Health Economics in Medical Nutrition: An Emerging Science

Mark Nuijten

Ars Accessus Medica BV, Amsterdam, The Netherlands

Abstract

Rational: The objective of this paper is to describe the applications of health economic theory to medical nutrition. *Background:* The published literature provides evidence that medical nutrition, e.g. oral nutritional supplements, is an effective treatment for patients with disease related malnutrition. Malnutrition is associated with mortality risk and complication rates, including infections. Malnutrition is not a new problem and with an ageing population it continues to become a major public health concern as increasing age is associated with an increased risk of malnutrition. *Findings:* This overview shows that in the case RCTs are providing the clinical evidence, there is no methodological difference between a cost-effectiveness analysis for pharmaceutical or nutrition. However, in nutrition the evidence may not always come from RCT data, but will be more often based on observational data. Therefore the clinical evidence of nutrition in itself is not the issue, but the handling of clinical evidence from observational studies. As the link between the consumption of a food product and a resulting health status is often more difficult to establish than the effect of a drug treatment it requires the further development of adapted methodologies in order to correctly predict the impact of food-related health effects and health economic outcomes from a broader perspective.

© 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

Rationale

Medical nutrition is a specific nutrition category either covering specific dietary needs and/or nutrient deficiency in patients or feeding patients unable to eat normally. It is exempted from the food regulation in Europe and in the US and regulated by specific rules, as it is dedicated to patients with nutritional deficien-

cies or inability to eat normally. Therefore, it is often not in all countries delivered under medical prescription and supervision by health care professionals.

Although these products have existed for more than two decades, the health economic evidence of medical nutrition interventions tends to be limited. An important reason is that medical nutrition does fall under the coverage requirements for reimbursement, like pharmaceuticals, which often require health economic data. Economic evaluations of pharmaceuticals and other health technologies, including devices, are common practice since the 1990s. Since that time, reimbursement agencies in different countries have developed evaluation guidelines, resulting in a large number of published research papers, comments, letters and editorials on economic evaluations of health technologies and policies [1], although health economic evaluations for medical nutrition are not common yet.

The objective of this paper is to describe the applications of the health economic theory for medical nutrition.

Background

Clinical Background

Medical nutrition comprises parenteral nutrition, which is regulated in pharmaceutical legislation, as well as all forms of nutritional support that are regulated as 'foods for special medical purposes' (FSMP), defined by the European Commission Directive 1999/21/EC independent of the route of application [2]. For the purposes of this article, the term medical nutrition is used only for FSMP, which is a category of dietary foods for particular nutritional uses specially processed or formulated, and intended for the dietary management of patients and to be used under medical supervision. One of the indications for the use of medical nutrition is malnutrition [European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines 2006; Fight against Malnutrition 2012]. The following definition of malnutrition is widely acknowledged, including the ESPEN members: 'A state of nutrition in which a deficiency, excess or imbalance of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome' [2]. Malnutrition thus includes both overnutrition (overweight and obesity) and undernutrition (insufficient nutrition). Although in some cases improvement in the quality or quantity of food supplied can ameliorate the problem, in many cases the person concerned is simply unable or unwilling to consume sufficient normal food to meet their requirements to manage the malnutrition. Particularly in the case of disease, it is literally of vital importance to

consider other options to improve nutritional intake, such as FSMP products, which include oral nutritional supplements (ONS) as well as enteral tube feeding (ETF) via nasogastric, naso-enteral or percutaneous tubes. Due to the catabolic state, loss of lean body mass leads to weight loss, which is an independent risk factor for mortality in chronically ill patients [3].

