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Nutrition economics: Are cost-effectiveness data in nutrition a double edged sword for nutrition companies?

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Abstract

The health economic evidence of nutrition tends to be limited. An important reason is that nutritionals do not always fall under the coverage requirements for reimbursement, like pharmaceuticals, which often require health economic data. The objective of this paper is to assess the relevance of proactively generating cost-effectiveness data from a nutrition company perspective. After a general introduction into health economics, we will address the key question of this paper: Are cost-effectiveness data in nutrition a double edged sword for nutrition companies?

The conclusion is that, as things currently stand, nutrition companies should be cautious in proactively generating cost-effectiveness data in terms of cost per QALY. Disaggregated economic and outcomes data may be more relevant and less risky for nutrition companies.

Introduction

Nutritional supplements are any dietary supplement that is intended to provide nutrients that may otherwise not be consumed in sufficient quantities; for example, vitamins, minerals, proteins, amino acids or other nutritional substances. Products are usually ingested in capsule, tablet or liquid form [1]. The market access for medicinal products (drugs) differs from nutritional products in the medical market. The main difference is that market access for (outpatient) medicinal products is a central procedure with specific requirements. The main target audiences are the central health authorities and health technology assessment (HTA) bodies e.g. the National Institute of Health and Clinical Excellence (NICE) in the UK, making decisions on reimbursement decisions. The market access for nutritional products is a more decentralized process, where the local payers (health insurance companies) are the main target audiences with different data requirements than the central health authorities. Table 1 shows the actual possibilities, including rare options.

Another important difference is that most prescription drugs are usually only available in the medical market. Some over-the-counter (OTC) drugs may be available in the consumer market, but they may only be reimbursed for a patient fulfilling specific clinical criteria, e.g. severe disease. Contrary many nutritionals are available as OTC.

Cost-effectiveness analysis has become common practice for informing reimbursement decisions for pharmaceuticals and other health technologies including devices. Nutritional interventions tend to be excluded from these processes, although healthcare decision-makers have begun to realize that nutrition plays an important role, not only in those already with disease, but also in the onset and evolution of lifestyle-related disorders [2,3]. Indeed, improving health through better population nutrition may contribute to the cost-effectiveness and sustainability of healthcare systems. Of course, increased health budget spending on nutritional products might divert funds away from other areas of healthcare, which is why formal economic evaluation is important. Formal guidelines exist for pharmaceutical products, but no systematic approach exists for the economic assessment of nutritional interventions [4].

Conventional foods and dietary supplements are traditionally used to meet daily nutritional requirements and preventing deficiency in the general population. However, some nutrients, like for instance vitamin E, have a benefit in managing disease or medical conditions in specific risk groups beyond their traditional nutritional function.

Consumer (OTC) market

Contrary to the healthcare market market, another option is positioning nutritional products in the consumer (OTC) market. The main target audiences are the consumers:

- There is no need for central reimbursement procedure or application for reimbursement by payers.
- There are no data requirements like clinical efficacy, cost-effectiveness and budget impact.
- The claims for efficacy of nutrition may not require high quality randomised clinical trials (RCTs) as for reimbursement claims, which would save costs and also increase time to launch.
- There would be no additional delay between market authorisation and market access. Contrary, the reimbursement procedure may require at least 9 months.

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Table 1. Stratification of nutritionals

Category	Clinical evidence	ICER	Central reimbursement	Payers	OTC
Severely ill patients in the hospital	Very high	Nutrition dominant	Maybe	No	No
Severely ill patients in ambulatory setting	High	< Threshold	Yes	Yes	May be
Medical nutrition for patients or persons at risk in an ambulatory setting	Medium	< or > Threshold	No	Yes	Yes
Nutrition for the prevention of disease in healthy persons.	Low	> Threshold	No	Maybe	Yes

- Pricing potential is based on the break-even price based on willingness to pay by consumers.
- The principal-agent problem is removed, since the consumer is now able to make all of his or her own decisions.

The objective of this paper is to assess the relevance of proactively generating cost-effectiveness data from a nutrition company perspective. After a general introduction into health economics, we will address the key question of this paper: Are cost-effectiveness data in nutrition a double edged sword for nutrition companies? The focus is on reimbursement policies, but we also address the impact on pricing policies at the end of this paper.

Reimbursement

Requirement for cost-effectiveness data

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 evaluate the trade-off between the incremental, clinical benefit and the extra cost of the new medicinal product versus an alternative or standard therapy [5,6]. Currently, formal methods of health technology assessment such as budget impact analysis (BIA) and cost-effectiveness analysis (CEA), are applied in order to make a value for money decision, which determines the final reimbursement decision.

