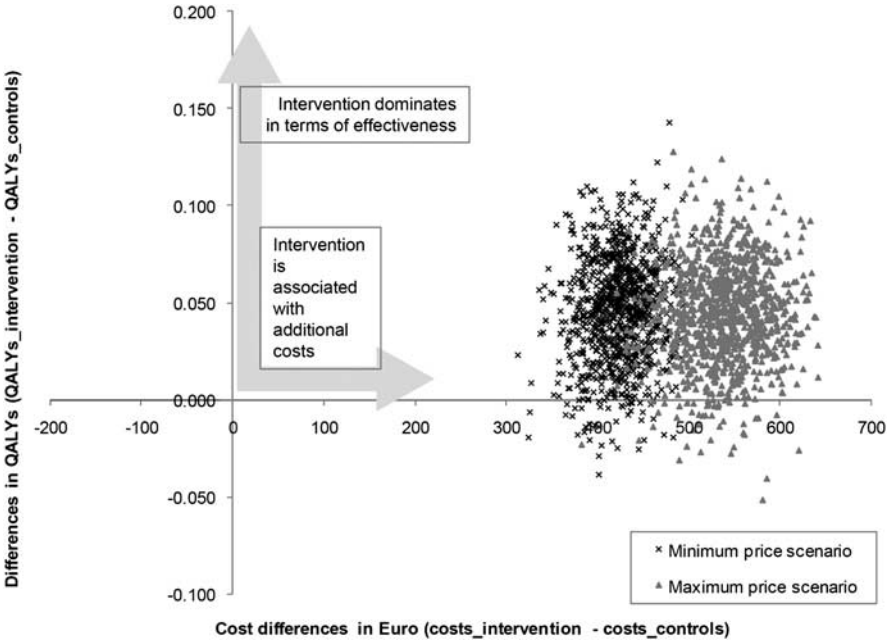

Figure 3 Cost-effectiveness plane of $n = 1000$ bootstrap samples (each for both scenarios).

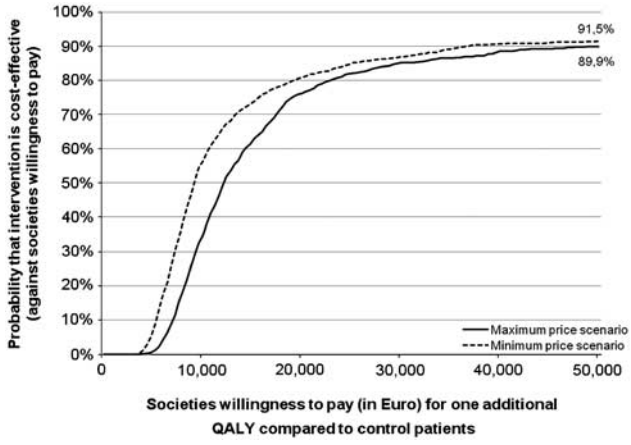

Figure 4 Cost-effectiveness acceptability curves.

cost-effective (Elia and Stratton, 2008). Varying, but mostly high, cost-effectiveness has also been demonstrated in the field of lifestyle intervention and obesity and diabetes prevention programmes as summarised by Dalziel and 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 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. As 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, re-hospitalisation, use of other health-care resources or indirect costs were not included in the pilot study design. Our findings do, therefore, not allow drawing conclusions about potential additional expenses in other areas of healthcare. However, considering the significantly higher readmission rate in the control group, it is likely that impact of cost 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, because of 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 in 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 6 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, for example, 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 health-care 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. As 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 re-hospitalisation 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.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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