The published literature (meta-analyses and systematic reviews) provides evidence that ONS are an effective treatment for patients with disease-related malnutrition (DRM). Without nutritional intake, mortality occurs already after about 28 days in chronically ill patients (approximately 70 days in healthy persons) caused by a 40% weight loss [3]. Mortality rates are significantly lower (odds ratio of 0.61; 95% CI 0.48–0.78) [4]. Similar findings were reported in other reviews [5]. Complication rates, including infections, are significantly reduced (odds ratio of 0.31; 95% CI 0.17–0.56) [6]. Another systematic review showed that nutritional support can significantly reduce the risk of developing pressure ulcers (by 25%) [6]. Therefore, in patients with DRM, or at risk of DRM, the appropriate use of nutritional support can prevent complications arising, produce other clinical, functional and financial benefits, and can be lifesaving in some situations. Stratton and Elia [4] discuss the evidence from systematic reviews and meta-analyses of the effectiveness of nutritional support. The conclusion of this review is that nutritional support, including oral nutritional supplements, ETF and parenteral nutrition, is an important part of the management of any patient.

For the purposes of this article, the term malnutrition is used only for undernutrition in health care, which is caused by changes in the body metabolism due to acute or chronic diseases and/or treatment interventions increasing the daily nutritional needs, also known as DRM.

Economic Impact
Malnutrition is not a new problem, and with an aging population it continues to become a major public health concern as increasing age is associated with an increased risk of malnutrition [7]. It is not confined to developing countries, but is highly prevalent in the European health care system and in other developed regions. In European Union countries, about 20 million patients are affected by DRM (EUR 33 million in Europe), costing EU governments up to EUR 120 billion annually (EUR 170 billion in Europe) [8–10].

To estimate the efficiency (costs in relation to effects) in high-quality economic evaluations of enteral medical nutrition for DRM in adults in the Western world (developed regions), Freijer et al. [11] conducted a systematic review of published studies on this topic. The results showed that managing several patient populations suffering from (or at risk of) DRM in different health care settings with enteral medical nutrition is an efficient intervention from a health

economical perspective. ONS was the most studied form and the duration of using enteral medical nutrition varied from 3 years in patients with a cerebrovascular accident receiving ETF to 17 days of ONS in abdominal surgery patients. The mean duration of using ONS was 3 months. The economic value of enteral medical nutrition was calculated for the Netherlands (63%), Germany (25%) and the UK (12%). In all of the economic evaluations done alongside a clinical trial or survey (62%), the use of ONS or ETF for malnourished patients was part of a protocolized multicomponent nutritional intervention, and the control group received usual or standard care that consisted of no (protocolized) nutritional support including no (standard) use of ONS. In the evaluations using the modeling technique, the intervention consisted of ONS only versus no use of ONS in the control group [12, 13]. Freijer and Nuijten [12] performed a health economic study to assess the cost-effectiveness of ONS in the Netherlands. The use of ONS reduces the costs with EUR 252 (7.6%) cost saving per patient. The costs of hospitalization reduce from EUR 3,318 to 3,044 per patient, which is a 8.3% cost saving and corresponds to a 0.72-day reduction in the length of stay. The use of ONS would lead to an annual cost saving of a minimum of EUR 40.4 million. This analysis shows that the use of medical nutrition, ONS in this case, is a cost-effective treatment in the Netherlands and is superior to standard care without medical nutrition: it leads to cost savings and a higher effectiveness. A similar study by Nuijten and Mittendorf [13] assessed the health economic impact of ONS in the community setting in Germany. This study shows that the extra costs for ONS (EUR 534) are offset by a reduction in hospitalization costs (EUR 768) leading to total cost savings of EUR 234 per patient. A scenario analysis based on the length of hospital stays and per diem costing instead of diagnosis-related group costs shows that the extra costs for ONS (EUR 534) are also offset by a reduction in hospitalization costs (EUR 791) leading to cost savings of EUR 257 per patient. As a consequence, the use of ONS might be considered cost-effective at a patient and also a population level.

Health Economics

Basic Concepts
Escalating costs have become a major concern for health care professionals, decision-makers and the public, prompting the implementation of new cost containment measures over the last decade, focusing especially on new medical therapies and to a lesser extent on medical devices. The increasing demand results from aging of the population and an increase in new innovative, expensive, medical technologies, which are meant to replace often less expensive standard therapies.