A cost-effectiveness analysis provides a cost per quality-adjusted life year (QALY), which is also defined as the incremental cost-effectiveness ratio (ICER). In the United Kingdom, NICE has adopted a cost effectiveness threshold range of £20,000 to £30,000 per QALY gained, which means that the English society is willing to pay up to at least £20,000 per QALY gained for a new, innovative, medicinal product. This also reflects the 'opportunity cost' of moving funds from one area to another. If an intervention cost more than £30,000 per QALY gained, NICE supposes that the money would generate more QALYs if left where it is currently directed, rather than giving up those interventions to pay for the new technology. In many countries, the HTA institutes take a broad society perspective, e.g. in The Netherlands. The societal perspective includes the direct medical costs but also direct non-medical costs (e.g. transportation to healthcare facility) and indirect costs due to lost productivity (i.e. time off work) [7]. In other countries, the HTA institute only takes a payer perspective including only the direct medical costs (e.g. NICE in the UK). The costs per QALY gained are higher when only medical costs, and no direct non-medical and indirect costs are included leading to a lower cost-effectiveness. However, the threshold may also be different, since the opportunity costs of indirect societal savings would also be considered.

A budgetary impact analysis shows the impact of a new medicinal product on the annual national medicinal product budget and total health expenditures. If the budget impact is considered too high, the prescription of the product may be restricted to a smaller subpopulation [8]. A positive reimbursement for restricted use may lead to a substantial reduction in potential sales, which may only be 10% to 30% of the total expected sales based on the registered indication. There is also a probability that the drug will not be reimbursed because of a negative assessment of the reimbursement dossier. The health authorities may not be convinced of the clinical benefit and/or the cost-effectiveness neither for the total population nor for a subpopulation. In this case there will be no formal reimbursement under the health insurance system, and manufacturers are confronted with selling the product to a highly selected population who can afford to pay for the product privately or under a private insurance. This type of value messages, in terms of cost-effectiveness and budget impact, are increasingly important for new treatment modalities in high prevalent diseases, because of its high budgetary implications.

Considerations for nutritional interventions

Cost-effectiveness analyses can be applied to nutrients, if clinical evidence exists. There are no fundamental differences in applying health economic concepts to drugs or nutritionals (modelling and costing methodologies). The availability of clinical evidence for nutritionals is the main constraint for cost-effectiveness studies in nutrition [9].

HTA bodies require clinical data on efficacy and safety data from classical randomised controlled trials (RCTs) for the assessment of clinical benefit for innovative products, which is also required for the input for the cost-effectiveness analysis. However, for nutritional products it is not always possible to perform classical RCTs. Nutrition is often used for long-term prevention of diseases and long-term follow-up of more than e.g. 2 years is not feasible (e.g. by the time that a trial has completed, the interventions and comparators may well have been superseded by other products). Therefore clinical evidence is often only based on short-term intermediate efficacy data, which may be insufficient for HTA bodies, who prefer hard endpoints (e.g. morbidity or mortality).

Nutrition for therapeutic purpose in disease suffers also from heterogeneity in patient populations and clinical outcomes resulting from multifactorial effect of nutrition. Heterogeneity may also prevent balancing for confounding variables. On the contrary, drugs usually have a direct relationship in a homogenous population with one primary outcome. Therefore, RCTs in nutrition may suffer also from sample size constraints to show a statistically significant difference in outcomes. Finally double blind randomisation may also be more difficult due to use of nutrition than for clinical trials for drugs.

The ICER for nutrition in prevention is usually high, because the initial investment in nutrition only avoids in the long-term costs and disutility associated with morbidity, which becomes small due to the discounting of future outcomes. In addition the heterogeneity in clinical outcomes may lead to high uncertainty leading to an unfavourable CE acceptability curve.

Finally the budget impact is especially important for nutritionals because the indication often is in high prevalent diseases and therefore the health authorities would probably impose a restriction to a more severe subpopulation.

Central reimbursement

Based on these considerations, we may question whether a central reimbursement route for nutrition comparable to drugs is the most appropriate route for nutrition because of requirement of RCT data and risk of high ICER, especially in prevention.