As a consequence, health care decision-makers have been forced to develop new and more stringent criteria in the decision-making process for uptake of innovative therapies in the health insurance package. Instead of only considering the clinical benefits available at registration (traditional data: efficacy, safety and quality parameters) and the price of the new treatment, the decision-makers have taken a broader perspective, including also other related costs in the health care system. Over approximately the last 10 years, we can distinguish various additional data requirements, which especially relate to the use of the medicinal product in real daily practice. The most important new data requirements are effectiveness, cost-effectiveness and budget impact. Other considerations may also be taken into account depending on the specific indication, e.g. equity and social values in case of lifestyle medicinal products or orphan medicinal products.

As a consequence, new treatment options, including preventive treatments, are evaluated from a clinical as well as a broader economic perspective, thereby taking into consideration the overall costs and the impact on quality of life (QoL). The decision of health authorities on coverage of a medicinal product in the health insurance package is based on the value for money of that medicinal product. Health authorities will make a trade-off between the incremental, clinical benefit and the extra costs of the new medicinal product versus standard therapy. Currently, more formal methods of health technology assessment, such as budget impact and cost-effectiveness analysis, and more standardized measures of patient benefit are applied in order to make a value for money decision. The current most important new data requirements for coverage decisions by health authorities are:

- Effectiveness, which is the actual health benefit achieved by a medicinal product in daily practice. This contrasts with efficacy, which is the benefit measured under ideal conditions in a homogeneous group of patients.
- Cost-effectiveness of a medicinal product is based on the costs that will result from its use, and the potential savings that will be made compared with other products and/or treatments and the health benefits to the patient. The most used measure of this health benefit is the quality-adjusted life year (QALY). The lower the ratio of cost per QALY gained, the more cost-effective a health intervention is said to be. Threshold values are often used in coverage decisions. Medicinal products with ratios above these threshold values are not given coverage under the national health insurance package. These threshold values vary considerably from country to country. Values ranging from USD 50,000 to 100,000 per QALY gained (EUR 37,000–74,000) are sometimes used as a threshold in the US [14], whereas in the UK, the National Institute of Health and Clinical Excellence has adopted a cost-effectiveness threshold range of GBP 20,000–30,000 per QALY gained (EUR 23,800–

35,700). In the case of end-of-life treatment, an incremental cost-effectiveness ratio up to GPB 55,000 (EUR 65,450) may be accepted [15]. Other proposals include a differential threshold value between diverse disease and treatment characteristics; in the Netherlands, for example, recently a range between EUR 20,000 and 80,000 per QALY [16] gained has been suggested depending on the burden of disease for the patient (high burden → high cost per QALY threshold). There is currently an increasing demand for health economic data in the decision-making process in Europe. Several countries now have formal requirements (e.g. England/Wales, Scotland, Sweden, The Netherlands, Belgium, Finland and Portugal).

- Budgetary impact data from a financial analysis illustrate the impact of a new medicinal product on the annual national medicinal product budget and total health care budget.

Quality-Adjusted Life Years

The cost/QALY is seen as the preferred cost-effectiveness outcome. The QALY gain is calculated by combining the utility gain (QoL gain) with the number of life years gained. QALY gained may therefore be the result of longer life expectancy, utility gain or both. For example, a patient who experiences a survival gain of 4 years at a utility level of 0.4 will achieve the same 1.6 QALY gain as a patient with a survival gain of 2 years at a utility level of 0.8. Therefore, QALY may even be gained without increasing life expectancy. Malnutrition may have a negative effect on QALY through a reduction in life expectancy and a QoL reduction. Meta-analyses on treatment of DRM with medical nutrition show an increased QoL [6, 17]. If the cost per QALY gained is not viewed as the most appropriate outcome, other cost-effectiveness outcomes may be considered, for example, the cost per complication avoided, which reflects the additional costs for the prevention of one complication, e.g. decubitus. As a complication is not only a clinical issue, but also one which may have major economic consequences, this outcome might be relevant for decision-makers.

There are generic QoL scales, e.g. EQ-5D, which are important in the decision-making process, but disease-specific QoL outcomes can be relevant as well. If there is a correlation between the QALY gains and improvement in disease-specific measures, it gives decision-makers more confidence that the effects of the treatment are producing the QALY gains (fig. 1).

Cost Assessment

A major issue for cost-effectiveness evaluation is getting good quality costing data (resource use data). Each country has its own rules for costing depending on the decision-making perspective. Ideally, the cost assessment is based on the

Fig. 1. Example of the effect of survival gain on the QALY.
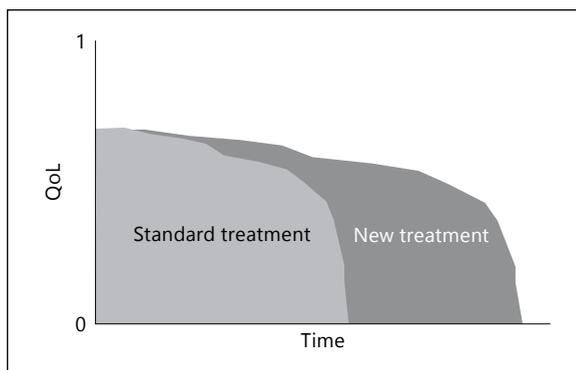
so-called opportunity costs of utilizing a technology, which are defined as the benefits to be gained from the best alternative use of the resources. In a system of perfectly competitive markets, price reflects value, and even though health care markets are imperfect, the market price is routinely used to measure the costs of health care goods and services. If a societal perspective is adopted prices paid are an approximate measure of opportunity costs, but with a health system perspective, prices paid reflect opportunity costs to the health sector. The methodological issues for the cost assessment in malnutrition are not much different from other diseases.

The societal perspective is important for malnutrition, as well as for other diseases such as Alzheimer's disease. Consequently, a study from a third party payer's perspective, which only includes direct medical costs, may underestimate the true value of a new treatment in malnutrition. Short-term costs may include productivity losses for children caring for their parents, as well as the costs of treatment. Long-term indirect costs may be due to productivity loss as a result of malnutrition. Therefore, the cost assessment in malnutrition should include not only direct medical and nonmedical costs, but also the indirect costs for the patient and caregivers in the short and long term.

In a cost-effectiveness analysis, measuring the extent of costs is an important step. Costs can be broadly divided into two discrete resource categories: direct costs and indirect costs (often labeled productivity costs). Direct costs reflect the monetary burden of the medical care and nonmedical care expenditures made in response to a disease. The cost of medicinal products is one type of direct medical cost. Other types of direct medical costs include costs of hospitalizations, physician visits, tests and procedures, and durable medical equipment. Direct nonmedical costs include the costs to patients, such as travel to obtain treatment, and the value of time spent by family and other nonprofessional caregivers in supporting patients. The main indirect cost is lost produc-

tivity from the patient being absent from work as a result of morbidity or premature mortality induced by the disease or its treatment. Productivity costs are only relevant when studies are conducted from a true societal perspective.

For the collection of data on utilization, a variety of approaches exist. These include subject interviews, subject surveys, provider surveys, medical record reviews, health care utilization diaries and data reviews of insurance claims [18]. Registries and observational studies may also be potential sources for the collection of actual medical costs in daily practice, as well as direct nonmedical costs and indirect costs. In malnutrition, primary cost data collection may be necessary due to the lack of historical databases containing information on the health care utilization costs of current standard care. The prospective collection of cost data might well be achievable.

Validity
Clinical trials can have a low external validity because they have strict inclusion and exclusion criteria and treatments are protocol driven, leading to potential overestimation of units of health care utilization. Considering the prospective approach, the concept of validity should be addressed. Internal validity is the extent to which the analytic inference derived from the study sample is correct for the target population. External validity or generalizability is the extent to which the results found in the study sample also apply to the population from which the sample was taken. Randomization is usually applied to balance confounding variables and, with double blinding, helps to support internal validity. However, the external validity of randomized controlled trials (RCT) is more questionable. Inclusion criteria for patients and selection of study sites may mean that the sample is not representative of the potential patient population. In addition, treatment patterns may be determined by the protocol [19]. Therefore, both clinical and economic outcomes may not be typical and do not correspond to usual practice. Hence, it should always be considered that, due to its restriction on external validity, the estimates of efficacy from RCT may not be representative of the effectiveness of the intervention in the target patient population.