We may stratify nutrition into four categories:

- Class I: Medical nutrition for severely ill patients in the hospital
- Class II: Severely ill patients in ambulatory setting
- Class III: Nutrition for patients or persons at risk in ambulatory setting
- Class IV: Nutrition for the prevention of disease in healthy persons

Table 1 shows an estimate of the level of clinical evidence for each category, as well as the expected ICER. These estimates are based on previous health economic evaluations by our group, as well expert option based on our experience [10,11,12]. For class I, a health economic analysis was performed to assess the cost-effectiveness of oral nutritional supplements in patients undergoing abdominal surgery in the Netherlands [10]. The analysis shows that the use of medical nutrition is dominant over standard care without medical nutrition: medical nutrition leads to cost savings and a higher effectiveness. The clinical evidence was based on observational data instead of RCT data. For class II, we assessed the health economic impact of oral nutritional supplement for patients with disease-related malnutrition in the community setting in Germany, which also shows that the extra costs for ONS (€534) are off-set by a reduction of hospitalisation costs (€768) leading to total cost savings of €234 per patient and therefore is dominant [11]. The primary clinical evidence was based on clinical studies that show that ONS results in a reduction in re-hospitalization, including a randomized double-blind placebo-controlled trial of nutritional supplementation [13].

In a study for class III, we estimated the cost-effectiveness of the use of prebiotics for the primary prevention of atopic dermatitis in The Netherlands [12]. The results show that the use of prebiotics results in a favourable ICER of €472, but the clinical evidence for development of asthma of 16 year period was derived not from the clinical trials, but it was indirectly derived from long-term studies, which may be questioned by HTA bodies.

For class IV, Pearson-Stuttard assessed the impact of reduction of sodium consumption over a period from 2017 to 2036 [14]. Sodium is a modifiable risk factor for higher blood pressure and cardiovascular disease. Although the analysis estimated with more than 80% probability to be cost-effective (incremental cost/QALY < $100,000), the effect estimates in the model are based on interventional and prospective observational studies. The outcomes are, therefore, subject to bias and confounding variables that may have influenced the outcomes of the model.

These examples confirm to a large extent the estimates in Table 1, but these estimates should be considered cautiously, because individual assessments for specific nutritionals may generate different outcomes. Nevertheless these estimates are relevant for this strategic assessment of the value of health economics for nutritionals.

Table 1 shows that a central drug-type reimbursement route for nutritionals may be considered only for severely ill patients in the ambulatory setting. For severely ill patients in the hospital setting, the relevance of cost-effectiveness data depends on the country reimbursement system for in-patient drugs. In Belgium, cost-effectiveness may be required, but not for the Netherlands, where an add-on DRG system is used. The current legislation for nutritionals determines if this split in separate four categories is realistic. If health authorities consider nutritionals only as one class of innovation following similar reimbursement procedures, the proactive use of health economics in appropriate categories (class I and class II), may also lead to similar requirements in the inappropriate categories (class III and class IV). If this split is legally not possible, we would not recommend the proactive generation of cost-effectiveness data for nutrition, which may also trigger stringent and unrealistic requirements by health authorities for generating classic RCT data for class III and class IV. If health authorities themselves are going to propose policy changes leading to requirements for nutritionals similar to drugs, nutrition companies may reactively challenge this approach from a conceptual clinical and health economic perspective. It is important to change the paradigm for generation of clinical evidence for nutritionals. As we mentioned there are many methodological arguments why it is not always possible to execute a classic RCT for nutrition (heterogeneous population, multivariate effect, confounding variables). In these cases, observational studies and registers may provide a scientific solution for proving the clinical evidence for nutrition, which therefore should not a priori be rejected by HTA bodies. Instead further research is required to address the standard criticisms on observational data (bias and confounding) and to develop statistical methods to handle these levels of uncertainty. Therefore the prove of the clinical benefit of nutrition is not the real hurdle here, but mainly the need for a change of paradigm by technology assessment bodies at health authorities. A different assessment of clinical evidence may require a different reimbursement path for nutritionals than for drugs, like for other medical innovation, e.g. devices, diagnostics, and surgery. Alternatively, the acceptance of observational data for cost-effectiveness analysis for drugs, may also contribute to a more scientifically appropriate assessment of drugs.

If the split in various categories is legally possible, we would only recommend the generation of cost-effectiveness data in class I and class II (severely ill patients), where a favourable cost-effectiveness may support the reimbursement of nutritionals, and may also support a higher price. If reimbursement rules for drugs are applied to nutritionals, also price laws for drugs should be applied to nutritionals instead of current price laws for nutritionals, which limit the price (see next section on price of nutritionals).

If the positive use of cost-effectiveness data for nutritionals implicitly means that a similar reimbursement procedure for drugs should be applied to nutritionals, this raises a separate assessment in terms of opportunities and threads:

- Reimbursement, like a pharmaceutical, may also imply following same pricing legislation for drugs, which may increase limited price potential for nutritional products.
- Reimbursement process comparable to pharmaceuticals, may give a nutrition a stamp of clinical approval and increase perception of clinical benefit for medical community and patients.
- No reimbursement of nutritional products avoids strict central legislation of drugs and yielding more options for directly targeting payers (see section "payers").