The statistical constraints and limitations of external validity may be alleviated by the use of registries. Registries use large, longitudinal, observational studies designed to measure the impact of a particular disease or condition on clinical and patient-specific outcomes, and to document the outcomes associated with different treatments or settings of care. Patients are followed prospectively, and data are collected on disease severity and clinical outcomes as reported by clinicians, as well as resource use, functional status and QoL as reported by the patient. Currently, targeted longitudinal observational databases, or patient registries, are being designed, which reflect the current treatment patterns

without influencing the treatments and without any interference with real practice (e.g. no randomization) being fully naturalistic and having a high external validity.

Observational data, however, may also have important limitations through the nonrandom decisions of clinicians that introduce bias [20]. In observational data, patients would often be treated differently based on the underlying condition [21]. By contrast, in a well-executed RCT, the patients' condition is independent of treatment, and one can therefore reasonably attribute observed effects to the particular variation in treatment being studied. In observational data, the treatment is not allocated randomly. As a result, the characteristics of those obtaining the treatment will generally differ from the characteristics of those who do get standard care (the controls). The differences may be observable characteristics such as age, in which case a regression equation can potentially control for them [22]. However, new methodologies have been developed, which may reduce the dependence of cost-effectiveness analyses on RCT data. For example, Newhouse and McCellan [21] presented an econometric technique (instrumental variables) that can be useful in estimating the effectiveness of clinical treatments in situations when a controlled trial cannot be done. This technique relies upon the existence of one or more variables that induce substantial variation in the treatment variable, but have no direct effect on the outcome variable of interest. The concept was illustrated with an application of aggressive treatment of acute myocardial infarction in the elderly, which showed that some of the differences in observed mortality between patients receiving catheterization and no catheterization could result from differences in the capabilities of the hospitals and physicians treating the two groups of patients, independently of the procedures given to them. For example hospitals with a catheterization unit are more likely to have other sophisticated treatments available to their patients, and their physicians and nurses may be more highly trained. These problems in general mean that while observational data are potentially useful, they must be used with caution, as there are a number of examples where observational data have resulted in conclusions about the effectiveness of therapy which have subsequently been shown to be wrong, such as the prophylactic administration of lidocaine in patients with acute myocardial infarction [23].

Design

(1) A health economic evaluation compares at least two alternative medical interventions by examining both their costs and consequences.

(2) Such health economic evaluations can either be performed alongside clinical trials (piggyback study), as observational naturalistic economic evaluations (measured in real-world settings) or on the basis of health economic modeling.

(3) Economic analyses alongside clinical trials are often inconclusive due to a limited time horizon, a possible focus on surrogate end points, a highly selected patient population (low external validity – results are not generalizable) and due to protocol-driven costs.

(4) The major limitations of observational naturalistic economic evaluations are the selection bias (selection among treatment options can be influenced by the clinical and socioeconomic status of the patient) and that they can be conducted only after registration – as they are implemented in real-world settings.

(5) The third type – economic modeling – is routinely used to predict the 'comparative product value' for market access and reimbursement purposes. Economic modeling has the advantage that it can handle limitations outlined for piggyback and observational economic evaluations. For example economic modeling may be used to translate efficacy outcomes obtained from RCT into effectiveness outcomes (expected under routine real-world conditions), to simulate long-term therapy effects and to translate surrogate parameters into patient-relevant outcomes. Furthermore, it enables estimating results to specific patient groups or local settings, which is crucial to ensure the relevance of national reimbursement decisions.

Health Economic Modeling in Medical Nutrition

The use of models in economic evaluation combines different types of data sources to extend available information. Models can be used to simulate costs of trial modalities, to generalize trial results, to translate evidence from RCT into daily practice or to explore the potential value of additional evidence from empirical research. Several types of models can be used in the area of nutrition. One of them is the decision tree, comparing two or more health strategies. It defines intervention pathways and then links costs and outcomes to all the possible options. Another type of model is the Markov model, which is organized around health states rather than around pathways. In this case, the data input will be based on probabilities of transitions between successive health states, and specific costs and utilities associated with the various health states. Modeling techniques usually extrapolate the available short-term evidence over time in order to estimate outcomes beyond the study period or to link intermediate end points to final outcomes. The need for long-term follow-up, in the general or in a healthy at-risk population, may be solved by extrapolation methods; these are not specifically related to nutrition, but more to underlying available evidence and relationships. The real evidence for the efficacy of a preventive treatment might come from observational studies. For the purpose of illustration, we pres-
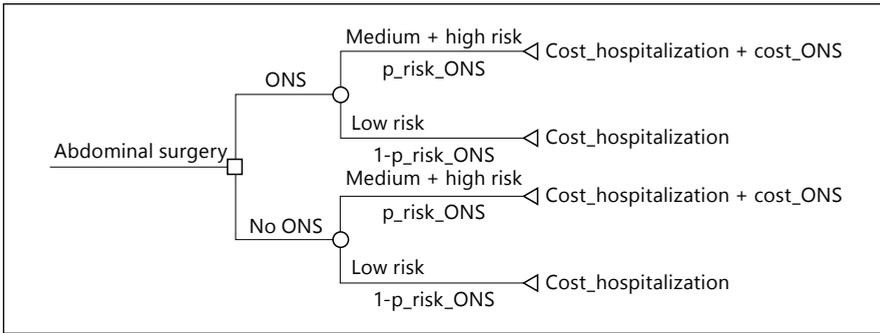
Fig. 2. Health economic model for malnutrition.

ent the linear decision analytic model, which was developed to estimate the health economic impact of ONS in the Netherlands and mentioned in the section Background [12]. The model calculates the medical costs for a virtual population of abdominal surgery patients with ONS and for a virtual population of abdominal surgery patients without ONS. The health economic impact of ONS is calculated using a linear model built in Excel reflecting treatment patterns and associated outcomes. Figure 2 shows the structure of the model for treatment with ONS. The first branch point in a tree is called a decision node because it corresponds to a choice of treatment – ONS or 'no ONS' – in patients eligible for ONS due to or at risk of DRM. A decision node is represented as a small square (□). Subsequent to the decision node, the structure of the decision tree is shown, and it is identical for both treatment options. The other branch points indicate probabilities. Data sources used included published literature, clinical trials and official Dutch price/tariff lists and national population statistics. The assumption of this study was that there were no clinical differences between the treatment arms, except for length of stay. The model shows that the use of ONS is cost-effective, because the additional costs for ONS are more than balanced by a reduction in hospitalization costs due to a reduction in the length of stay.

Discussion

This example shows that in case RCT are providing the clinical evidence, there is no methodological difference between a cost-effectiveness analysis for pharmaceuticals and nutrition. However, in nutrition, the evidence may not always come from RCT data but will be more often based on observational data. Therefore, the clinical evidence of nutrition in itself is not the issue, but the handling of clinical evidence from observational studies. There have been requirements for health

economics for pharmaceuticals for more than a decade, which resulted in formal academic guidelines for the appropriate execution of health economic evaluations. However, these so-called pharmacoeconomic guidelines are based on the clinical evidence specifically required for pharmaceuticals. As the link between the consumption of a food product and a resulting health status is often more difficult to establish than the effect of a drug treatment, it requires further development of adapted methodologies in order to correctly predict the impact of food-related health effects and health economic outcomes from a broader perspective.

The definition of standard care is a specific issue in cost-effectiveness analyses for nutrition. The normal daily food intake in the intervention group as well as in the control group can interfere with the medical nutrition intervention, very likely affecting the results. Moreover, randomization between groups as well as within the intervention group might be necessary to cope with the heterogeneity. Heterogeneity in the study population may have a significant bearing on the size of the treatment effect estimated. Another complicating issue is that multiple systems in the body can be affected, which may lead to a high variance in efficacy, contributing to a statistical power problem in RCT.