Nutrition is often not reimbursed and therefore a direct cost for patient, which would be avoided by reimbursement comparable to drugs.

Payers

Local payers (as opposed to centralized bodies) seldom use cost-effectiveness ratios such as cost per QALY gained. More relevant criteria for payers are: efficacy, safety, total budget impact and particularly drug budget impact. The payers may consider reimbursement of nutritionals for the following reasons.

The payers are convinced of the clinical benefit of nutrition contributing to the quality of care and quality of life of the patient. The payers rely for the judgment of the clinical benefit on the medical community, who will consider RCT data as most important data, but may also willing to consider other strong scientific data e.g. observational evidence. The inclusion of nutrition in a local or national clinical guideline would also contribute to listing by payers.

A cost-effectiveness analysis is not usually required for local payers, although it may support the societal value of nutritional product. Payers may consider potential cost savings by nutritionals more important and therefore a cost-minimization model might be sufficient. The cost savings per patient can be extended to a budget impact analysis at population level by including epidemiology data on number of patients. The break-even price for nutrition from the payer perspective is based on the savings in medical costs due to reduction of morbidity.

As a consequence, we may consider a 'payers' route of market access for nutritional products:

- Local payers may not require a formal drug status for nutrition interventions.
- Local payers are willing to consider other strong scientific data than only RCT data. e.g. observational evidence.
- There is no requirement for cost per QALY outcomes, but a cost-minimisation approach would be sufficient, which would show cost savings (price nutrition < break-even price nutrition) or neutral costs (price nutrition = break-even price for nutrition) at patient level and population level, where total savings are based on the total number of eligible patients.
- Local payers would probably also impose a restriction to a more severe subpopulation in order to control budget impact.
- A central route of market access would be more interesting than the payers route because a break-even price based on the ICER is higher than a break-even price based on the cost-minimisation approach.

The payers route for reimbursement for nutritionals may seem more attractive than a central route because of less stringent clinical and health economic requirements (Table 1). This route can be supported by health economic data without the risk of future requirements, if we only provide disaggregated health economic evaluation not combining costs and outcomes in an ICER. Therefore health economic outcomes should be presented, based on a cost-minimisation design with only quantification of monetary outcomes. The decision makers in these organizations are usual managers being more familiar with financial models than typical cost-effectiveness models (e.g. Markov models). The cost minimisation model is more transparent and may correspond more with their financial models, also because it only reports mainly monetary outcomes.

A cost-minimisation model provides cost per patient, After application of incidence/prevalence, this model becomes a budget impact model showing the impact on the payer's budget. A budget impact model should also provide a comprehension of the impact of the nutrition program on the treatment practice and the resulting substitution effects leading to shifts between the various cost types and budgets.

The cost-minimization model may provide clinical outcomes, e.g. reduction of complications or comorbidity. Quality of life is important as well for payers, but it should not be reported in QALYs, which allows the calculation of an ICER possibly exceeding the threshold. Therefore disease specific generic quality of life scales could be instead of EQ-5D, which is basis for calculation of QALYs and, subsequently, the ICER. An example is the health economic model for Optifast, which leads over a period of 3 years to cost-savings of USD 9,285 per class I and II obese patient (BMI 30-39.9 kg/m^2) as compared to liraglutide and USD 685 as compared to naltrexone/bupropion [15].

Despite the considerations above, it is also important to consider the impact of opportunity costs. If local payers divert funds towards nutritional products, these funds will have to be cut from somewhere else in the health system. It would be important, then, for the payer to have some mechanism to determine whether or not the benefits accruing from the nutritional intervention will outweigh the losses occurring because of the foregone interventions.

Employers

A cost-minimization model and a budget impact model can be used to show to the employer the potential cost savings by paying for nutritional interventions. This is not yet a real option for reimbursement of nutritionals as well as drugs, and is not addressed further in this paper, but it may become relevant in new business models in near future.

Pricing of nutrionals

Cost-effectiveness data for pricing of nutritionals

We recently performed an analysis which raised questions on the appropriate pricing of nutritionals [16]. This calculation included the break-even price for medical nutrition in malnutrition based on the incremental cost-effectiveness threshold from the payer and society perspectives. The results showed that the break-even price was at least 10 times higher than the actual price of €2 per day in the most conservative analysis. There was a huge variance in the outcomes based on the underlying assumptions of the calculations.

Considerations

Our analyses show that this price setting does not reflect the clinical value of nutritionals from a health economic perspective. The willingness to pay for medical nutrition seems, currently, low compared with pharmaceuticals. In addition, payers may require price discounts or they may want to have price-volume arrangements. However current price laws for nutrition limit the pricing potential of nutrition. If reimbursement rules for drugs are applied to nutritionals, also price laws for drugs could be applied to nutritionals instead of current price laws for nutrition, which limit the price. The current price law for nutrition are based euro per unit of ingredient, e.g. protein. Prices for drugs are not constrained by costs of ingredients and therefore the market determines the price. If nutrition price is based on the actual costs of ingredients, this is incorrect, as it would mean that a product should always have a price because of costs of the ingredients. Value is not similar to prices and costs and, therefore, we also do not favour this use of 'cost plus pricing' for nutrition [17].

A central reimbursement pathway for nutrition is only interesting, if regulatory and pricing legislation is changed and allows free pricing of nutrition. The current price law does not allow upper price setting based on the ICER and therefore cost-effectiveness data have no advantage for nutrition in diseases (class I and class I). However for nutrition in prevention (class III), there is a serious risk that ICER is higher than threshold, which would endanger reimbursement and may lead to no reimbursement or price negotiations, if nutritionals are not stratified in various categories (class I to IV). Hence there is only a one-sided risk for nutrition companies, when ICER data is used in a reimbursement procedure. Therefore the price law for nutritionals should be become more flexible and price should be based on real clinical economic value instead of cost plus method. Secondly nutrition should be stratified in various categories and for each category separate price and reimbursement policies should be developed.

Summary of key issues

- Cost-effectiveness analyses can be applied to nutrients, if clinical evidence exists. There are no fundamental differences in applying health economic concepts to drugs or nutritionals: e.g. modelling and costing methodologies. The availability of clinical evidence for nutritionals is the main constraint for cost-effectiveness studies in nutrition.
- HTA bodies require clinical data on efficacy and safety from classical RCTs for the assessment of clinical benefit for innovative products, which is also required for the input for the cost-effectiveness assessment. However, for nutritionals it is not always possible to perform classical RCTs, especially in prevention. Therefore we question if a central reimbursement route for nutrition comparable to drugs is the most appropriate route for nutritionals (requirement of RCT data, risk of high ICER).
- It is important to change the paradigm for generation of clinical evidence for nutritionals. The prove of the clinical benefit of nutrition is not the real hurdle, but mainly the need for a change of paradigm by HTA bodies to consider also non-RCT data.
- Payers seldom use cost-effectiveness ratios such as cost per QALY gained. More relevant criteria are: efficacy, safety, total budget impact and particularly drug budget impact. Payers may consider potential cost savings by nutritional more important and therefore a cost-minimization model and budget impact model might be sufficient. However, a mechanism is still needed to determine whether the benefits outweigh the opportunity costs of diverting funds from elsewhere.
- The break-even prices show that the prices for nutritionals do not reflect the full economic value from a society perspective. The willingness to pay for medical nutrition seems inappropriately lower compared with pharmaceuticals. A central reimbursement pathway for nutrition is only interesting, if regulatory and pricing legislation is changed and allows free pricing of nutrition. The price law for nutritionals should be become more flexible and the price should be based on real clinical economic value instead of cost plus method. Secondly nutrition should be stratified in various categories and for each category separate price and reimbursement policies should be developed.
- If those methodological and procedural constraints are not solved, the OTC market remains most attractive market for nutritionals. The price law limits the price and therefore only volume can generate sufficient revenues. The reimbursement route would reduce the potential market size in number of patients and therefore a price increase is needed to have at least break even revenues. There is a risk that this price increase may exceed the lower price limit based on price law for nutritionals. If price increase is allowed, the price may exceed the other extreme of the ICER threshold.

Conclusion

Our conclusion is that, currently, the use of cost-effectiveness data for nutrition may lead to a number of challenges. If the expectations for data for nutritional products are as high as those expected for pharmaceutical products, it is unlikely that any nutritional products would be approved. This is a similar situation to that faced by the medical devices industry when devices were first assessed using HTA. In time, the formal requirements for device evaluation have been adapted to better capture the realistic evidence that can be generated for devices. We hope that this will be the case for nutritional products too. Of course, it is important to address the issue of clinical evidence for nutritionals, which requires further research. Besides this methodological issue, there are important questions on the reimbursement and pricing procedures for nutritionals. Further research is required on healthcare policy of nutritionals, and especially if same rules for drugs should be applied to nutritionals. Therefore we recommend strategy to develop a joint strategy with association of nutrition companies exploring the current clinical and policy issues before generating cost-effectiveness data.

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