Finally, we want to address some policy issues. The pharmaceutical world is regulated at all levels starting with the execution of early clinical trials, followed by marketing authorization requirements (e.g. the European Medical Agency) towards the pricing and reimbursement assessment at national, regional and local levels. Furthermore, in most markets (or countries), the user of health care is not the provider and not the payer ('triangle of health care'), which might have adverse impacts on the utilization and demand of medical care. Nutrition interventions tend to be excluded from these processes, although health care decision-makers have begun to realize that food plays an important role, not only in those already with disease, but also in the onset and evolution of lifestyle-related disorders. Indeed, improving health through better population nutrition may contribute to the cost-effectiveness and sustainability of health care systems. However, cost-effectiveness analyses have been mainly associated with drug and medical device reimbursement decisions, where, in many countries, financial considerations of affordability may be as important as clinical effectiveness and cost-effectiveness. Medical nutrition could improve health, which may contribute to the cost-effectiveness and sustainability of health care systems.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

References

1 Hutton J: 'Health economics' and the evolution of economic evaluation of health technologies. Health Econ 2012;21:13–18.

2 Lochs H, Allison SP, Meier R, et al: Introductory to the ESPEN guidelines on enteral nutrition: terminology, definitions and general topics. Clin Nutr 2006;25:180–186.

3 Sauerwein HP, Romijn JA: More consideration to dietary protein in the nutrition of chronically ill adults with tendency to weight loss (in Dutch). Ned Tijdschr Geneeskd 1999; 143:886–889.

4 Stratton RJ, Elia M: Who benefits from nutritional support: what is the evidence? Eur J Gastroenterol Hepatol 2007;19:353–358.

5 Potter JM: Oral supplements in the elderly. Curr Opin Clin Nutr Metab Care 2001;4:21–28.

6 Stratton RJ, Ek AC, Engfer M, et al: Enteral nutritional support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. Ageing Res Rev 2005;4:422–450.

7 Russell C, Elia M: Nutrition Screening Week in the UK and Republic of Ireland in 2011. Hospitals, Care Homes and Mental Health Units. Redditch, British Association for Parenteral and Enteral Nutrition, 2012.

8 Ljungqvist O, van Gossum A, Sanz M, de Man F: The European fight against malnutrition. Clin Nutr 2010;29:149–150.

9 Ljungqvist O, de Man F: Under nutrition – a major health problem in Europe. Nutr Hosp 2009;24:368–370.

10 Freijer K, Tan SS, Koopmanschap MA, et al: The economic costs of disease related malnutrition. Clin Nutr 2013;32:136–141.

11 Freijer K, Bours MJ, Nuijten MJ, et al: The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. J Am Med Dir Assoc 2014;15:17–29.

12 Freijer K, Nuijten MJC: Analysis of the health economic impact of medical nutrition in the Netherlands. Eur J Clin Nutr 2010;64:1229–1234.

13 Nuijten M, Mittendorf T: The health economic impact of oral nutritional supplements (ONS) in Germany. Aktuel Ernährungsmed 2012;37:126–133.

14 Rabinovich M, Greenberg D, Shemer J: Threshold values for cost-effectiveness ratio and public funding of medical technologies. Harefuah 2007;146:453–458, 500.

15 Nuijten MJ, Dubois DJ: Cost-utility analysis: current methodological issues and future perspectives. Front Pharmacol 2011;2:29.

16 Zicht op zinnige en duurzame zorg. Zoetermeer, Raad voor de Volksgezondheid en Zorg, 2006.

17 Elia M, Stratton RJ, Russell C, et al: The Cost of Disease-Related Malnutrition in the UK and Economic Considerations for the Use of Oral Nutritional Supplements (ONS) in Adults. Redditch, British Association for Parenteral and Enteral Nutrition, 2005.

18 Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM: The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. J Clin Epidemiol 2000;53:688–695.

19 Sloan FA: Valuing Health Care. Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies. Cambridge, Cambridge University Press, 1995.

20 Rosenbaum PR: Discussing hidden bias in observational studies. Ann Intern Med 1991; 115:901–905.

21 Newhouse JP, McCellan M: Econometrics in outcomes research: the use of instrumental variables. Annu Rev Public Health 1998;19: 17–34.

22 Bowden RJ, Turkington DA: Instrument Variables. Cambridge, Cambridge University Press, 1984.

23 Hine LK, Laird N, Hewitt P, Chalmers T: Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. Arch Intern Med 1989;149:2694–2698.